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Orientation to Pharmacology

Four Basic Terms

Properties of an Ideal Drug

The Big Three: Effectiveness, Safety, and Selectivity

Additional Properties of an Ideal Drug

Because No Drug Is Ideal . . .

The Therapeutic Objective

Factors That Determine the Intensity of Drug Responses

Administration

Pharmacokinetics

Pharmacodynamics

Sources of Individual Variation

By now, you've been hitting the books for many years, and have probably asked yourself, "What's the purpose of all this education?" In the past your question may have lacked a satisfying answer. Happily, now you have one: You've spent most of your life in school so you could study pharmacology!

There's good reason why you haven't approached pharmacology before now. Pharmacology is a science that draws on information from multiple disciplines, among them anatomy, physiology, chemistry, microbiology, and psychology. Consequently, before you could study pharmacology, you had to become familiar with these other sciences. Now that you've established the requisite knowledge base, you're finally ready to learn about drugs.

FOUR BASIC TERMS

At this point, I'd like to define four basic terms: *drug*, *pharmacology*, *clinical pharmacology*, and *therapeutics*. As we consider these definitions, I will indicate the kinds of information that we will and will not discuss in this text.

Drug. A drug is defined as *any chemical that can affect living processes*. By this definition, virtually all chemicals can be considered drugs, since, when exposure is sufficiently high, all chemicals will have some effect on life. Clearly, it is beyond the scope of this text to address all compounds that fit the definition of a drug. Accordingly, rather than discussing all drugs, we will focus primarily on drugs that have therapeutic applications.

Pharmacology. Pharmacology can be defined as *the study of drugs and their interactions with living systems*. Given this definition, the science of pharmacology can claim a huge body of knowledge as its own. Under our definition,

pharmacology encompasses the study of the physical and chemical properties of drugs as well as their biochemical and physiologic effects. In addition, pharmacology includes knowledge of the history, sources, and uses of drugs as well as knowledge of drug absorption, distribution, metabolism, and excretion. Because pharmacology encompasses such a broad spectrum of information, it would be inappropriate (not to mention impossible) to address the entire scope of pharmacology in this text. Consequently, we limit consideration to information that is *clinically relevant*.

Clinical Pharmacology. Clinical pharmacology is defined as *the study of drugs in humans*. This discipline includes the study of drugs in *patients* as well as in *healthy volunteers* (during new drug development). Because clinical pharmacology encompasses all aspects of the interaction between drugs and people, and since our primary interest is the use of drugs to treat patients, clinical pharmacology includes some information that is outside the scope of this text.

Therapeutics. Therapeutics, also known as *pharmaco-therapeutics*, is defined as *the use of drugs to diagnose, prevent, or treat disease or to prevent pregnancy*. Alternatively, therapeutics can be defined simply as *the medical use of drugs*.

In this text, therapeutics is our principal concern. Accordingly, much of our discussion focuses on the basic science that underlies the clinical use of drugs. This information is intended to help you understand how drugs produce their effects—both therapeutic and adverse; the reasons for giving a particular drug to a particular patient; and the rationale underlying selection of dosage, route, and schedule of administration. This information will also help you understand the strategies employed to promote beneficial drug effects and to minimize undesired effects. Armed with this knowledge, you will be well prepared to provide drug-related patient care and education. In addition, by making drugs less mysterious, this knowledge should make working with drugs more comfortable, and perhaps even more satisfying.

PROPERTIES OF AN IDEAL DRUG

If we were developing a new drug, we would want it to be the best drug possible. In order to approach perfection, our drug should have certain properties, such as effectiveness and safety. In the discussion below, we consider these two characteristics as well as others that an ideal drug might have. Please note, however, that the ideal medication exists in theory only: In reality, *there's no such thing as a perfect drug*. The truth of this statement will become apparent as we consider the properties that an ideal drug should have.

The Big Three: Effectiveness, Safety, and Selectivity

The three most important characteristics that any drug can have are effectiveness, safety, and selectivity.

Effectiveness. An effective drug is one that elicits the responses for which it is given. *Effectiveness is the most important property a drug can have.* Regardless of its other virtues, if a drug is not effective—that is, if it doesn't do anything useful—there is no justification for giving it. Current U.S. law requires that all new drugs be proved effective prior to release for marketing.

Safety. A safe drug is defined as one that cannot produce harmful effects—even if administered in very high doses and for a very long time. *There is no such thing as a safe drug.* All drugs have the ability to cause injury, especially with high doses and prolonged use. The chances of producing adverse effects can be reduced by proper drug selection and proper dosing. However, the risk of adverse effects can never be eliminated. The following examples illustrate this point:

- Certain anticancer drugs (eg, cyclophosphamide, methotrexate), at usual therapeutic doses, always increase the risk of serious infection.
- Opioid analgesics (eg, morphine, meperidine), at high therapeutic doses, can cause potentially fatal respiratory depression.
- Aspirin and related drugs, when taken chronically in high therapeutic doses, can cause life-threatening gastric ulceration, perforation, and bleeding.

Clearly, drugs are not safe. This fact may explain why the Greeks chose the word *pharmakon*, which can be translated as *poison*, as a name for these agents.

Selectivity. A selective drug is defined as one that elicits only the response for which it is given. A selective drug would not produce side effects. *There is no such thing as a selective drug: All medications cause side effects.* Common examples include the drowsiness that can be caused by many antihistamines; the morning sickness, cramps, and depression that can be caused by oral contraceptives; and the sexual dysfunction (eg, impotence, anorgasmia) commonly caused by fluoxetine [Prozac] and related antidepressants.

Additional Properties of an Ideal Drug

Reversible Action. For most drugs, it is important that effects be reversible. That is, in most cases, we want drug actions to subside within an appropriate time. General anesthetics, for example, would be useless if patients never woke up. Likewise, it is unlikely that oral contraceptives would find wide acceptance if they caused permanent sterility. And, despite what some gentlemen (and gentlewomen) might think, sildenafil [Viagra] would be more curse than blessing if it produced a perpetual gallant salute. For a few drugs, however, reversibility is not desirable. With antibiotics, for example, we want toxicity to microbes to endure.

Predictability. It would be very helpful if, prior to drug administration, we could know with certainty just how a given patient will respond. Unfortunately, since each patient is unique, the accuracy of predictions cannot be guaranteed. Accordingly, in order to maximize the chances of eliciting desired responses, we must tailor therapy to the individual.

Ease of Administration. An ideal drug should be simple to administer: The route should be convenient, and the number of doses per day should be low. Diabetic patients, who must inject insulin multiple times a day, are not likely to judge this drug ideal. Similarly, nurses who must set up and monitor IV infusions are unlikely to consider intravenous drugs ideal.

In addition to convenience, ease of administration has two other benefits: (1) it can enhance patient adherence and (2) it can decrease administration errors. Patients are more likely to adhere to a dosing schedule that consists of one daily dose rather than several. Similarly, hospital personnel are less likely to commit medication errors when administering oral drugs than when preparing and administering intravenous agents.

Freedom from Drug Interactions. When a patient is taking two or more drugs, those drugs can interact. These interactions may augment or reduce drug responses. For example, respiratory depression caused by diazepam [Valium], which is normally minimal, can be greatly *intensified* by alcohol. Conversely, the antibacterial effects of tetracycline can be greatly *reduced* by taking the drug with iron or calcium supplements. Because of the potential for interaction among drugs, when a patient is taking more than one agent, the possible impact of drug interactions must be considered. An ideal drug would not interact with other agents. Unfortunately, few medicines are devoid of significant interactions.

Low Cost. An ideal drug would be easy to afford. The cost of drugs can be a substantial financial burden. As an extreme example, treatment with adalimumab [Humira], a drug for rheumatoid arthritis and Crohn's disease, can cost \$50,000 or more per year. More commonly, expense becomes a significant factor when a medication must be taken chronically. For example, people with hypertension, arthritis, or diabetes must take medications every day for life. The cumulative expense of such treatment can be huge—even for drugs of moderate price.

Chemical Stability. Some drugs lose effectiveness during storage. Others that may be stable on the shelf can rapidly lose effectiveness when put into solution (eg, in preparation for infusion). These losses in efficacy result from chemical instability. Because of chemical instability, stocks of certain drugs must be periodically discarded. An ideal drug would retain its activity indefinitely.

Possession of a Simple Generic Name. Generic names of drugs are usually complex, and hence difficult to remember and pronounce. As a rule, the trade name for a drug is much simpler than its generic name. Examples of drugs that have complex generic names and simple trade names include acetaminophen [Tylenol], ciprofloxacin [Cipro], and simvastatin [Zocor]. Since generic names are preferable to trade names (for reasons discussed in Chapter 3), an ideal drug should have a generic name that is easy to recall and pronounce.

Because No Drug Is Ideal . . .

From the preceding, we can see that available medications are not ideal. No drug is safe. All drugs produce side effects. Drug responses may be difficult to predict and may be altered by drug interactions. Drugs may be expensive, unstable, and hard to administer. Because medications are not

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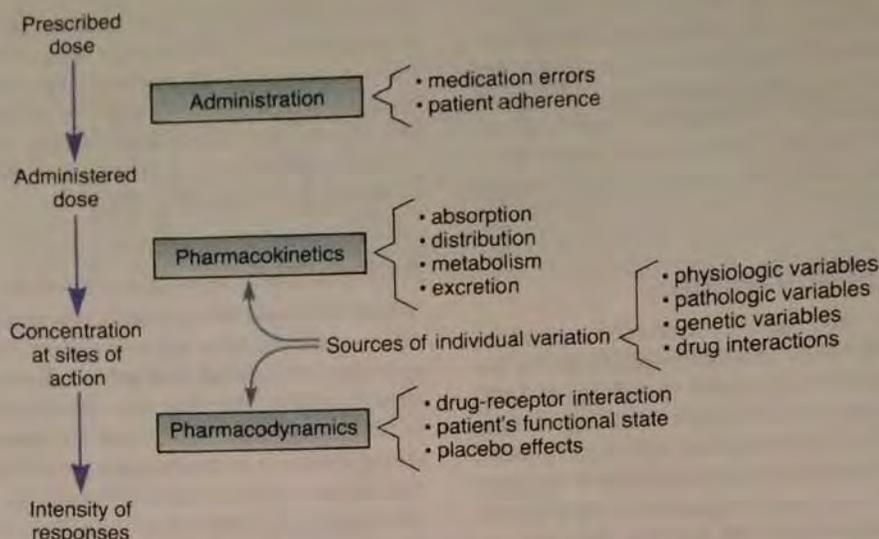


Figure 1-1 • Factors that determine the intensity of drug responses.
 (Adapted from Koch-Weser J: Drug therapy: serum drug concentrations as therapeutic guides. N Engl J Med 287:227, 1972.)

ideal, all members of the healthcare team must exercise care to promote therapeutic effects and minimize drug-induced harm.

THE THERAPEUTIC OBJECTIVE

The objective of drug therapy is to provide maximum benefit with minimum harm. If drugs were ideal, we could achieve this objective with relative ease. However, because drugs are not ideal, we must exercise skill and care if treatment is to result in more good than harm. As detailed in Chapter 2, you have a critical responsibility in achieving the therapeutic objective. In order to meet this responsibility, you must understand drugs. The primary purpose of this text is to help you achieve that understanding.

FACTORS THAT DETERMINE THE INTENSITY OF DRUG RESPONSES

Multiple factors determine how an individual will respond to a prescribed dose of a particular drug (Fig. 1-1). By understanding these factors, you will be able to think rationally about how drugs produce their effects. As a result, you will be able to contribute maximally to achieving the therapeutic objective.

Our ultimate concern when administering a drug is the intensity of the response. Working our way up from the bottom of Figure 1-1, we can see that the intensity of the response is determined by the concentration of a drug at its sites of action. As the figure suggests, the primary determinant of this concentration is the administered dose. When administration is performed correctly, the dose that was given will bear a close relationship to the dose that was prescribed. The steps leading from prescribed dose to intensity of the response are considered below.

Administration

Dosage size and the route and timing of administration are important determinants of drug responses. Accordingly, the prescriber will consider these variables with care. Unfortunately, because of poor patient adherence and medication errors by hospital staff, drugs are not always administered as prescribed. The result may be toxicity (if the dosage is too high) or treatment failure (if the dosage is too low). To help minimize errors caused by poor adherence, you should give patients complete instruction about their medication and how to take it.

Medication errors made by hospital staff may result in a drug being administered by the wrong route, in the wrong dose, or at the wrong time; the patient may even be given the wrong drug. These errors can be made by pharmacists, physicians, and nurses. Any of these errors will detract from achieving the therapeutic objective. Medication errors are discussed at length in Chapter 7.

Pharmacokinetics

Pharmacokinetic processes determine how much of an administered dose gets to its sites of action. There are four major pharmacokinetic processes: (1) drug absorption, (2) drug distribution, (3) drug metabolism, and (4) drug excretion. Collectively, these processes can be thought of as the *impact of the body on drugs*. These pharmacokinetic processes are discussed at length in Chapter 4.

Pharmacodynamics

Once a drug has reached its sites of action, pharmacodynamic processes determine the nature and intensity of the response. Pharmacodynamics can be thought of as the *impact of drugs on the body*. In most cases, the initial step leading to a response is the binding of a drug to its receptor. This drug-receptor interaction is followed by a sequence of events that

ultimately results in a response. As indicated in Figure 1-1, the patient's "functional state" can influence pharmacodynamic processes. For example, a patient who has developed tolerance to morphine will respond less intensely to a particular dose than will a patient who lacks tolerance. Placebo (psychologic) effects also help determine the responses that a drug elicits. Pharmacodynamics is discussed at length in Chapter 5.

Sources of Individual Variation

Characteristics unique to each patient can influence pharmacokinetic and pharmacodynamic processes and, by doing so, can help determine the patient's response to a drug. As indicated in Figure 1-1, sources of individual variation include drug interactions; physiologic variables (eg, age, gender, weight); pathologic variables (especially diminished function of the kidneys and liver, the major organs of drug elimination); and genetic variables. Genetic factors can alter the me-

tabolism of drugs and can predispose the patient to unique drug reactions. Because individuals differ from one another, no two patients will respond identically to the same drug regimen. Accordingly, in order to achieve the therapeutic objective, we must tailor drug therapy to the individual. Individual variation in drug responses is the subject of Chapter 8.

SUMMARY

Whenever medicines are used, our goal is to promote desired effects and minimize adverse effects. In order to achieve this objective, we need to understand pharmacokinetics and pharmacodynamics, the principal determinants of drug responses. In addition, we must account for potential sources of individual variation in drug responses. When all of these considerations are made, the resulting regimen will be tailored to the individual, and hence should produce maximum benefit with minimum harm.

KEY POINTS

- The most important properties of an ideal drug are effectiveness, safety, and selectivity.
- If a drug is not effective, it should not be used.
- There is no such thing as a safe drug: All drugs can cause harm.
- There is no such thing as a selective drug: All drugs can cause side effects.

- The objective of drug therapy is to provide maximum benefit with minimum harm.
- Because all patients are unique, drug therapy must be tailored to each individual.

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Application of Pharmacology in Nursing Practice

Evolution of Nursing Responsibilities Regarding Drugs

Application of Pharmacology in Patient Care

Preadministration Assessment

Dosage and Administration

Evaluating and Promoting Therapeutic Effects

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Our principal goal in this chapter is to answer the question “Why should a nursing student learn pharmacology?” By addressing this question, I want to give you some extra motivation to study. Why do I think you might need some motivation? Because I have known many students who, at the beginning of my pharmacology course, questioned the value of learning the material. With some luck, when you complete the chapter, you will be convinced that understanding drugs is essential for nursing practice, and that putting time and effort into learning about drugs will be a good investment. If you are already convinced that understanding pharmacology is important, then just scan the chapter quickly. However, if you are skeptical, then read it carefully. Hopefully, doing so will help you see the light, and thereby boost your motivation for the job ahead.

EVOLUTION OF NURSING RESPONSIBILITIES REGARDING DRUGS

In the past, a nurse’s responsibility regarding medications focused on the *Five Rights of Drug Administration*, namely, give the right drug to the right patient in the right dose by the right route at the right time. More recently, a Sixth Right—*right documentation*—was added. Clearly, the Six Rights are im-

portant. However, although these basics are important, much more is required to achieve the therapeutic objective. The Six Rights guarantee only that a drug will be administered as prescribed. Correct administration, without additional interventions, cannot ensure that treatment will result in maximum benefit and minimum harm.

The limitations of the Six Rights can be illustrated with this analogy: The nurse who sees his or her responsibility as being done following correct drug administration would be like a major league baseball pitcher who felt that his responsibility was over once he had thrown the ball toward the batter. As the pitcher must be ready to respond to the consequences of the interaction between ball and bat, you must be ready to respond to the consequences of the interaction between drug and patient. Put another way, although both the nurse and the pitcher have a clear obligation to deliver their respective “pills” in the most appropriate fashion, proper delivery is only the beginning of their responsibilities: *Important events will take place after the “pill” is delivered, and these must be responded to.* Like the pitcher, the nurse can respond rapidly and effectively only by anticipating (knowing in advance) what the possible reactions to the pill might be.

In order to anticipate possible reactions, both the nurse and the pitcher require certain kinds of knowledge. Just as the pitcher must understand the abilities of the opposing batter, you must understand the patient and the disorder for which he or she is being treated. As the pitcher must know the most appropriate pitch (eg, fast ball, curve, slider) to deliver in specific circumstances, you must know what medications are appropriate for the patient and must check to ensure that the medication ordered is among them. Conversely, as the pitcher must know what pitches *not* to throw at a particular batter, you must know what drugs are *contraindicated* for the patient. As the pitcher must know the most likely outcome after the ball and bat interact, you must know the probable consequences of the interaction between drug and patient.

Although this analogy is not perfect (the nurse and patient are on the same team, whereas the pitcher and batter are not), it does help us appreciate that the nurse’s responsibility extends well beyond the Six Rights. Consequently, in addition to the limited information needed to administer drugs in accordance with the Six Rights, you must acquire a broad base of pharmacologic knowledge so as to contribute fully to achieving the therapeutic objective.

In drug therapy today, nurses, together with physicians and pharmacists, participate in a system of checks and balances designed to promote beneficial effects and minimize harm. Nurses are especially important in this system because it is the nurse—not the physician or pharmacist—who follows the patient’s status most closely. As a result, you are likely to be

the first member of the healthcare team to observe and evaluate drug responses, and to intervene if required. In order to observe and evaluate drug responses, and in order to intervene rapidly and appropriately, you must know *in advance* the responses that a medication is likely to elicit. Put another way, in order to provide professional care, you must understand drugs. The better your knowledge of pharmacology, the better you will be able to *anticipate* drug responses and not simply react to them after the fact.

Within our system of checks and balances, the nurse has an important role as patient advocate. It is your responsibility to detect mistakes made by pharmacists and prescribers—and mistakes *will* be made. For example, the prescriber may overlook potential drug interactions, or may be unaware of alterations in the patient's status that would preclude use of a particular drug, or may select the correct drug but may order an inappropriate dosage or route of administration. Because the nurse actually administers drugs, the nurse is the last person to check medications before they are given. Consequently, *you are the patient's last line of defense against medication errors*. It is ethically and legally unacceptable for you to administer a drug that is harmful to the patient—even though the medication has been prescribed by a licensed prescriber and dispensed by a licensed pharmacist. In your role as patient advocate, you must protect the patient against medication errors made by other members of the healthcare team. In serving as patient advocate, it is impossible to know too much about drugs.

APPLICATION OF PHARMACOLOGY IN PATIENT CARE

The two major areas in which you can apply pharmacologic knowledge are patient care and patient education. Patient care is considered in this section. Patient education is considered in the section that follows. In discussing the applications of pharmacology in patient care, we focus on seven aspects of drug therapy: (1) preadministration assessment, (2) dosage and administration, (3) evaluating and promoting therapeutic effects, (4) minimizing adverse effects, (5) minimizing adverse interactions, (6) making PRN decisions, and (7) managing toxicity.

Preadministration Assessment

All drug therapy begins with assessment of the patient. Assessment has three basic goals: (1) collecting baseline data needed to evaluate therapeutic and adverse responses, (2) identifying high-risk patients, and (3) assessing the patient's capacity for self-care. The first two goals are highly specific for each drug. Accordingly, we cannot achieve these goals without understanding pharmacology. The third goal applies generally to all drugs, and hence it does not usually require specific knowledge of the drug you are about to give. Preadministration assessment is discussed here and again under *Application of the Nursing Process in Drug Therapy*.

Collecting Baseline Data. Baseline data are needed to evaluate drug responses, both therapeutic and adverse. For example, if we plan to give a drug to lower blood pressure, we must know the patient's blood pressure prior to treat-

ment. Without these data, we would have no way of determining the effectiveness of our drug. Similarly, if we are planning to give a drug that can damage the liver, we need to assess baseline liver function in order to evaluate the potential toxicity. Obviously, in order to collect appropriate baseline data, we must first know the effects that our drug is likely to produce.

Identifying High-Risk Patients. Multiple factors can predispose an individual to adverse reactions from specific drugs. Important predisposing factors are pathophysiology (especially liver and kidney impairment), genetic factors, drug allergies, pregnancy, old age, and extreme youth.

Patients with penicillin allergy provide a dramatic example of those at risk: Giving penicillin to such a patient can be fatal. Accordingly, whenever treatment with penicillin is under consideration, we must determine if the patient has had an allergic reaction to a penicillin in the past. If there is a history of penicillin allergy, an alternative antibiotic should be employed. If there is no effective alternative, facilities for managing a severe reaction should be in place before the drug is given.

From the preceding example, we can see that, when planning drug therapy, we must identify patients who are at high risk of reacting adversely. To identify such patients, we use three principal tools: the patient history, physical examination, and laboratory data. Of course, if identification is to be successful, you must know what to look for (ie, you must know the factors that can increase the risk of severe reactions to the drug in question). Once the high-risk patient has been identified, we can take steps to reduce the risk. We might select an alternative drug, or, if no alternative is available, we can at least prepare in advance to manage a possible adverse event.

Dosage and Administration

Earlier we noted the Six Rights of Drug Administration and agreed on their importance. Although you can implement the Six Rights without a detailed knowledge of pharmacology, having this knowledge can help reduce your contribution to medication errors. The following examples illustrate this point:

- Certain drugs have more than one indication, and dosage may differ depending on which indication the drug is used for. Aspirin, for example, is given in low doses to relieve pain and in high doses to suppress inflammation (eg, in patients with arthritis). If you don't know about these differences, you might administer too much aspirin to the patient with pain or too little to the patient with inflammation.
- Many drugs can be administered by more than one route, and dosage may differ depending upon the route selected. Morphine, for example, may be administered by mouth or by injection (eg, subcutaneous, intramuscular, intravenous). Oral doses are generally much larger than injected doses. Accordingly, if a large dose intended for oral use were to be mistakenly administered by injection, the result could prove fatal. The nurse who understands the pharmacology of morphine is unlikely to make this error.
- Certain intravenous agents can cause severe local injury if the line through which they are being infused becomes

extravasated. Accordingly, when such drugs are given, special care must be taken to prevent extravasation. The infusion must be monitored closely, and, if extravasation occurs, corrective steps must be taken immediately. The nurse who doesn't understand these drugs will be unprepared to work with them safely.

The following basic guidelines can help ensure correct administration:

- Read the medication order carefully. If the order is unclear, verify it with the prescriber.
- Verify the identity of the patient by comparing the name on the wristband with the name on the drug order or medication administration record.
- Read the medication label carefully. Verify the identity of the drug, the amount of drug (per tablet, volume of liquid, etc.), and its suitability for administration by the intended route.
- Verify dosage calculations.
- Implement any special handling the drug may require.
- Don't administer any drug if you don't understand the reason for its use.

Measures to minimize medication errors are discussed further in Chapter 7 (Adverse Drug Reactions and Medication Errors).

Evaluating and Promoting Therapeutic Effects

Evaluating Therapeutic Responses. Evaluation is one of the most important aspects of drug therapy. After all, this is the process that tells us whether or not a drug is doing anything useful. Because the nurse follows the patient's status most closely, the nurse is in the best position to evaluate therapeutic responses.

In order to make an evaluation, you must know the rationale for treatment and the nature and time course of the intended response. If you lack this knowledge, you will be unable to evaluate the patient's progress. When beneficial responses develop as hoped for, ignorance of expected effects might not be so bad. However, when desired responses do *not* occur, it may be essential to identify the failure quickly, so that timely implementation of alternative therapy may be ordered.

When evaluating responses to a drug that has more than one application, you can do so only if you know the specific indication for which the drug is being used. Nifedipine, for example, is given for two cardiovascular disorders: hypertension and angina pectoris. When the drug is used for hypertension, you should monitor for a reduction in blood pressure. In contrast, when this drug is used for angina, you should monitor for a reduction in chest pain. Clearly, if you are to make the proper evaluation, you must understand the reason for drug use.

Promoting Patient Adherence. Adherence—also known as compliance or concordance—may be defined as the extent to which a patient's behavior coincides with medical advice. If we are to achieve the therapeutic objective, adherence is essential. Drugs that are self-administered in the wrong dose, by the wrong route, or at the wrong time cannot produce maximum benefit—and may even prove harmful. Obviously, successful therapy requires active and informed participation by the pa-

tient. By educating patients about the drugs they are taking, you can help elicit the required participation.

Implementing Nondrug Measures. Drug therapy can often be enhanced by nonpharmacologic measures. Examples include (1) enhancing drug therapy of asthma through breathing exercises, biofeedback, and emotional support; (2) enhancing drug therapy of arthritis through exercise, physical therapy, and rest; and (3) enhancing drug therapy of hypertension through weight reduction, smoking cessation, and sodium restriction. As a nurse, you may provide these supportive measures directly, through patient education, or by coordinating the activities of other healthcare providers.

Minimizing Adverse Effects

All drugs have the potential to produce undesired effects. Common examples include gastric erosion caused by aspirin, sedation caused by older antihistamines, hypoglycemia caused by insulin, and excessive fluid loss caused by diuretics. When drugs are employed properly, the incidence and severity of such events can be reduced. Measures to reduce adverse events include identifying high-risk patients through the patient history, ensuring proper administration through patient education, and forewarning patients about activities that might precipitate an adverse event.

When untoward effects cannot be avoided, discomfort and injury can often be minimized by appropriate intervention. For example, timely administration of glucose will prevent brain damage from insulin-induced hypoglycemia. In order to help reduce adverse effects, you must know the following about the drugs you are working with:

- The major adverse effects the drug can produce
- When these reactions are likely to occur
- Early signs that an adverse reaction is developing
- Interventions that can minimize discomfort and harm

Minimizing Adverse Interactions

When a patient is taking two or more drugs, those drugs may interact with one another to diminish therapeutic effects or intensify adverse effects. For example, the ability of oral contraceptives to protect against pregnancy can be reduced by concurrent therapy with carbamazepine (an antiseizure drug), and the risk of thromboembolism from oral contraceptives can be increased by smoking cigarettes.

As a nurse, you can help reduce the incidence and intensity of adverse interactions in several ways. These include taking a thorough drug history, advising the patient to avoid over-the-counter drugs that can interact with the prescribed medication, monitoring for adverse interactions *known* to occur between the drugs the patient is taking, and being alert for as-yet *unknown* interactions.

Making PRN Decisions

A PRN medication order is one in which the nurse has discretion regarding how much drug to give and when to give it. (PRN stands for *pro re nata*, a Latin phrase meaning *as needed* or *as the occasion arises*.) PRN orders are common

for drugs that promote sleep, relieve pain, and reduce anxiety. In order to implement a PRN order rationally, you must know the reason for drug use and be able to assess the patient's medication needs. Clearly, the better your knowledge of pharmacology, the better your PRN decisions are likely to be.

Managing Toxicity

Some adverse drug reactions are extremely dangerous. Hence, if toxicity is not diagnosed early and responded to quickly, irreversible injury or death can result. In order to minimize harm, you must know the early signs of toxicity and the procedure for toxicity management.

APPLICATION OF PHARMACOLOGY IN PATIENT EDUCATION

Very often, the nurse is responsible for educating patients about medications. In your role as educator, you must give the patient the following information:

- Drug name and therapeutic category (eg, penicillin: antibiotic)
- Dosage size
- Dosing schedule
- Route and technique of administration
- Expected therapeutic response and when it should develop
- Non-drug measures to enhance therapeutic responses
- Duration of treatment
- Method of drug storage
- Symptoms of major adverse effects, and measures to minimize discomfort and harm
- Major adverse drug-drug and drug-food interactions
- Whom to contact in the event of therapeutic failure, severe adverse reactions, or severe adverse interactions

In order to communicate this information effectively and accurately, you must first understand it. That is, to be a good drug educator, you must know pharmacology.

In the discussion below, we consider the relationship between patient education and the following aspects of drug therapy: dosage and administration, promoting therapeutic effects, minimizing adverse effects, and minimizing adverse interactions.

Dosage and Administration

Drug Name. The patient should know the name of the medication he or she is taking. If the drug has been prescribed by trade name, the patient should be given its generic name too. This information will reduce the risk of overdose that can result when a patient fails to realize that two prescriptions that bear different names actually contain the same medicine.

Dosage Size and Schedule of Administration. Patients must be told how much drug to take and when to take it. For some medications, dosage must be adjusted by the patient. Insulin is a good example. For insulin therapy to be most beneficial, the patient must adjust doses to accommodate changes in caloric intake. How to make this adjustment is taught by the nurse.

With PRN medications, the schedule of administration is not fixed. Rather, these drugs are taken as conditions require.

For example, some people with asthma experience exercise-induced bronchospasm. To minimize such attacks, they can take supplementary medication prior to anticipated exertion. It is your responsibility to teach patients when PRN drugs should be taken.

The patient should know what to do if a dose is missed. With certain oral contraceptives, for example, if one dose is missed, the omitted dose should be taken together with the next scheduled dose. However, if three or more doses are missed, a new cycle of administration must be initiated.

Some patients have difficulty remembering whether or not they have taken their medication. Possible causes include mental illness, advanced age, and complex regimens. To facilitate accurate dosing, you can provide the patient with a pill box that has separate compartments for each day of the week, and then teach him or her to load the compartments weekly. To determine if they have taken their medicine, patients can simply examine the box.

Technique of Administration. Patients must be taught how to administer their drugs. This is especially important for routes that may be unfamiliar (eg, sublingual for nitroglycerin) and for techniques that can be difficult (eg, subcutaneous injection of insulin). Patients taking oral medications may require special instructions. For example, some oral preparations must not be chewed or crushed; some should be taken with fluids; and some should be taken with meals, whereas others should not. Careful attention must be paid to the patient who, because of disability (eg, visual or intellectual impairment, limited manual dexterity), may find self-medication difficult.

Duration of Drug Use. Just as patients must know when to take their medicine, they must know when to stop. In some cases (eg, treatment of acute pain), patients should discontinue drug use as soon as symptoms subside. In other cases (eg, treatment of hypertension), patients should know that therapy will probably continue lifelong. For other conditions (eg, gastric ulcers), medication may be prescribed for a specific time interval, after which the patient should return for re-evaluation.

Drug Storage. Certain medications are chemically unstable and hence deteriorate rapidly if stored improperly. Patients who are using unstable drugs must be taught how to store them correctly (eg, under refrigeration, in a light-proof container). All drugs should be stored where children can't reach them.

Promoting Therapeutic Effects

In order to participate fully in achieving the therapeutic objective, patients must know the nature and time course of expected beneficial effects. With this knowledge, patients can help evaluate the success or failure of treatment. By recognizing treatment failure, the informed patient will be able to seek timely implementation of alternative therapy.

With some drugs, such as those used to treat depression and schizophrenia, beneficial effects are delayed, taking several weeks to become maximal. Awareness that treatment may not produce immediate results allows the patient to have realistic expectations and helps reduce anxiety about therapeutic failure.

As noted, non-drug measures can complement drug therapy. For example, although drugs are useful in managing high cholesterol, exercise and diet are also important. Teaching the

patient about nondrug measures can greatly increase the chances of success.

Minimizing Adverse Effects

Knowledge of adverse drug effects will enable the patient to avoid some adverse effects and minimize others through early detection. The following examples underscore the value of educating patients about the undesired effects of drugs:

- Insulin overdose can cause blood glucose levels to drop precipitously. Early signs of hypoglycemia include sweating and increased heart rate. The patient who has been taught to recognize these early signs can respond by ingesting glucose-rich foods, thereby restoring blood sugar to a safe level. In contrast, the patient who fails to recognize evolving hypoglycemia and does not ingest glucose may become comatose, and may even die.
- Many anticancer drugs predispose patients to acquiring serious infections. The patient who is aware of this possibility can take steps to avoid contagion (eg, avoiding contact with people who have an infection; avoiding foods likely to contain pathogens). In addition, the informed patient is in a position to notify the prescriber at the first sign that an infection is developing, thereby allowing rapid treatment. In contrast, the patient who has not received adequate education is at increased risk of illness or death from an infectious disease.
- Some side effects, although benign, can be disturbing if they occur without warning. For example, rifampin (a drug for tuberculosis) imparts a harmless red-orange color to urine, sweat, saliva, and tears. Your patient will appreciate knowing about this in advance.

Minimizing Adverse Interactions

Patient education can help avoid hazardous drug-drug and drug-food interactions. For example, phenelzine (an antidepressant) can cause dangerous elevations in blood pressure if taken in combination with certain drugs (eg, amphetamines) or certain foods (eg, figs, avocados, most cheeses). Accordingly, it is essential that patients taking phenelzine be given explicit and emphatic instruction regarding the drugs and foods they must avoid.

APPLICATION OF THE NURSING PROCESS IN DRUG THERAPY

The nursing process is a conceptual framework that nurses employ to guide healthcare delivery. In this section we consider how the nursing process can be applied in drug therapy.

Review of the Nursing Process

Before discussing the nursing process as it applies to drug therapy, we need to review the process itself. Since you are probably familiar with the process already, this review is brief.

In its simplest form, the nursing process can be viewed as a cyclic procedure that has five basic steps: (1) assessment, (2) analysis (including nursing diagnoses), (3) planning, (4) implementation, and (5) evaluation.

Assessment. Assessment consists of collecting data about the patient. These data are used to identify actual and potential health problems. The database established during assessment provides a foundation for subsequent steps in the process. Important methods of data collection are the patient interview, medical and drug-use histories, the physical examination, observation of the patient, and laboratory tests.

Analysis: Nursing Diagnoses. In this step, the nurse analyzes the database to determine actual and potential health problems. These problems may be physiologic, psychologic, or sociologic. Each problem is stated in the form of a *nursing diagnosis*, which can be defined as an actual or potential health problem that nurses are qualified and licensed to treat.

A complete nursing diagnosis consists of two statements: (1) a statement of the patient's actual or potential health problem, followed by (2) a statement of the problem's probable cause or risk factors. Typically, the statements are separated by the phrase *related to*, as in this example of a drug-associated nursing diagnosis: "noncompliance with the prescribed regimen [the problem] related to inability to self-administer medication [the cause]."

Planning. In the planning step, the nurse delineates specific interventions directed at solving or preventing the problems identified in analysis. The plan must be individualized for each patient. When creating a care plan, the nurse must define goals, set priorities, identify nursing interventions, and establish criteria for evaluating success. In addition to nursing interventions, the plan should include interventions performed by other healthcare providers. Planning is an ongoing process that must be modified as new data are gathered.

Implementation (Intervention). Implementation begins with carrying out the interventions identified during planning. Some interventions are collaborative while others are independent. Collaborative interventions require a physician's order, whereas independent interventions do not. In addition to carrying out interventions, implementation involves coordinating actions of other members of the healthcare team. Implementation is completed by observing and documenting the outcomes of treatment. Documentation should be thorough and precise.

Evaluation. This step is performed to determine the degree to which treatment has succeeded. Evaluation is accomplished by analyzing the data collected during implementation. Evaluation should identify those interventions that should be continued, those that should be discontinued, and potential new interventions that might be implemented. Evaluation completes the initial cycle of the nursing process and provides the basis for beginning the cycle anew.

Applying the Nursing Process in Drug Therapy

Having reviewed the nursing process itself, we can now discuss the process as it pertains to drug therapy. Recall that the overall objective in drug therapy is to produce maximum benefit with minimum harm. To accomplish this, we must take into account the unique characteristics of each patient. That is, we must individualize therapy. The nursing process is well suited to this goal. As the discussion below indicates, in order to apply the nursing process in drug therapy, you must first have a solid knowledge of pharmacology. You will also see

that applying the nursing process to drug therapy is, in large part, an exercise in common sense.

Preadministration Assessment

Preadministration assessment establishes the baseline data needed to tailor drug therapy to the individual. By identifying the variables that can affect an individual's responses to drugs, we can adapt treatment so as to maximize benefits and minimize harm. Preadministration assessment has four basic goals:

- Collection of baseline data needed to evaluate therapeutic responses
- Collection of baseline data needed to evaluate adverse effects
- Identification of high-risk patients
- Assessment of the patient's capacity for self-care

The first three goals are specific to the particular drug being used. Accordingly, in order to achieve these goals, you must know the pharmacology of the drug under consideration. The fourth goal applies more or less equally to all drugs—although this goal may be more critical for some drugs than others.

Important methods of data collection include interviewing the patient and family, observing the patient, performing a physical examination, ordering laboratory tests, and taking the patient's medical and drug histories. The drug history should include prescription drugs, over-the-counter drugs, herbal remedies, and drugs taken for nonmedical purposes (alcohol, nicotine, caffeine, illicit drugs). Prior adverse drug reactions should be noted, including drug allergies and idiosyncratic reactions (ie, reactions unique to the individual).

Baseline Data Needed to Evaluate Therapeutic Effects. Drugs are administered to achieve a desired response. In order to know if we have produced that response, we need to establish baseline measurements of the parameter that therapy is directed at changing. For example, if we are giving a drug to lower blood pressure, we need to know what the patient's blood pressure was prior to treatment. Without this information, we have no basis for determining the effect of our drug. And if we can't determine whether or not a drug is working, there's little justification for giving it. From the above example, it should be obvious that, in order to know what baseline measurements to make, you must first know the reason for drug use. This knowledge comes from studying pharmacology.

Baseline Data Needed to Evaluate Adverse Effects. All drugs have the ability to produce undesired effects. In most cases, the adverse effects that a particular drug can produce are known. In many cases, development of an adverse effect will be completely obvious in the absence of any baseline data. For example, we don't need special baseline data to know that hair loss following cancer chemotherapy was caused by the drug. However, in other cases, baseline data are needed to determine whether or not an adverse effect has occurred. For example, some drugs can impair liver function. In order to know if a drug has compromised liver function, we need to know the state of liver function prior to drug use. Without this information, we can't tell from later measurements whether liver dysfunction was pre-existing or caused by the drug. Clearly, in cases like this, baseline data are needed. As noted earlier, knowing what data to collect comes directly from your knowledge of the drug under consideration.

Identification of High-Risk Patients. Because of his or her individual characteristics, a particular patient may be at high risk of experiencing an adverse response to a particular drug. Just which individual characteristics will predispose a patient to an adverse reaction depends on the drug under consideration. For example, if a drug is eliminated from the body primarily by renal excretion, an individual with impaired kidney function will be at risk of having this drug accumulate to a toxic level. Similarly, if a drug is eliminated by the liver, an individual with impaired liver function will be at risk of having that drug accumulate to a toxic level. The message here is that, in order to identify the patient at risk, you must know the pharmacology of the drug to be administered.

Multiple factors can increase the patient's risk of adverse reactions to a particular drug. Impaired liver and kidney function were just mentioned. Other factors include age, body composition, pregnancy, diet, genetic heritage, other drugs being used, and practically any pathophysiologic condition. These factors are discussed at length in Chapter 6 (Drug Interactions), Chapter 7 (Adverse Drug Reactions and Medication Errors), Chapter 8 (Individual Variation in Drug Responses), Chapter 9 (Drug Therapy During Pregnancy and Breast-Feeding), Chapter 10 (Drug Therapy in Pediatric Patients), and Chapter 11 (Drug Therapy in Geriatric Patients).

When identifying factors that put the patient at risk, you should distinguish between factors that put the patient at extremely high risk versus factors that put the patient at moderate or low risk. The terms *contraindication* and *precaution* can be used for this distinction. A *contraindication* is defined as a pre-existing condition that precludes use of a particular drug under all but the most desperate circumstances. For example, a previous severe allergic reaction to penicillin (which can be life threatening) would be a contraindication to using penicillin again—unless the patient has a life-threatening infection that cannot be controlled with another antibiotic. A *precaution*, by contrast, can be defined as a pre-existing condition that significantly increases the risk of an adverse reaction to a particular drug, but not to a degree that is life threatening. For example, a previous mild allergic reaction to penicillin would constitute a precaution to using this drug again. That is, the drug may be used, but greater than normal caution must be exercised. Preferably, an alternative drug would be selected.

Assessment of the Patient's Capacity for Self-Care. If drug therapy is to succeed, the outpatient must be willing and able to self-administer medication as prescribed. Accordingly, his or her capacity for self-care must be determined. If assessment reveals that the patient is incapable of self-medication, alternative care must be arranged.

Multiple factors can affect the capacity for self-care and the probability of adhering to the prescribed regimen. Patients with reduced visual acuity or limited manual dexterity may be unable to self-medicate, especially if the technique for administration is complex. Patients with limited intellectual ability may be incapable of understanding or remembering what they are supposed to do. Patients with severe mental illness (eg, depression, schizophrenia) may lack the understanding or motivation needed to self-medicate. Some patients may lack the money to pay for drugs. Others may fail to take medications as prescribed because of individual or cultural attitudes toward drugs. Among geriatric patients, a common cause for failed self-medication is a conviction that the drug was simply

TABLE 2-1 • Examples of Nursing Diagnoses That Can Be Derived from Knowledge of Adverse Drug Effects

Drug	Adverse Effect	Related Nursing Diagnosis
Amphetamines	CNS stimulation	Disturbed sleep pattern related to drug-induced CNS excitation
Aspirin	Gastric erosion	Pain related to aspirin-induced gastric erosion
Atropine	Urinary retention	Urinary retention related to drug therapy
Bethanechol	Stimulation of GI smooth muscle	Bowel incontinence related to drug-induced increase in bowel motility
Clonidine	Impotence	Sexual dysfunction related to drug-induced impotence
Cyclophosphamide	Reduction in white blood cell counts	Risk for infection related to drug-induced neutropenia
Digoxin	Dysrhythmias	Ineffective tissue perfusion related to drug-induced cardiac dysrhythmias
Furosemide	Excessive urine production	Deficient fluid volume related to drug-induced diuresis
Gentamicin	Damage to the eighth cranial nerve	Disturbed sensory perception: hearing impairment related to drug therapy
Glucocorticoids	Thinning of the skin	Impaired skin integrity related to drug therapy
Haloperidol	Involuntary movements	Low self-esteem related to drug-induced involuntary movements
Nitroglycerin	Hypotension	Risk for injury related to dizziness caused by drug-induced hypotension
Propranolol	Bradycardia	Decreased cardiac output related to drug-induced bradycardia
Warfarin	Spontaneous bleeding	Risk for injury related to drug-induced bleeding

CNS = central nervous system, GI = gastrointestinal.

not needed in the dosage prescribed. A thorough assessment will identify all of these factors, thereby enabling you to account for them when formulating nursing diagnoses and the patient care plan.

Analysis and Nursing Diagnoses

With respect to drug therapy, the analysis phase of the nursing process has three objectives. First, you must judge the appropriateness of the prescribed regimen. Second, you must identify potential health problems that the drug might cause. Third, you must determine the patient's capacity for self-care.

As the last link in the patient's chain of defense against inappropriate drug therapy, you must analyze the data collected during assessment to determine if the proposed treatment has a reasonable likelihood of being effective and safe. This judgment is made by considering the medical diagnosis, the known actions of the prescribed drug, the patient's prior responses to the drug, and the presence of contraindications to the drug. You should question the drug's appropriateness if (1) the drug has no actions that are known to benefit individuals with the patient's medical diagnosis, (2) the patient failed to respond to the drug in the past, (3) the patient had a serious adverse reaction to the drug in the past, or (4) the patient has a condition or is using a drug that contraindicates the prescribed drug. If any of these conditions apply, you should consult with the prescriber to determine if the drug should be given.

Analysis must identify potential adverse effects and drug interactions. This is accomplished by integrating knowledge of the drug under consideration and the data collected during assessment. Knowledge of the drug itself will indicate adverse effects that practically all patients are likely to experience. Data on the individual patient will indicate additional adverse effects and interactions to which the particular patient is predisposed. Once potential adverse effects and interactions have been identified, pertinent nursing diagnoses can be easily formulated. For example, if treatment is likely to cause respi-

ratory depression, an appropriate nursing diagnosis would be "impaired gas exchange related to drug therapy." Table 2-1 presents additional examples of nursing diagnoses that can be readily derived from your knowledge of adverse effects and interactions that treatment may cause.

Analysis must characterize the patient's capacity for self-care. The analysis should indicate potential impediments to self-care (eg, visual impairment, reduced manual dexterity, impaired cognitive function, insufficient understanding of the prescribed regimen) so that these factors can be addressed in the care plan. To varying degrees, nearly all patients will be unfamiliar with self-medication and the drug regimen. Accordingly, a nursing diagnosis applicable to almost every patient is "deficient knowledge related to the drug regimen."

Planning

Planning consists of defining goals, establishing priorities, identifying specific interventions, and establishing criteria for evaluating success. Good planning will allow you to promote beneficial drug effects. Of equal or greater importance, good planning will allow you to anticipate adverse effects—rather than react to them after the fact.

Defining Goals. In all cases, the goal of drug therapy is to produce maximum benefit with minimum harm. That is, we want to employ drugs in such a way as to maximize therapeutic responses while preventing or minimizing adverse reactions and interactions. The objective of planning is to formulate ways to achieve this goal.

Setting Priorities. This requires knowledge of the drug under consideration and the patient's unique characteristics—and even then, setting priorities can be difficult. Highest priority is given to life-threatening conditions (eg, anaphylactic shock, ventricular fibrillation). These may be drug induced or the result of disease. High priority is also given to reactions that cause severe, acute discomfort and to reactions that can result in long-term harm. Since we cannot manage all prob-

lems simultaneously, less severe problems must wait until the patient and care provider have the time and resources to address them.

Identifying Interventions. The heart of planning is identification of nursing interventions. These interventions can be divided into four major groups: (1) drug administration, (2) interventions to enhance therapeutic effects, (3) interventions to minimize adverse effects and interactions, and (4) patient education (which encompasses information in the first three groups).

When planning drug administration, you must consider dosage size and route of administration as well as less obvious factors, including timing of administration with respect to meals and with respect to administration of other drugs. Timing with respect to side effects is also important. For example, if a drug causes sedation, it may be desirable to give the drug at bedtime, rather than in the morning or during the day.

Nondrug measures can help promote therapeutic effects and should be included in the plan. For example, drug therapy of hypertension can be combined with weight loss (in overweight patients), salt restriction, and smoking cessation.

Interventions to prevent or minimize adverse effects are of obvious importance. When planning these interventions, you should distinguish between reactions that develop quickly and reactions that are delayed. A few drugs can cause severe adverse reactions (eg, anaphylactic shock) shortly after administration. When planning to administer such a drug, you should ensure that facilities for managing possible reactions are immediately available. Delayed reactions can often be minimized, if not avoided entirely. The plan should include interventions to do so.

Well-planned patient education is central to success. The plan should account for the patient's capacity to learn, and it should address the following: technique of administration, dosage size and timing, duration of treatment, method of drug storage, measures to promote therapeutic effects, and measures to minimize adverse effects. Patient education is discussed at length above.

Establishing Criteria for Evaluation. The need for objective criteria by which to measure desired drug responses is obvious: Without such criteria we could not determine if our drug was doing anything useful. As a result, we would have no rational basis for making dosage adjustments or for deciding how long treatment should last. If the drug is to be used on an outpatient basis, follow-up visits for evaluation should be planned.

Implementation

Implementation of the care plan in drug therapy has four major components: (1) drug administration, (2) patient education, (3) interventions to promote therapeutic effects, and (4) interventions to minimize adverse effects. These critical nursing activities are discussed at length above.

Evaluation

Over the course of drug therapy, the patient must be evaluated for (1) therapeutic responses, (2) adverse drug reactions and interactions, (3) adherence to the prescribed regimen, and (4) satisfaction with treatment. How frequently evaluations are performed depends on the expected time course of therapeutic and adverse effects. Like assessment, evaluation is

based on laboratory tests, observation of the patient, physical examination, and patient interviews. The conclusions drawn during evaluation provide the basis for modifying nursing interventions and the drug regimen.

Therapeutic responses are evaluated by comparing the patient's current status with the baseline data. In order to evaluate treatment, you must know the reason for drug use, the criteria for success (as defined during planning), and the expected time course of responses (some drugs act within minutes, whereas others may take weeks to produce beneficial effects).

The need to anticipate and evaluate adverse effects is self-evident. To make these evaluations, you must know which adverse effects are likely to occur, how they manifest, and their probable time course. The method of monitoring is determined by the expected effect. For example, if hypotension is expected, blood pressure is monitored; if constipation is expected, bowel function is monitored; and so on. Since some adverse effects can be fatal in the absence of timely detection, it is impossible to overemphasize the importance of monitoring and being prepared for rapid intervention.

Evaluation of adherence is desirable in all patients—and is especially valuable when therapeutic failure occurs or when adverse effects are unexpectedly severe. Methods of evaluating adherence include measurement of plasma drug levels, interviewing the patient, and counting pills. The evaluation should determine if the patient understands when to take medication, what dosage to take, and the technique of administration.

Patient satisfaction with drug therapy increases quality of life and promotes adherence. If the patient is dissatisfied, an otherwise effective regimen may not be taken as prescribed. Factors that can cause dissatisfaction include unacceptable side effects, inconvenient dosing schedule, difficulty of administration, and high cost. When evaluation reveals dissatisfaction, an attempt should be made to alter the regimen to make it more acceptable.

Use of a Modified Nursing Process Format to Summarize Nursing Implications in This Text

Throughout this text, nursing implications are *integrated into the body of each chapter*. The reason for integrating nursing information with basic science information is to reinforce the relationship between pharmacologic knowledge and nursing practice. In addition to being integrated, nursing implications are *summarized at the end of most chapters*. The purpose of the summaries is to provide a concise and readily accessible reference on patient care and patient education related to specific drugs and drug families.

The format employed for summarizing nursing implications reflects the nursing process (Table 2-2). However, as you can see, I have modified the headings somewhat. This was done to accommodate the needs of pharmacology instruction and to keep the summaries concise. The components of the format are discussed below.

Preadministration Assessment. This section summarizes the information you should have before giving a drug. Each section begins by stating the reason for drug use. This is followed by a summary of the baseline data needed to evalu-

TABLE 2-2 • Modified Nursing Process Format Used for Summarizing Nursing Implications in This Text

Preadministration Assessment
Therapeutic Goal
Baseline Data
Identifying High-Risk Patients
Implementation: Administration
Routes
Administration
Implementation: Measures to Enhance Therapeutic Effects
Ongoing Evaluation and Interventions
Summary of Monitoring
Evaluating Therapeutic Effects
Minimizing Adverse Effects
Minimizing Adverse Interactions
Managing Toxicity

ate therapeutic and adverse effects. After this, contraindications and precautions are summarized, under the heading *Identifying High-Risk Patients*.

Implementation: Administration. This section summarizes routes of administration, guidelines for dosage adjustment, and special considerations in administration, such as timing with respect to meals, preparation of intravenous solutions, and unusual techniques of administration.

Implementation: Measures to Enhance Therapeutic Effects. This section addresses issues such as diet modification, measures to increase comfort, and ways to promote adherence to the prescribed regimen.

Ongoing Evaluation and Interventions. This section summarizes nursing implications that relate to drug responses, both therapeutic and undesired. As indicated in Table 2-2, the section has five subsections: (1) summary of monitoring, (2) evaluating therapeutic effects, (3) minimizing adverse effects, (4) minimizing adverse interactions, and (5) managing toxicity. The monitoring section summarizes the physiologic and psychologic parameters that must be monitored in order to evaluate therapeutic and adverse responses. The section on therapeutic effects summarizes criteria and procedures for evaluating therapeutic responses. The section on adverse effects summarizes the major adverse reactions that should be monitored for and presents interventions to minimize harm. The section on adverse interactions summarizes the major drug interactions to be alert for and gives interventions to minimize them. The section on toxicity describes major symptoms of toxicity and treatment.

Patient Education. This topic does not have a section of its own. Rather, patient education is integrated into the other sections. That is, as we summarize the nursing implications that relate to a particular topic, such as drug administration or

a specific adverse effect, patient education related to that topic is discussed concurrently. This integration is done to promote clarity and efficiency of communication. In order to make this important information stand out, it appears in **colored type**.

What About Diagnosis and Planning? These headings are not used in the summaries. There are several reasons for the omission, the dominant one being efficiency of communication.

Nursing diagnoses have been left out because they are extremely numerous and largely self-evident. Yes, I could have included a list of diagnoses for each drug. However, since nursing diagnoses derive from drug effects, and since all drugs cause many effects (primarily adverse), the list of diagnoses for each drug would be very long. Accordingly, since nursing diagnoses can be readily formulated from one's knowledge of pharmacology, and since a long list of diagnoses would dilute the impact of other important information, I decided to omit nursing diagnoses from the summaries.

Planning has not been used as a heading for three reasons. First, planning applies primarily to the overall management of the disorder for which a particular drug is being used—and much less to the drug itself. Second, because planning is discussed at length and more appropriately in nonpharmacology nursing texts, such as those on medical-surgical nursing, there is no need to repeat this information here. Third, most planning is done with the aid of standardized nursing care plans—either computerized or in print format. These standardized plans are sufficient for most drug-related planning. Please note, however, that although we don't have a separate heading for planning, critical issues in planning are nonetheless included.

SUMMARY

We began this chapter by asking, "Why should a nursing student learn pharmacology?" To answer the question, we explored the applications of pharmacology in nursing practice. We observed that nursing responsibilities regarding drugs go far beyond the Six Rights of Drug Administration. We observed also that the nurse has a critical role as patient advocate, serving as the patient's last line of defense against medication errors. We then discussed multiple ways in which pharmacologic knowledge can be put to practical use in patient care and patient education. We saw that, by applying knowledge of pharmacology, you can have a positive influence on virtually all aspects of drug therapy, thereby helping to maximize benefits and minimize harm. Hopefully, your appreciation of the importance of pharmacology in nursing practice, coupled with your desire to provide optimal care, will provide the motivation you will need to develop an in-depth understanding of drugs.

KEY POINTS

- Nursing responsibilities with regard to drugs extend far beyond the Six Rights of Drug Administration.
- You are the patient's last line of defense against medication errors.
- Your knowledge of pharmacology has a wide variety of practical applications in patient care and patient education.
- By applying your knowledge of pharmacology, you will make a large contribution to achieving the therapeutic objective of maximum benefit with minimum harm.
- Application of the nursing process in drug therapy is directed at individualizing treatment, which is critical to achieving the therapeutic objective.
- The goal of preadministration assessment is to gather data needed for (1) evaluation of therapeutic and adverse effects, (2) identification of high-risk patients, and (3) assessment of the patient's capacity for self-care.
- The analysis and diagnosis phase of treatment is directed at (1) judging the appropriateness of the prescribed therapy, (2) identifying potential health problems treatment might cause, and (3) characterizing the patient's capacity for self-care.
- Planning is directed at (1) defining goals, (2) establishing priorities, and (3) establishing criteria for evaluating success.
- In the evaluation stage, the objective is to evaluate (1) therapeutic responses, (2) adverse reactions and interactions, (3) patient adherence, and (4) patient satisfaction with treatment.

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Drug Regulation, Development, Names, and Information

Landmark Drug Legislation

New Drug Development

The Randomized Controlled Trial

Stages of New Drug Development

Limitations of the Testing Procedure

Exercising Discretion Regarding New Drugs

Drug Names

The Three Types of Drug Names

Which Name to Use, Generic or Trade?

Over-the-Counter Drugs

Sources of Drug Information

People

Published Information

In this chapter we complete our introduction to pharmacology by considering five diverse but important topics. These are (1) drug regulation, (2) new drug development, (3) the annoying problem of drug names, (4) over-the-counter drugs, and (5) sources of drug information.

LANDMARK DRUG LEGISLATION

The history of drug legislation in the United States reflects an evolution in our national posture toward regulating the pharmaceutical industry. That posture has changed from one of minimal control to one of extensive control. For the most part, increased regulation has been beneficial, resulting in safer and more effective drugs.

The first American law to regulate drugs was the *Federal Pure Food and Drug Act* of 1906. This law was very weak: It required only that drugs be *free of adulterants*. The law said nothing about safety or effectiveness.

The *Food, Drug and Cosmetic Act*, passed in 1938, was much stronger than the Pure Food and Drug Act, and was the first legislation to address drug safety. The motivation behind the 1938 law was a tragedy in which more than 100 people died following use of a new medication. The lethal preparation contained an antibiotic (sulfanilamide) plus a solubilizing agent (diethylene glycol). Tests showed that the solvent was the cause of death. (Diethylene glycol is commonly used as automotive antifreeze.) To reduce the chances of another such tragedy, Congress required that all new drugs undergo testing for toxicity. The results of these tests were to be reviewed by the *Food and Drug Administration*

(FDA), and only those drugs judged safe would receive FDA approval for marketing.

In 1962, Congress passed the *Harris-Kefauver Amendments* to the Food, Drug and Cosmetic Act. This law was created in response to the thalidomide tragedy that occurred in Europe in the early 1960s. Thalidomide is a sedative now known to cause birth defects and fetal death. Because the drug was used widely by pregnant women, thousands of infants were born with phocomelia, a rare birth defect characterized by the gross malformation or complete absence of arms or legs. This tragedy was especially poignant in that it resulted from nonessential drug use: The women who took thalidomide could have done very well without it. Thalidomide was not a problem in the United States because the drug never received approval by the FDA (see Chapter 107, Box 107-1).

Because of the European experience with thalidomide, the Harris-Kefauver Amendments sought to strengthen all aspects of drug regulation. A major provision of the bill required that drugs be proved *effective* before marketing. Remarkably, this was the first law to demand that drugs actually offer some benefit. The new act also required that all drugs that had been introduced between 1932 and 1962 undergo testing for effectiveness; any drug that failed to prove useful would be withdrawn. Lastly, the Harris-Kefauver Amendments established rigorous procedures for testing new drugs. These procedures are discussed below under *New Drug Development*.

In 1970, Congress passed the *Controlled Substances Act* (Title II of the Comprehensive Drug Abuse Prevention and Control Act). This legislation set rules for the manufacture and distribution of drugs considered to have the potential for abuse. One provision of the law defines five categories of controlled substances, referred to as Schedules I, II, III, IV, and V. Drugs in Schedule I have no accepted medical use in the United States and are deemed to have a high potential for abuse. Examples include heroin, mescaline, and lysergic acid diethylamide (LSD). Drugs in Schedules II through V have accepted medical applications but also have the potential for abuse. The abuse potential of these agents becomes progressively less as we proceed from Schedule II to Schedule V. The Controlled Substances Act is discussed further in Chapter 37 (Drug Abuse: Basic Considerations).

In 1992, FDA regulations were changed to permit *accelerated approval* of drugs for acquired immunodeficiency syndrome (AIDS) and cancer. Under these guidelines, a drug could be approved for marketing prior to completion of Phase III trials (see below), provided that rigorous follow-up studies (Phase IV trials) were performed. The rationale for this change was that (1) medications are needed, even if their ben-

efits may be marginal, and (2) the unknown risks associated with early approval are balanced by the need for more effective drugs. Although accelerated approval seems like a good idea, in actual practice, it has two significant drawbacks. First, manufacturers often fail to conduct or complete the required follow-up studies. Second, if the follow-up studies—which are more rigorous than the original—fail to confirm a clinical benefit, the guidelines have no clear mechanism for removing the drug from the market.

The *Prescription Drug User Fee Act* (PDUFA), passed in 1992, was a response to complaints that the FDA takes too long to review applications for new drugs. Under the Act, drug sponsors pay the FDA fees (about \$500,000 per drug) that are used to fund additional reviewers. In return, the FDA must adhere to strict review timetables. Because of the PDUFA, new drugs now reach the market much sooner than in the past.

The *Food and Drug Administration Modernization Act* (FDAMA) of 1997—an extension of the Prescription Drug User Fee Act—called for widespread changes in FDA regulations. Implementation is in progress. For health professionals, four provisions of the act are of particular interest:

- The fast-track system created for AIDS drugs and cancer drugs now includes drugs for other serious and life-threatening illnesses.
- Manufacturers who plan to stop making a drug must inform patients at least 6 months in advance, thereby giving them time to find another source.
- A clinical trial database will be established for drugs directed at serious or life-threatening illnesses. These data will allow clinicians and patients to make informed decisions about using experimental drugs.
- Drug companies can now give prescribers journal articles and certain other information regarding “off-label” uses of drugs. (An “off-label” use is a use that has not been evaluated by the FDA.) Prior to the new act, clinicians were allowed to prescribe a drug for an off-label use, but the manufacturer was not allowed to promote the drug for that use—even if promotion was limited to providing potentially helpful information, including reprints of journal articles. In return for being allowed to give prescribers information regarding off-label uses, manufacturers must promise to do research to support the claims made in the articles.

Two laws—the *Best Pharmaceuticals for Children Act* (BPCA), passed in 2002, and the *Pediatric Research Equity Act* (PREA) of 2003—were designed to promote much-needed research on drug efficacy and safety in children. The BPCA offers a 6-month patent extension to manufacturers who evaluate a drug already on the market for its safety, efficacy, and dosage in children. The PREA gives the FDA the power, for the first time, to require drug companies to conduct pediatric clinical trials on new medications that might be used by children. (In the past, drugs were not tested in children. Hence, there is a general lack of reliable information upon which to base therapeutic decisions.)

In 2007, Congress passed the *FDA Amendments Act* (FDAAA), the most important legislation on drug safety since the Harris-Kefauver Amendments of 1962. The FDAAA expands the mission of the FDA to include rigorous oversight of drug safety *after* a drug has been approved. (Prior to this act, the FDA focused on drug efficacy and safety *prior* to ap-

proval, but had limited resources and authority to address drug safety after a drug was released for marketing.) Under the new law, the FDA has the legal authority to require post-marketing safety studies, to order changes in a drug’s label to include new safety information, and to restrict distribution of a drug based on safety concerns. In addition, the FDA is required to establish an active postmarketing risk surveillance system, mandated to include 25 million patients by July 2010, and 100 million by July 2012. Because of the FDAAA, adverse effects that were not discovered prior to drug approval will come to light much sooner than in the past, and the FDA now has the authority to take action (eg, limit distribution of a drug) if postmarketing information shows a drug to be less safe than previously understood.

In 2009, Congress passed the *Family Smoking Prevention and Tobacco Control Act*, which, at long last, allows the FDA to regulate cigarettes, the single most dangerous product available to U.S. consumers. Under the Act, the FDA can now strengthen advertising restrictions, including a prohibition on marketing to youth; require revised and more prominent warning labels; require disclosure of all ingredients in tobacco products and restrict harmful additives; and monitor nicotine yields and mandate gradual reduction of nicotine to nonaddictive levels.

NEW DRUG DEVELOPMENT

The development and testing of new drugs is an expensive and lengthy process, requiring 6 to 12 years for completion. Of the thousands of compounds that undergo testing, only a few enter clinical trials, and of these, only 1 in 5 gains approval. Because of this high failure rate, the cost of developing a new drug can exceed \$1 billion.

Rigorous procedures for testing have been established so that newly released drugs might be both safe and effective. Unfortunately, although testing can determine effectiveness, it cannot guarantee that a new drug will be safe: Significant adverse effects may evade detection during testing, only to become apparent after a new drug has been released for general use.

The Randomized Controlled Trial

Randomized controlled trials (RCTs) are the most reliable way to objectively assess drug therapies. Accordingly, RCTs are used to evaluate all new drugs. RCTs have three distinguishing features: use of controls, randomization, and blinding. All three serve to minimize the influence of personal bias on the results.

Use of Controls. When a new drug is under development, we want to know how it compares with a standard drug used for the same disorder, or perhaps how it compares with no treatment at all. In order to make these comparisons, some subjects in the RCT are given the new drug and some are given either (1) a standard treatment or (2) a placebo (ie, an inactive compound formulated to look like the experimental drug). Subjects receiving either the standard drug or the placebo are referred to as *controls*. Controls are important because they help us determine if the new treatment is more (or less) effective than standard treatments, or at least if the new treatment is better (or worse) than no treatment at all. Like-

wise, controls allow us to compare the safety of the new drug with that of the old drug, a placebo, or both.

Randomization. In an RCT, subjects are randomly assigned to either the control group or the experimental group (ie, the group receiving the new drug). The purpose of randomization is to prevent allocation bias, which results when subjects in the experimental group are different from those in the control group. For example, in the absence of randomization, researchers could load the experimental group with patients who have mild disease and load the control group with patients who have severe disease. In this case, any differences in outcome may well be due to the severity of the disease rather than differences in treatment. And even if researchers try to avoid bias by purposely assigning subjects who appear similar to both groups, allocation bias can result from *unknown* factors that can influence outcome. By assigning subjects randomly to the control and experimental groups, all factors—known and unknown, important and unimportant—should be equally represented in both groups. As a result, the influences of these factors on outcome should tend to cancel each other out, leaving differences in the treatments as the best explanation for any differences in outcome.

Blinding. A blinded study is one in which the people involved do not know to which group—control or experimental—individual subjects have been randomized. If only the subjects have been “blinded,” the trial is referred to as *single blind*. If the researchers as well as the subjects are kept in the dark, the trial is referred to as *double blind*. Of the two, double-blind trials are more objective. Blinding is accomplished by administering the experimental drug and the control compound (either placebo or comparison drug) in identical formulations (eg, green capsules, purple pills) that bear a numeric code. At the end of the study, the code is accessed to reveal which subjects were controls and which received the experimental drug. When subjects and researchers are not blinded, their preconceptions about the benefits and risks of the new drug can readily bias the results. Hence, blinding is done to minimize the impact of personal bias.

Stages of New Drug Development

The testing of new drugs has two principal steps: *preclinical testing* and *clinical testing*. Preclinical tests are performed in animals. Clinical tests are done in humans. The steps in drug development are outlined in Table 3-1.

Preclinical Testing

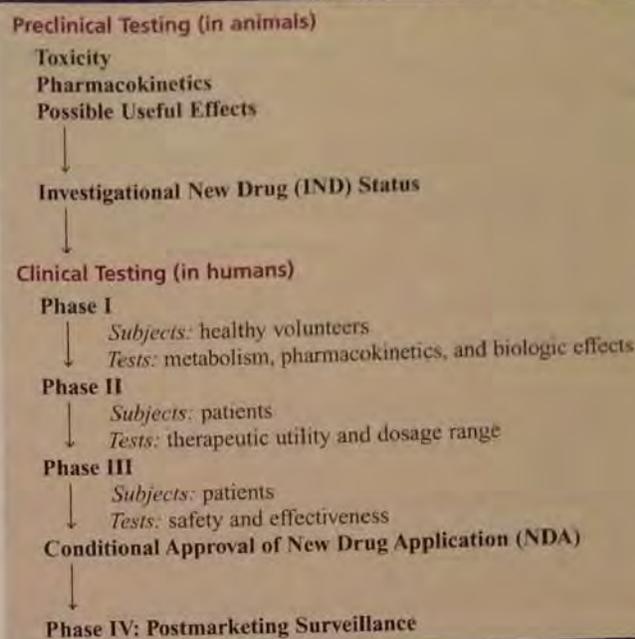
Preclinical testing is required before a new drug may be tested in humans. During preclinical testing, drugs are evaluated for *toxicities*, *pharmacokinetic properties*, and *potentially useful biologic effects*. Preclinical tests may take 1 to 5 years. When sufficient preclinical data have been gathered, the drug developer may apply to the FDA for permission to begin testing in humans. If the application is approved, the drug is awarded *Investigational New Drug* status and clinical trials may begin.

Clinical Testing

Clinical trials occur in four phases and may take 2 to 10 years to complete. The first three phases are done before a new drug is marketed. The fourth is done after marketing has begun.

Phase I. Phase I trials are usually conducted in *healthy volunteers*. However, if a drug is likely to have severe side

TABLE 3-1 • Steps in New Drug Development



effects, as many anticancer drugs do, the trial is done in volunteer patients who have the disease under consideration. Phase I testing has three goals: evaluating drug metabolism, pharmacokinetics, and biologic effects.

Phases II and III. In these trials, drugs are tested in *patients*. The objective is to determine therapeutic effects, dosage range, safety, and effectiveness. During Phase II and Phase III trials, only 500 to 5000 patients receive the drug, and only a few hundred take it for more than 3 to 6 months. Upon completing Phase III, the drug manufacturer applies to the FDA for conditional approval of a *New Drug Application*. If conditional approval is granted, Phase IV may begin.

Phase IV: Postmarketing Surveillance. In Phase IV, the new drug is released for general use, permitting observation of its effects in a large population. Thanks to the FDAAA of 2007, postmarketing surveillance is now much more effective than in the past.

Limitations of the Testing Procedure

It is important for nurses and other healthcare professionals to appreciate the limitations of the drug development process. Two problems are of particular concern. First, until recently, information on drug use in women and children has been limited. Second, new drugs are likely to have adverse effects that were not detected during clinical trials.

Limited Information in Women and Children

Women. Until recently, very little drug testing was done in women. In almost all cases, women of child-bearing age were excluded from early clinical trials. The reason? Concern for fetal safety. Unfortunately, FDA policy took this concern to an extreme, effectively barring *all* women of child-bearing age from Phase I and Phase II trials—even if the women were

TABLE 3-2 • Some New Drugs That Were Withdrawn from the U.S. Market for Safety Reasons

Drug	Indication	Year Introduced/ Year Withdrawn	Months on the Market	Reason for Withdrawal
Rotigotine* [Neupro]	Parkinson's disease	2007/2008	10	Patch formulation delivered erratic dosages
Natalizumab† [Tysabri]	Multiple sclerosis	2004/2005	3	Progressive multifocal leukoencephalopathy
Rapacuronium [Raplon]	Neuromuscular blockade	1999/2001	19	Bronchospasm, unexplained fatalities
Alosetron† [Lotronex]	Irritable bowel syndrome	2000/2000	9	Ischemic colitis, severe constipation, deaths have occurred
Troglitazone [Rezulin]	Type 2 diabetes	1999/2000	12	Fatal liver failure
Grepafloxacin [Raxar]	Infection	1997/1999	19	Severe cardiovascular events, including seven deaths
Bromfenac [Duract]	Acute pain	1997/1998	11	Severe hepatic failure
Mibefradil [Posicor]	Hypertension, angina pectoris	1997/1998	11	Inhibits drug metabolism, causing toxic accumulation of many drugs
Dexfenfluramine [Redux]	Obesity	1996/1997	16	Valvular heart disease
Flosequinan [Manoplax]	Heart failure	1992/1993	4	Increased hospitalization; decreased survival
Temafloxacin [Omniflox]	Infection	1992/1992	4	Hypoglycemia; hemolytic anemia, often associated with renal failure, hepatotoxicity, and coagulopathy

*Note that rotigotine was withdrawn because the *formulation* was unsafe, not because the drug itself is inherently dangerous.

†Alosetron and natalizumab were returned to the market in 2002 and 2006, respectively. These two drugs and one other—tegaserod [Zelnorm]—are the only drugs the Food and Drug Administration has ever reapproved after withdrawing them for safety reasons. With all three drugs, risk management guidelines must be followed.

not pregnant and were using adequate birth control. The only women allowed to participate in early clinical trials were those with a life-threatening illness that might respond to the drug under study.

Because of limited drug testing in women, we don't know with precision how women will respond to drugs. We don't know if beneficial effects in women will be equivalent to those seen in men. Nor do we know if adverse effects will be equivalent to those in men. We don't know how timing of drug administration with respect to the menstrual cycle will affect beneficial and adverse responses. We don't know if drug disposition (absorption, distribution, metabolism, and excretion) will be the same in women as in men. Furthermore, of the drugs that might be used to treat a particular illness, we don't know if the drugs that are most effective in men will also be most effective in women. Lastly, we don't know about the safety of drug use during pregnancy.

During the 1990s, the FDA issued a series of guidelines mandating participation of women (and minorities) in trials of new drugs. In addition, the FDA revoked a 1977 guideline that barred women from most trials. Because of these changes, the proportion of women in trials of most new drugs now equals the proportion of women in the population. The data generated since the implementation of the new guidelines have been reassuring: Most gender-related effects have been limited to pharmacokinetics. More importantly, for most drugs, gender has shown little impact on efficacy, safety, or dosage. However, although the new guidelines are an important step forward, even with them, it will take a long time to close the gender gap in our knowledge of drugs.

Children. Until recently, children, like women, had been excluded from clinical trials. As a result, information on dosage, therapeutic responses, and adverse effects in children has been limited. As noted above, the FDA can now force drug companies to conduct clinical trials in children. However, it will still be a long time before we have the information needed to use drugs safely and effectively in young patients.

Failure to Detect All Adverse Effects

The testing procedure cannot detect all adverse effects before a new drug is released. There are three reasons why: (1) during clinical trials, a relatively small number of patients are given the drug; (2) because these patients are carefully selected, they do not represent the full spectrum of individuals who will eventually take the drug; and (3) patients in trials take the drug for a relatively short time. Because of these unavoidable limitations in the testing process, effects that occur infrequently, effects that take a long time to develop, and effects that occur only in certain types of patients can go undetected. Hence, despite our best efforts, when a new drug is released, it may well have adverse effects of which we are as yet unaware. In fact, about half of the drugs that reach the market have serious adverse effects that were not detected until after they were released for general use.

The hidden dangers in new drugs are illustrated by the data in Table 3-2. This table presents information on 11 drugs that were withdrawn from the U.S. market soon after receiving FDA approval. In all cases, the reason for withdrawal was a serious adverse effect that went undetected in clinical trials.

Admittedly, only a few hidden adverse effects are as severe as the ones in the table. Hence, most do not necessitate drug withdrawal. Nonetheless, the drugs in the table should serve as a strong warning about the unknown dangers that a new drug may harbor.

Because adverse effects may go undetected, when working with a new drug, you should be especially watchful for previously unreported drug reactions. If a patient taking a new drug begins to show unusual symptoms, it is prudent to suspect that the new drug may be the cause—even though the symptoms are not yet mentioned in the literature.

Exercising Discretion Regarding New Drugs

When thinking about prescribing a new drug, clinicians would do well to follow this guideline: *Be neither the first to adopt the new nor the last to abandon the old.* Recall that the therapeutic objective is to produce maximum benefit with minimum harm. To achieve this objective, we must balance the potential benefits of a drug against its inherent risks. As a rule, new drugs have actions very similar to those of older agents. That is, it is rare for a new drug to be able to do something that an older drug can't do already. Consequently, the need to treat a particular disorder seldom constitutes a compelling reason to select a new drug over an agent that has been available for years. Furthermore, new drugs generally present greater risks than the old ones. As noted, at the time of its introduction, a new drug is likely to have adverse effects that have not yet been reported, and these effects may prove very bad for some patients. In contrast, older, more familiar drugs are less likely to cause unpleasant surprises. Consequently, when we weigh the benefits of a new drug against its risks, it is likely that the benefits will be insufficient to justify the risks—especially when an older drug, whose properties are well known, would probably provide adequate treatment. Accordingly, when it comes to the use of new drugs, it is usually better to adopt a wait-and-see policy, letting more adventurous prescribers discover the hidden dangers that a new drug may hold.

DRUG NAMES

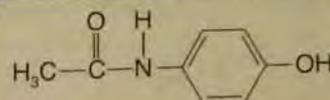
The topic of drug names is important and confusing. The topic is important because the names we employ affect our ability to communicate about medicines. The subject is confusing because we have evolved a system in which any drug can have a large number of names.

In approaching drug names, we begin by defining the types of names that drugs have. After that we consider (1) the complications that arise from assigning multiple names to a drug, and (2) the benefits of using just one name: the generic (nonproprietary) name.

The Three Types of Drug Names

Drugs have three types of names: (1) a chemical name, (2) a generic or nonproprietary name, and (3) a trade or proprietary name. Examples appear in Table 3-3. All of the names in the table are for the same drug, a compound most familiar to us under the trade name *Tylenol*.

TABLE 3-3 • The Three Types of Drug Names



Type of Drug Name	Examples
Chemical Name	<i>N</i> -acetyl- <i>para</i> -aminophenol
Generic Name (nonproprietary name)	Acetaminophen
Trade Name (proprietary name)	Acphen, Aminofen, Apap, Cetafen, Ed-Apap Children's, ElixSure Children's Fever Reducer, FeverAll, Genapap, Infantaire Drops, Mapap, Masophen, Nortemp Children's, Pain and Fever, Pain Reliever, Q-Pap, Quick Melts Children's Non-Aspirin, Silapap, Tylenol, Valorin

The chemical, generic, and trade names listed are all names for the drug whose structure is pictured in this table. This drug is most familiar to us as Tylenol, one of its trade names.

Chemical Name. The chemical name constitutes a description of a drug using the nomenclature of chemistry. As you can see from the example in Table 3-3, a drug's chemical name can be long and complex. Because of their complexity, chemical names are inappropriate for everyday use. For example, few people would communicate using the chemical term *N*-acetyl-*para*-aminophenol when a more simple generic name (*acetaminophen*) or trade name (eg, *Tylenol*) could be used.

Generic Name. The generic name of a drug is assigned by the United States Adopted Names Council. Each drug has only one generic name. The generic name is also known as the *nonproprietary* name or *United States Adopted Name*. Generic names are less complex than chemical names but typically more complex than trade names.

In many cases, the final syllables of the generic name indicate a drug's pharmacologic class. For example, the syllables *cillin* at the end of *amoxicillin* indicate that amoxicillin belongs to the penicillin class of antibiotics. Similarly, the syllables *statin* at the end of *lovastatin* indicate that lovastatin is an HMG-CoA reductase inhibitor, our most effective class of drugs for lowering cholesterol. Table 3-4 presents additional examples of generic names whose final syllables indicate the class to which the drug belongs.

For reasons presented below, generic names are preferable to trade names for general use.

Trade Name. Trade names, also known as *proprietary* or *brand* names, are the names under which a drug is marketed. These names are created by drug companies with the intention that they be easy for nurses, physicians, pharmacists, and consumers to recall and pronounce. Since any drug can be marketed in different formulations and by multiple companies, the number of trade names that a drug can have is large. By way of illustration, Table 3-3 gives 19 American trade

TABLE 3-4 • Generic Drug Names Whose Final Syllables Indicate Pharmacologic Class

Representative Drugs	Class-Indicating Final Syllable(s)	Pharmacologic Class	Therapeutic Use
Amoxicillin Ticarcillin	cillin	Penicillin antibiotic	Infection
Lovastatin Simvastatin	statin	HMG-CoA reductase inhibitor	High cholesterol
Propranolol Metoprolol	olol	Beta-adrenergic blocker	Hypertension, angina
Phenobarbital Secobarbital	barbital	Barbiturate	Epilepsy, anxiety
Benazepril Captopril	pril	Angiotensin-converting enzyme inhibitor	Hypertension, heart failure
Candesartan Valsartan	sartan	Angiotensin II receptor blocker	Hypertension, heart failure
Nifedipine Amlodipine	dipine	Dihydropyridine calcium channel blocker	Hypertension
Eletriptan Sumatriptan	triptan	Serotonin _{1B/1D} receptor agonist	Migraine
Dalteparin Enoxaparin	parin	Low-molecular-weight heparin	Anticoagulation
Sildenafil Tadalafil	afil	Phosphodiesterase type 5 inhibitor	Erectile dysfunction
Rosiglitazone Pioglitazone	glitazone	Thiazolidinedione	Type 2 diabetes
Omeprazole Pantoprazole	prazole	Proton pump inhibitor	Peptic ulcer disease
Alendronate Zoledronate	dronate	Bisphosphonate	Osteoporosis
Ciprofloxacin Norfloxacin	floxacin	Fluoroquinolone antibiotic	Infection

names, including Tylenol, that currently exist for the drug whose generic name is *acetaminophen*.

Trade names must be approved by the FDA. The review process tries to ensure that no two trade names are too similar. In addition, trade names are not supposed to imply unlikely efficacy—which may be why *Orlistat* (a diet pill) is named *Xenical*, rather than something more suggestive, like *Fat-B-Gone* or *PoundsOff*. However, despite the rule against suggestive names, some still slip by FDA scrutiny, like these two gems: *Flomax* (tamsulosin) and *Rapaflo* (silodosin). Can you guess what these drugs are used for? (Hint: It's an old guy malady.)

Which Name To Use, Generic or Trade?

We employ drug names in two ways: (1) for written and oral communication about medicines and (2) for labeling medication containers. In both cases, accurate communication is imperative. For communication to be accurate, when we read or hear a drug name, we must know what compound that name is referring to. We can't know what's in a pill if we don't know what the name on its bottle means. Likewise, we can't communicate orally about drugs if the names we employ go unrecognized. Clearly, if we are to communicate accurately, name recognition is essential. For reasons discussed below,

name recognition would be facilitated through universal use of generic names.

The Little Problems with Generic Names

In almost all cases, the generic name for a drug is more complicated than its trade name. This fact is illustrated in Table 3-5, which compares the generic and trade names for six common drugs. A simple analysis reveals that the average generic name in the table has 4.3 syllables. In contrast, the average trade name has only 2.3 syllables. That is, the generic names are nearly twice as long as the trade names.

Because generic names are more complex than trade names, generic names can be more difficult to remember and pronounce. As an exercise, try pronouncing the names in Table 3-5. While trade names like *Motrin* and *Prozac* roll off the tongue with ease, their generic counterparts—*ibuprofen* and *fluoxetine*—tend to tie the tongue in knots.

Why is it that generic names are more complicated than trade names? One reason is that the pharmaceutical industry has an important role in establishing generic names. When a pharmaceutical company has developed a new drug, that company submits a suggested generic name to the United States Adopted Names Council, the body responsible for assigning a drug its generic name. As a rule, the Council adopts the name the company suggests. Since, from a marketing

TABLE 3-5 • Generic Names and Trade Names of Some Common Drugs

Generic Name	Trade Name
Acetaminophen	Tylenol
Ciprofloxacin	Cipro
Fluoxetine	Prozac
Furosemide	Lasix
Ibuprofen	Motrin
Sildenafil	Viagra

perspective, it is to the company's advantage to have a product whose trade name is more easily recognized than its generic name, it seems unlikely that a company will suggest a simple, euphonious generic name. Also contributing to the complexity of generic names are the guidelines established by the Council for naming drugs.

The Big Problems with Trade Names

A Single Drug Can Have Multiple Trade Names. The principal objection to trade names is their vast number. Although a drug can have only one generic name, it can have unlimited trade names. As the number of trade names for a single drug expands, the burden of name recognition becomes progressively heavier. By way of illustration, the drug whose generic name is acetaminophen has at least 19 trade names (see Table 3-3). Although most clinicians will recognize this drug's generic name, few are familiar with all the trade names. As you can see, recalling a single generic name—even if it's complex—is still easier than recalling a host of trade names. Accordingly, if generic names were employed universally, accurate communication would be facilitated. Conversely, using multiple trade names does nothing but create confusion.

By clouding communication about drugs, use of trade names can result in "double medication"—with potentially disastrous results. Because patients frequently see more than one physician or nurse practitioner, a patient may receive prescriptions for the same drug by two (or more) prescribers. If those prescriptions are written for different brand names, then the two bottles the patient receives will be labeled with different names. Consequently, although both bottles contain the same drug, the patient may not know it. If both medications are taken as prescribed, excessive dosing will result. However, if generic names had been used, both labels would bear the same name, thereby informing the patient that both bottles contain the same drug. Given this information, the patient is likely to consult the prescribers to determine if both prescriptions should be honored.

Over-the-Counter (OTC) Products with the Same Trade Name May Have Different Active Ingredients. As indicated in Table 3-6, OTC products that have similar or identical trade names can actually contain different drugs. For example, although the two Lotrimin AF products have identical trade names, they actually contain two different drugs: miconazole and clotrimazole. Confusion would be avoided by labeling these products *miconazole spray* and *clotrimazole cream*, rather than labeling both Lotrimin AF.

The problem becomes even more complex for products that contain two or more drugs. When such combination prod-

TABLE 3-6 • Some OTC Products That Share the Same Trade Name

Product Name	Drugs in the Product
Lotrimin AF	Miconazole (spray)
Lotrimin AF	Clotrimazole (cream)
Excedrin Migraine	Acetaminophen + aspirin + caffeine
Excedrin P.M.	Acetaminophen + diphenhydramine
4-Way 12-Hour Nasal Spray	Oxymetazoline
4-Way Fast-Acting Nasal Spray	Phenylephrine
Kaopectate	Originally formulated as <i>kaolin + pectin</i> Reformulated to <i>attapulgit</i> in the late 1980s Reformulated to <i>bismuth subsalicylate</i> in 2003

ucts are referred to by trade name, the name is unlikely to indicate either the number of drugs present or their identity. Referring to the Excedrin products in Table 3-6, there is nothing about the trade name *Excedrin Migraine* to suggest that the product consists of three different drugs: acetaminophen, aspirin, and caffeine. Moreover, there is nothing in the trade names *Excedrin Migraine* and *Excedrin P.M.* to tell us that these two products have different compositions. By discarding the trade names and labeling one product *acetaminophen plus aspirin plus caffeine* and the other *acetaminophen plus diphenhydramine*, we could eliminate any confusion.

The two 4-Way products listed in Table 3-6 further illustrate the potential for confusion. If nothing else, the name *4-Way* suggests that the product contains more than one drug. In fact, the name seems to imply the presence of *four* drugs. However, this implication is not correct. Neither 4-Way preparation is composed of four drugs. Rather, they both contain only one drug. Furthermore, note that these similarly named products are, in fact, completely different; they have no ingredients in common. Hence, in the case of these 4-Way products, we can see that the trade name cannot be taken to mean either (1) the presence of four different drugs or (2) that these preparations that bear similar names have the same composition. Had generic names been employed to label these products, there could be no confusion about their makeup.

Perhaps the most disturbing aspect of trade names is illustrated by the reformulation of *Kaopectate*, a well-known anti-diarrheal product. In 2003, the manufacturer switched the active ingredient in *Kaopectate* from *attapulgit* (which had replaced kaolin and pectin in the late 1980s) to *bismuth subsalicylate*. However, although the active ingredient changed, the brand name did not. As a result, current bottles of *Kaopectate* contain a drug that is completely different from the one found in bottles of *Kaopectate* produced in 2002—posing a risk for patients who should not take salicylates, but may be unaware of their presence in the newer product. This example illustrates an important point: Manufacturers of OTC drugs can reformulate brand-name products whenever they want—without changing the name at all. Hence, there is no guarantee

TABLE 3-7 • Products from the United States and Canada That Have the Same Trade Name but Different Active Ingredients in Other Countries

Trade Name	Country	Active Drug	Indication
Norpramin	United States, Canada	Desipramine	Depression
	Spain	Omeprazole	Peptic ulcer disease
Flomax	United States, Canada	Tamsulosin	Enlarged prostate
	Italy	Morniflumate	Inflammation
Allegra	United States, Canada	Fexofenadine	Allergies
	Germany	Frovatriptan	Migraine
Mobic	United States, Canada	Meloxicam	Inflammation, pain
	India	Amoxicillin	Bacterial infection
Avastin	United States, Canada	Bevacizumab	Cancer, macular degeneration
	India	Atorvastatin	High cholesterol
Vantin	United States, Canada	Cefpodoxime	Bacterial infection
	Mexico	Naproxen	Inflammation, pain

that the brand-name product you buy today contains the same drug as the brand-name product you bought last week, last month, or last year.

In the spring of 1999, the FDA issued a ruling to help reduce the confusion created by OTC trade names. Under the ruling, generic names for the drugs in OTC products are now clearly and prominently listed on the label, using a standardized format.

Trade Names Can Endanger International Travelers.

For people who travel to other countries, trade names present two kinds of problems. First, the trade name used in one country may differ from the trade name used in another country. Hence, if you have a prescription for a trade-name product, a foreign pharmacist may not be able to identify the drug that you need. The second (and more disturbing) problem is this: Products with the *identical* trade name may have *different* active ingredients, depending on where you buy the drug (Table 3-7). As a result, when a prescription for a trade-name product is filled in another country, the patient may receive the wrong drug. For example, when visiting Mexico, Americans (or Canadians) with a prescription for *Vantin* will be given naproxen (an anti-inflammatory drug) rather than the cefpodoxime (an antibiotic) that they were expecting. Not only can this lead to unnecessary side effects (possible kidney damage and GI ulceration), but the target infection will continue unabated. Hence, the patient is exposed to all the risks of medication without getting any of the benefits. To ensure that travelers get the medicine they need, prescriptions should bear generic drug names, not trade names.

Trade Names Can Endanger International Book Sales.

Because of trade names, a pharmacology text written for nursing students in one country—the United States, for example—may lack acceptance by nursing schools in another country, like Canada, for example. Fortunately, the Canadian-American problem has a solution. His name is Dr. Shallen Letwin, Executive Director, Lower Mainland Pharmacy Services, British Columbia (Canada), and Clinical Assistant Professor, Faculty of Pharmaceutical Sciences, University of British Columbia. To promote international communication about drugs, as well as good will between our two great countries, Dr. Letwin has identified Canadian trade names for inclusion in this book.

Thank you, Shallen. Nonetheless, although we've managed to solve the problem, keep in mind that, were it not for the tyranny of trade names, Shallen would have been spared his arduous task, more Canadian students could have been enjoying this book, and agent Johnson (of the U.S. Internal Revenue Service) would have been happier, too, there being more money to pick from my pocket.

What If Peas Were Marketed Like Drugs?

Given the problems that trade names create, why do we use trade names at all? We use trade names because the pharmaceutical industry wants them. Why? Because trade names give this industry a unique and powerful tool for marketing. As we shall see, the extent to which trade names are exploited to promote drug sales is without parallel in the marketing of any other product.

To understand the immense marketing benefit that trade names have, let's consider the marketing of a product that is *not* a drug. Take peas, for example. All companies that sell peas use the same name—*peas*—to identify their product. When we buy peas, no matter whose, all pea packages say "PEAS" in big letters on the label. Pea packages even have a picture of peas to help us identify what's inside. Consequently, when we choose a package of peas, we know with certainty what we're buying.

When we want to compare different *brands* of peas, the task is easy. Company A's peas are easily distinguished from those of company B or company C by the presence of a company name and logo on the label. Consequently, thanks to the way peas are marketed, we have no trouble understanding just what we are buying and who made it. As a result, we can easily select the product we want from the manufacturer we like best.

Now let's consider what we could expect if peas were marketed like drugs. Under the new system, pea packages would have no pictures of peas. Nor would pea packages proclaim "PEAS" in big letters to help us identify their contents. Instead, pea packages would be emblazoned with trade names like *Végi-P* or *Producin* or *NuPod-500's*. If peas were marketed using trade names, when we went shopping for peas we'd be obliged to read a lot of fine print to find the product we wanted. And, once we finally did turn up a package with

peas in it—for example, the one labeled *NuPod-500's*—we'd probably buy *NuPod-500's* for life, it being too much trouble to figure out which of the other packages with meaningless names also contain peas. From the point of view of the people who sell *NuPod-500's*, this technique of marketing by trade names is a terrific arrangement. Consumers will be loyal to their product not because that product is better or cheaper than someone else's, but because product labeling with trade names makes it very difficult to identify the competition so that comparisons can be made. Fortunately, we don't allow this kind of marketing for peas. When we shop for peas, we demand that all pea packages bear the word *peas*—not *Vegi-P* or *NuPod-500's* or any other trade name. Why we permit medicines to be marketed in any less informative a manner is a disturbing question.

When we consider that drugs, unlike peas, cannot be identified by simple observation, the use of trade names for marketing becomes especially unsettling. With peas, once we open the package, we no longer need the label to identify the contents. We know what peas look like. Hence, even if peas were marketed like drugs, we would not be completely dependent upon labeling to identify the product. With drugs we have no options: Since we cannot identify a drug by looking at it, we cannot escape reliance on package labeling to inform us about the medicine inside. It is ironic that a product whose label is so essential for identification can be marketed under a system that employs multiple trade names, thereby making product identification needlessly and dangerously difficult.

Generic Products Versus Brand-Name Products

To complete our discussion of drug names, we need to address two questions: (1) Do significant differences exist between different brands of the same drug? and (2) If such differences do exist, do they justify the use of trade names? The answer to both questions is NO!

Are Generic Products and Brand-Name Products Therapeutically Equivalent? When a new drug comes to market, it is sold under a trade name by the company that developed it. When that company's patent expires, other companies can produce the drug and market it under its generic name. Our question, then, is, "Are the generic formulations equivalent to the brand-name formulation produced by the original manufacturer?"

Because all equivalent products—generic or brand name—contain the same dose of the same drug, the only real concern with generic formulations is their rate and extent of absorption. For a few drugs (eg, phenytoin, warfarin), a slight increase in absorption can result in toxicity, and a slight decrease can result in therapeutic failure. Hence, for these agents, a small difference in absorption can be important. In the past, there was concern that generic formulation of these drugs were not as safe or reliable as the brand-name formulation. However, there is no well-documented evidence to support this concern. Hence, it is reasonable to conclude that *all FDA-approved generic products are therapeutically equivalent to their brand-name counterparts*.^{*} A list of FDA-

approved generic equivalents is available online at www.fda.gov/cder/ob/default.htm.

Would a Difference Between Brand-Name and Generic Products Justify the Use of Trade Names? Even if generic formulations were significantly different from brand-name formulations, this would not justify using trade names to identify preferred products. If clinicians want to prescribe a drug made by a particular company, they needn't resort to trade names to do so; their preference can be indicated simply by including the manufacturer's name on the prescription. As with peas, if we prefer a particular brand (eg, BIRDS EYE), that's what we ask for. We haven't found it necessary to create a complicated system of alternative names for peas in order to distinguish one brand from another. On the contrary, common sense tells us that such a system of trade names would make it more difficult—not easier—for us to clearly communicate our needs. Perhaps some day we will market medicines with as much common sense as we use for vegetables.

Conclusion Regarding Generic Names and Trade Names

In the preceding discussion, we considered the advantages and disadvantages associated with trade names and generic names. We noted that, although generic names may be long, this disadvantage is more than offset by the fact that each drug has only one generic name. In contrast, the sole virtue of trade names—ease of recall and pronunciation—is far outweighed by the problems that stem from the existence of multiple trade names for a single drug. Multiple trade names can impede name recognition and can thereby promote medication errors and miscommunication about drugs. With generic names, the opposite is achieved: facilitation of communication and promotion of safe and effective drug use. Clearly, generic names are preferable to trade names. Accordingly, until such time as trade names are outlawed, the least we can do is actively discourage their use. In this text, generic names are employed for routine discussion. Although trade names are presented, they are not emphasized. We may eventually see the day when trade names are abandoned and generic names are employed universally. On that day, our ability to achieve the therapeutic objective will be greatly enhanced.

OVER-THE-COUNTER DRUGS

Over-the-counter drugs are defined as drugs that can be purchased without a prescription. These agents are used for a wide variety of complaints, including mild pain, motion sickness, allergies, colds, constipation, and heartburn. Whether a drug is available by prescription or over the counter is ultimately determined by the FDA.

OTC drugs are an important part of healthcare. When used properly, these agents can provide relief from many ailments while saving consumers the expense and inconvenience of visiting a prescriber. The following facts underscore how important the OTC market is:

- Americans spend about \$20 billion annually on OTC drugs.
- OTC drugs account for 60% of all doses administered.
- Forty percent of Americans take at least one OTC drug every 2 days.

^{*}There is one important exception to this statement: levothyroxine. As discussed in Chapter 58 (Drugs for Thyroid Disorders), the FDA maintains that certain generic formulations of levothyroxine are interchangeable with brand name formulations (Synthroid, Levoxyl, Unithroid). However, leading authorities strongly disagree.

- Four times as many illnesses are treated by a consumer using an OTC drug as by a consumer visiting a prescriber.
- With most illnesses (60% to 95%), initial therapy consists of self-care, including self-medication with an OTC drug.
- The average home medicine cabinet contains 24 OTC preparations.

Some drugs that were originally sold only by prescription are now sold over the counter. Since the 1970s, over 60 prescription drugs have been switched to OTC status. About 50 more are under FDA consideration for the change. Because of this process, more and more highly effective drugs are becoming directly available to consumers. Unfortunately, most consumers lack the knowledge needed to choose the most appropriate drug from among the steadily increasing options.

In 2006, the FDA began phasing in new labeling requirements for OTC drugs. The goal is to standardize labels and to make them more informative and easy to understand. The labels, titled *Drug Facts*, are to be written in plain language, have a user-friendly format, and use type that is big enough to read. Active ingredients will be listed first, followed by uses, warnings, directions, and inactive ingredients. This information is designed to help consumers select drugs that can provide the most benefit with the least risk.

In contrast to some texts, which present all OTC drugs in a single chapter, this text presents OTC drugs throughout. Why? Because this format allows discussion of OTC drugs in their proper pharmacologic and therapeutic contexts. I believe this makes more sense than lumping these drugs together solely because they can be purchased without a prescription.

SOURCES OF DRUG INFORMATION

There is much more to pharmacology than we can address in this text. When you need additional information, the sources discussed below should help.

People

Clinicians and Pharmacists. Nurses and other clinicians can be invaluable sources of information about medicines. Pharmacists know a great deal about drugs and are usually eager to share their insight.

Poison Control Centers. Poison control centers are located throughout the United States and Canada. These centers are accessible by telephone, permitting rapid access to information about poisoning with medicines and toxic compounds. In the United States, calling the national emergency hotline (1-800-222-1222) will connect you with the certified poison center nearest you. In Canada, each province has its own contact number.

Pharmaceutical Sales Representatives. Pharmaceutical sales representatives (drug representatives, detail persons) can be useful sources of drug information. These people know their own products very well, and they can provide detailed, authoritative information about them. Keep in mind, however, that the ultimate job of the drug representative is sales, not education. Because their objective is sales, drug representatives may fail to volunteer negative information about their product. Likewise, they are unlikely to point out superior qualities in a competing drug. (Is a Honda salesperson going

TABLE 3-8 ■ Some Important Drug References

General Information on Drug Actions, Pharmacokinetics, Therapeutics, Adverse Effects, and Drug Interactions

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th ed. (Brunton L, Chabner B, Knollman B, eds.). New York: McGraw-Hill, 2011.

Pharmacotherapy: A Pathophysiologic Approach, 8th ed. (DiPiro JT, et al., eds.). New York: McGraw-Hill, 2011.

Applied Therapeutics: The Clinical Use of Drugs, 9th ed. (Koda-Kimble MA, et al., eds.). Philadelphia: Lippincott Williams & Wilkins, 2009.

Detailed Information on Specific Drugs and Drug Families

AHFS Drug Information. (McEvoy GK, et al., eds.). Bethesda, MD: American Society of Hospital Pharmacists. [updated annually]

Drug Facts and Comparisons, Loose-leaf ed. St. Louis: Wolters Kluwer. [updated monthly]

Physicians' Desk Reference. Montvale, NJ: Medical Economics Data Production Co. [updated annually]

Very Current Information

The Medical Letter on Drugs and Therapeutics. New Rochelle, NY: The Medical Letter, Inc. [published bimonthly]

Prescriber's Letter. Stockton, CA: Therapeutic Research Center. [published monthly]

to extol the virtues of a Ford?) Such a lack of complete candor does not mean that drug representatives are unethical; they are simply doing their job. However, since full disclosure may be inconsistent with successful sales, the drug representative may not be your best source of information—especially if you are trying to establish an unbiased comparison between the representative's product and a drug from a competing manufacturer.

Published Information

The publications described below are general references. These works cover a broad range of topics but in limited depth. Accordingly, these references are most useful as initial sources of information. If more detail is needed, specialty publications should be consulted. Some important drug references, including the ones described below, are listed in Table 3-8.

Text-like Books

Goodman & Gilman's The Pharmacological Basis of Therapeutics is the classic text/reference on pharmacology used by generations of medical students and practicing physicians. As its name implies, this book focuses on the basic science information that underlies drug use—and not on therapeutics per se. New editions are released every 4 to 5 years.

Pharmacotherapy: A Pathophysiologic Approach is a comprehensive text on drug therapy. Each chapter focuses on the treatment of a specific disorder. To facilitate understanding of drug therapy, the book presents thorough reviews of pathophysiology.

Applied Therapeutics: The Clinical Use of Drugs is another comprehensive text on drug therapy, with each chapter focusing on a specific disorder. However, this book is different from the others in that it employs a case-study approach to present content on pharmacology and therapeutics.

Newsletters

The Medical Letter on Drugs and Therapeutics is a bimonthly publication that gives current information on drugs. A typical issue addresses two or three agents. Discussions consist of a summary of data from clinical trials plus a conclusion regarding the drug's therapeutic utility. The conclusions can be a valuable guide when deciding whether or not to use a new drug.

Prescriber's Letter is a monthly publication with very current information. Unlike *The Medical Letter*, which usually focuses on just two or three drugs, this newsletter addresses (briefly) most major drug-related developments—from new drugs to FDA warnings to new uses of older agents. In addition, subscribers can access an Internet site that provides expanded information on all topics addressed in the monthly letter.

Reference Books

The *Physicians' Desk Reference*, also known as the PDR, is a reference work financed by the pharmaceutical industry. The information on each drug is identical to the information on its package insert. In addition to textual content, the PDR has a pictorial section for product identification. The PDR is updated annually.

Drug Facts and Comparisons is a comprehensive reference that contains monographs on virtually every drug marketed in the United States. Information is provided on drug actions, indications, warnings, precautions, adverse reactions, dosage, and administration. In addition to describing the properties of single medications, the book lists the contents of most combination products sold in this country. Indexing is by generic name and trade name. *Drug Facts and Comparisons* is available in a loose-leaf format (updated monthly), an online format (updated monthly), and a hard-cover format (published annually).

A number of drug references have been compiled expressly for nurses. All address topics of special interest to nurses, including information on administration, assessment, evaluation, and patient education. Representative nursing drug references include *Saunders Nursing Drug Handbook* and *Mosby's Drug Guide for Nurses*, both published annually.

The Internet

The Internet can be a valuable source of drug information. However, since anyone, regardless of qualifications, can post information, not everything you find will be accurate. Accordingly, you need to exercise discretion when searching for information. A list of reliable sites for drug-related information is available online at <http://evolve.elsevier.com/Lehne>.

KEY POINTS

- The Food, Drug and Cosmetic Act of 1938 was the first legislation to regulate drug safety.
- The Harris-Kefauver Amendments, passed in 1962, were the first legislation to demand that drugs actually be of some benefit.
- The Controlled Substances Act, passed in 1970, set rules for the manufacture and distribution of drugs considered to have potential for abuse.
- The FDA Amendments Act, passed in 2007, expanded the mission of the FDA to include rigorous oversight of drug safety *after* a drug has been released for marketing.
- Development of a new drug is a very expensive process that takes years to complete.
- The randomized controlled trial is the most reliable way to objectively assess drug efficacy and safety.
- Drug testing in Phase II and Phase III clinical trials is limited to a relatively small number of patients, most of whom take the drug for a relatively short time.
- Since women and children have been excluded from drug trials in the past, our understanding of drug efficacy and safety in these groups is limited.
- When a new drug is released for general use, it may well have adverse effects that have not yet been detected. Consequently, when working with a new drug, you should be especially watchful for previously unreported adverse events.
- Drugs have three types of names: a chemical name, a generic or nonproprietary name, and a trade or proprietary name.
- Each drug has only one generic name but can have many trade names.
- With OTC products, the same trade name may be used for more than one drug.
- Trade names for the same drug may differ from one country to another.
- Generic names facilitate communication and therefore are good. Trade names confuse communication and should be outlawed. (Even science writers are allowed to voice an opinion now and then.)
- Over-the-counter (OTC) drugs are defined as drugs that can be purchased without a prescription.
- Since the job of the drug representative is sales and not education, this person may not be your best source of drug information—especially if you are trying to establish an unbiased comparison between the representative's product and a drug from a competing manufacturer.
- As pharmacology students, you should know that *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (aka *G & G*) is the classic text/reference on pharmacology.

Please visit <http://evolve.elsevier.com/Lehne> for chapter-specific NCLEX® examination review questions.

Application of Pharmacokinetics in Therapeutics**A Note to Chemophobes****Passage of Drugs Across Membranes****Membrane Structure****Three Ways to Cross a Cell Membrane****Polar Molecules****Ions****Absorption****Factors Affecting Drug Absorption****Characteristics of Commonly Used Routes of Administration****Pharmaceutical Preparations for Oral Administration****Additional Routes of Administration****Distribution****Blood Flow to Tissues****Exiting the Vascular System****Entering Cells****Metabolism****Hepatic Drug-Metabolizing Enzymes****Therapeutic Consequences of Drug Metabolism****Special Considerations in Drug Metabolism****Enterohepatic Recirculation****Excretion****Renal Drug Excretion****Nonrenal Routes of Drug Excretion****Time Course of Drug Responses****Plasma Drug Levels****Single-Dose Time Course****Drug Half-Life****Drug Levels Produced with Repeated Doses**

The term *pharmacokinetics* is derived from two Greek words: *pharmakon* (drug or poison) and *kinesis* (motion). As this derivation implies, pharmacokinetics is the study of drug movement throughout the body. Pharmacokinetics also includes drug metabolism and drug excretion.

There are four basic pharmacokinetic processes: *absorption*, *distribution*, *metabolism*, and *excretion* (Fig. 4-1). Absorption is defined as the movement of a drug from its site of administration into the blood. Distribution is defined as drug movement from the blood to the interstitial space of tissues and from there into cells. Metabolism (biotransformation) is defined as enzymatically mediated alteration of drug structure. Excretion is the movement of drugs and their metabolites out of the body. The combination of metabolism plus excretion is called *elimination*. The four pharmacokinetic

processes, acting in concert, determine the concentration of a drug at its sites of action.

APPLICATION OF PHARMACOKINETICS IN THERAPEUTICS

By applying knowledge of pharmacokinetics to drug therapy, we can help maximize beneficial effects and minimize harm. Recall that the intensity of the response to a drug is directly related to the concentration of the drug at its site of action. To maximize beneficial effects, we must achieve concentrations that are high enough to elicit desired responses; to minimize harm, we must avoid concentrations that are too high. This balance is achieved by selecting the most appropriate route, dosage, and dosing schedule. The only way we can rationally choose the most effective route, dosage, and schedule is by considering pharmacokinetic factors.

As a nurse, you will have ample opportunity to apply knowledge of pharmacokinetics in clinical practice. For example, by understanding the reasons behind selection of route, dosage, and dosing schedule, you will be less likely to commit medication errors than will the nurse who, through lack of this knowledge, administers medications by blindly following prescribers' orders. Also, as noted in Chapter 2, prescribers do make mistakes. Accordingly, you will have occasion to question or even challenge prescribers regarding their selection of dosage, route, or schedule of administration. In order to alter a prescriber's decision, you will need a rational argument to support your position. To present that argument, you will need to understand pharmacokinetics.

Knowledge of pharmacokinetics can increase job satisfaction. Working with medications is a significant component of nursing practice. If you lack knowledge of pharmacokinetics, drugs will always be somewhat mysterious and, as a result, will be a potential source of unease. By helping to demystify drug therapy, knowledge of pharmacokinetics can decrease some of the stress of nursing practice and can increase intellectual and professional satisfaction.

A NOTE TO CHEMOPHOBES

Before we proceed, some advance notice (and encouragement) are in order for chemophobes (students who fear chemistry). Because drugs are chemicals, we cannot discuss pharmacology meaningfully without occasionally talking about chemistry. This chapter has some chemistry in it. In fact, the chemistry presented here is the most difficult in the book. Accordingly, once you've worked your way through this chapter, the chapters that follow will be a relative breeze. Because the concepts addressed here are fundamental, and because they

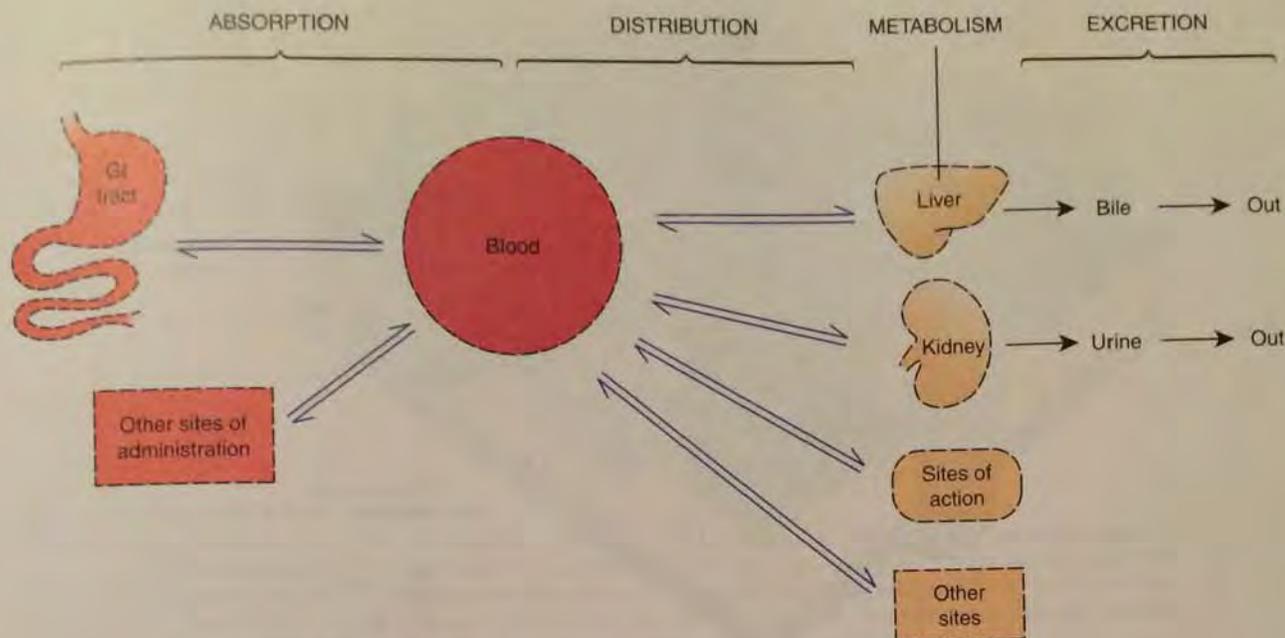


Figure 4-1 • The four basic pharmacokinetic processes.

Dotted lines represent membranes that must be crossed as drugs move throughout the body.

reappear frequently, all students, including chemophobes, are encouraged to learn this material now, regardless of the effort and anxiety involved.

I also want to comment on the chemical structures that appear in the book. Structures are presented only to illustrate and emphasize concepts. They are not intended for memorization, and they are certainly not intended for exams. So, relax, look at the pictures, and focus on the concepts I am trying to help you grasp.

PASSAGE OF DRUGS ACROSS MEMBRANES

All four phases of pharmacokinetics—absorption, distribution, metabolism, and excretion—involve drug movement. To move throughout the body, drugs must cross membranes. Drugs must cross membranes to enter the blood from their site of administration. Once in the blood, drugs must cross membranes to leave the vascular system and reach their sites of action. In addition, drugs must cross membranes to undergo metabolism and excretion. Accordingly, the factors that determine the passage of drugs across biologic membranes have a profound influence on all aspects of pharmacokinetics.

Membrane Structure

Biologic membranes are composed of layers of individual cells. The cells composing most membranes are very close to one another—so close, in fact, that drugs must usually pass *through* cells, rather than between them, in order to cross the membrane. Hence, the ability of a drug to cross a biologic membrane is determined primarily by its ability to pass through single cells. The major barrier to passage through a

cell is the cytoplasmic membrane (the membrane that surrounds every cell).

The basic structure of the cell membrane is depicted in Figure 4-2. As indicated, the basic membrane structure consists of a double layer of molecules known as *phospholipids*. Phospholipids are simply lipids (fats) that contain an atom of phosphate.

In Figure 4-2, the phospholipid molecules are depicted as having a round head (the phosphate-containing component) and two tails (long-chain hydrocarbons). The large objects embedded in the membrane represent protein molecules, which serve a variety of functions.

Three Ways to Cross a Cell Membrane

The three most important ways by which drugs cross cell membranes are (1) passage through channels or pores, (2) passage with the aid of a transport system, and (3) direct penetration of the membrane itself. Of the three, direct penetration of the membrane is most common.

Channels and Pores

Very few drugs cross membranes via channels or pores. The channels in membranes are extremely small (approximately 4 angstroms), and are specific for certain molecules. Consequently, only the smallest of compounds (molecular weight below 200) can pass through these channels, and then only if the channel is the right one. Compounds with the ability to cross membranes via channels include small ions, such as potassium and sodium.

Transport Systems

Transport systems are carriers that can move drugs from one side of the cell membrane to the other. Some transport systems require the expenditure of energy; others do not. All

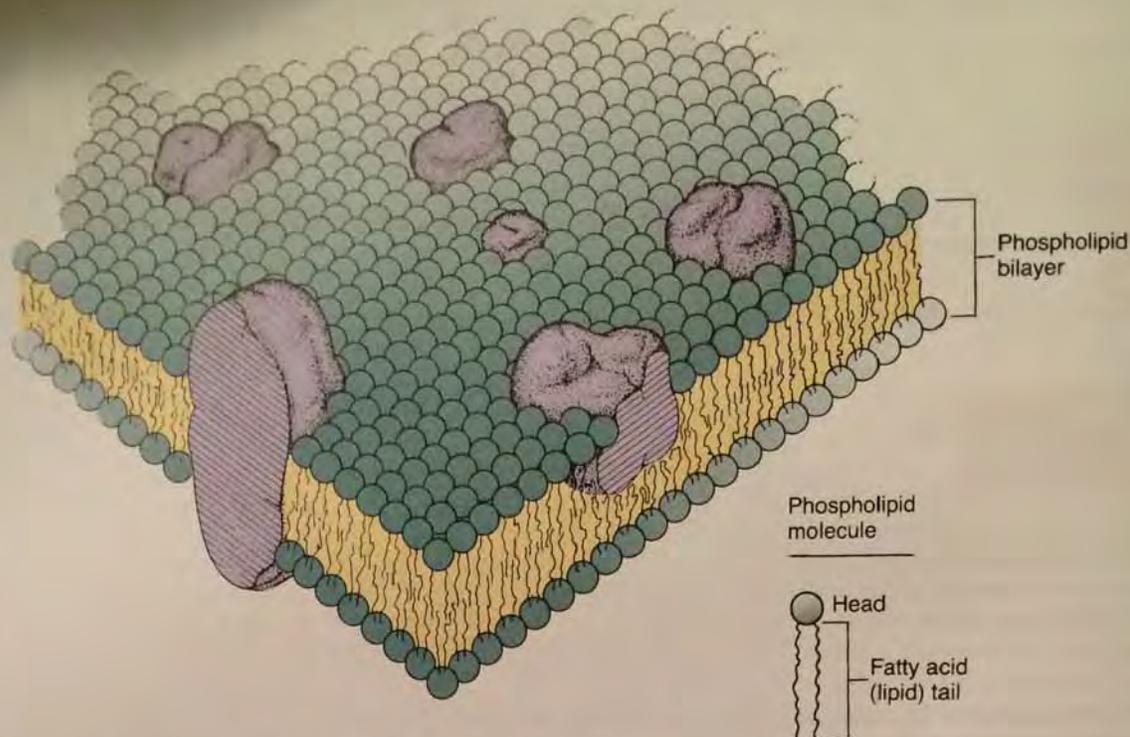


Figure 4-2 = Structure of the cell membrane.

The cell membrane consists primarily of a double layer of phospholipid molecules. The large globular structures represent protein molecules imbedded in the lipid bilayer. (Modified from Singer SJ, Nicolson GL: The fluid mosaic model of the structure of cell membranes. *Science* 175:720, 1972.)

transport systems are selective: They will not carry just any drug. Whether a transporter will carry a particular drug depends on the drug's structure.

Transport systems are an important means of drug transit. For example, certain orally administered drugs could not be absorbed unless there were transport systems to move them across the membranes that separate the lumen of the intestine from the blood. A number of drugs could not reach intracellular sites of action without a transport system to move them across the cell membrane. Renal excretion of many drugs would be extremely slow were it not for transport systems in the kidney that can pump drugs from the blood into the renal tubules.

P-Glycoprotein. One transporter, known as *P-glycoprotein* or *multidrug transporter protein*, deserves special mention. P-glycoprotein is a transmembrane protein that transports a wide variety of drugs *out* of cells. This transporter is present in cells at many sites, including the liver, kidney, placenta, intestine, and capillaries of the brain. In the liver, P-glycoprotein transports drugs into the bile for elimination. In the kidney, it pumps drugs into the urine for excretion; in the placenta, it transports drugs back into the maternal blood, thereby reducing fetal drug exposure. In the intestine, it transports drugs into the intestinal lumen, and can thereby reduce drug absorption into the blood. And in brain capillaries, it pumps drugs into the blood, thereby limiting drug access to the brain.

Direct Penetration of the Membrane

For most drugs, movement throughout the body is dependent on the ability to penetrate membranes directly. Why? Because (1) most drugs are too large to pass through channels or pores

and (2) most drugs lack transport systems to help them cross all of the membranes that separate them from their sites of action, metabolism, and excretion.

In order to directly penetrate membranes, a drug must be *lipid soluble* (lipophilic). Recall that membranes are composed primarily of lipids. Consequently, if a drug is to penetrate a membrane, it must be able to dissolve into the lipids the membrane is made of.

Certain kinds of molecules are *not* lipid soluble and therefore cannot penetrate membranes. This group consists of *polar molecules* and *ions*.

Polar Molecules

Polar molecules are molecules with uneven distribution of electrical charge. That is, positive and negative charges within the molecule tend to congregate separately from one another. Water is the classic example. As depicted in Figure 4-3A, the electrons (negative charges) in the water molecule spend more time in the vicinity of the oxygen atom than in the vicinity of the two hydrogen atoms. As a result, the area around the oxygen atom tends to be negatively charged, whereas the area around the hydrogen atoms tends to be positively charged. Kanamycin (Fig. 4-3B), an antibiotic, is an example of a polar drug. The hydroxyl groups, which attract electrons, give kanamycin its polar nature.

Although polar molecules have an uneven *distribution* of charge, they have no *net* charge. Polar molecules have an equal number of protons (which bear a single positive charge) and electrons (which bear a single negative charge). As a re-

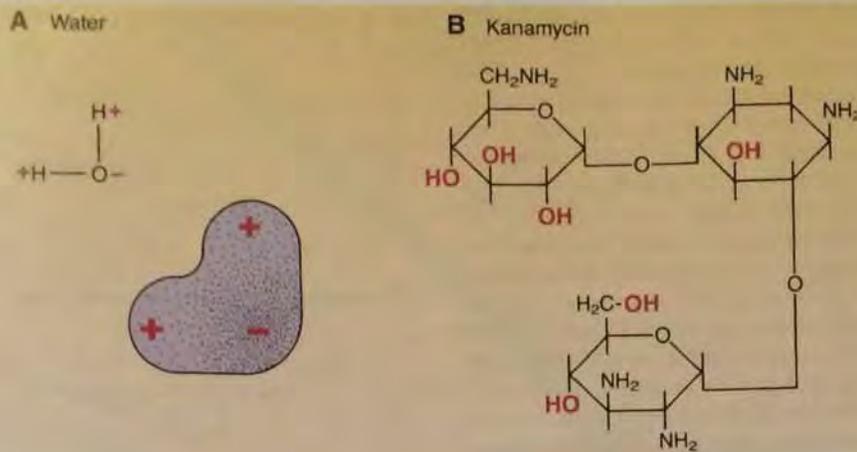


Figure 4-3 • Polar molecules.

A, Stippling shows the distribution of electrons within the water molecule. As indicated, water's electrons spend more time near the oxygen atom than near the hydrogen atoms, making the area near the oxygen atom somewhat negative and the area near the hydrogen atoms more positive. **B**, Kanamycin is a polar drug. The 2 -OH groups of kanamycin attract electrons, thereby causing the area around these groups to be more negative than the rest of the molecule.

sult, the positive and negative charges balance each other exactly, and the molecule as a whole has neither a net positive charge nor a net negative charge. Molecules that *do* bear a net charge are called *ions*. These are discussed below.

There is a general rule in chemistry that states: "like dissolves like." In accord with this rule, polar molecules will dissolve in *polar* solvents (such as water) but not in *nonpolar* solvents (such as oil). Table sugar provides a common example. I'm sure you've observed that sugar, a polar compound, readily dissolves in water but not in salad oil, butter, and other lipids, which are nonpolar compounds. Just as sugar is unable to dissolve in lipids, polar drugs are unable to dissolve in the lipid bilayer of the cell membrane.

Ions

Ions are defined as molecules that have a *net electrical charge* (either positive or negative). Except for very small molecules, *ions are unable to cross membranes*.

Quaternary Ammonium Compounds

Quaternary ammonium compounds are molecules that contain at least one atom of nitrogen and *carry a positive charge at all times*. The constant charge on these compounds results from atypical bonding to the nitrogen. In most nitrogen-containing compounds, the nitrogen atom bears only three chemical bonds. In contrast, the nitrogen atoms of quaternary ammonium compounds have four chemical bonds (Fig. 4-4A). Because of the fourth bond, quaternary ammonium compounds always carry a positive charge. And because of the charge, these compounds are unable to cross most membranes.

Tubocurarine (Fig. 4-4B) is a representative quaternary ammonium compound. Until recently, purified tubocurarine was employed as a muscle relaxant for surgery and other procedures. A crude preparation—curare—is used by South American Indians as an arrow poison. When employed for hunting, tubocurarine (curare) produces paralysis of the dia-

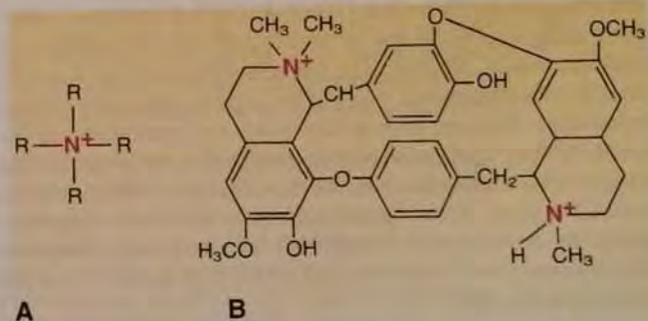


Figure 4-4 • Quaternary ammonium compounds.

A, The basic structure of quaternary ammonium compounds. Because the nitrogen atom has bonds to four organic radicals, quaternary ammonium compounds always carry a positive charge. Because of this charge, quaternary ammonium compounds are not lipid soluble and cannot cross most membranes. **B**, Tubocurarine is a representative quaternary ammonium compound. Note that tubocurarine contains two "quaternized" nitrogen atoms.

phragm and other skeletal muscles, causing death by asphyxiation. Interestingly, even though meat from animals killed with curare is laden with poison, it can be eaten with no ill effect. Why? Because tubocurarine, being a quaternary ammonium compound, cannot cross membranes, and therefore cannot be absorbed from the intestine; as long as it remains in the lumen of the intestine, curare can do no harm. As you might gather, when tubocurarine was used clinically, it could not be administered by mouth. Instead, it had to be injected. Once in the bloodstream, tubocurarine then had ready access to its sites of action on the surface of muscles.

pH-Dependent Ionization

Unlike quaternary ammonium compounds, which always carry a charge, certain drugs can exist in either a charged or uncharged form. Many drugs are either weak organic acids or

weak organic bases, which can exist in charged and uncharged forms. Whether a weak acid or base carries a charge is determined by the pH of the surrounding medium.

A review of acid-base chemistry should help. An acid is defined as a compound that can give up a hydrogen ion (proton). Put another way, *an acid is a proton donor*. A base is defined as a compound that can take on a hydrogen ion. That is, *a base is a proton acceptor*. When an acid gives up its proton, which is positively charged, the acid itself becomes negatively charged. Conversely, when a base accepts a proton, the base becomes positively charged. These reactions are depicted in Figure 4-5, which shows aspirin as a representative acid and amphetamine as a representative base. Because the process of an acid giving up a proton or a base accepting a proton converts the acid or base into a charged particle (ion), the process for either an acid or a base is termed *ionization*.

The extent to which a weak acid or weak base becomes ionized is determined in part by the pH of its environment. The following rules apply:

- *Acids tend to ionize in basic (alkaline) media.*
- *Bases tend to ionize in acidic media.*

To illustrate the importance of pH-dependent ionization, let's consider the ionization of aspirin. Being an acid, aspirin tends to give up its proton (become ionized) in basic media. Conversely, aspirin keeps its proton and remains nonionized in acidic media. Accordingly, when aspirin is in the stomach (an acidic environment), most of the aspirin molecules remain nonionized. Because aspirin molecules are nonionized in the stomach, they can be absorbed across the membranes that separate the stomach from the bloodstream. When aspirin molecules pass from the stomach into the small intestine, where the environment is relatively alkaline, they change to their ionized form. As a result, absorption of aspirin from the intestine is impeded.

Ion Trapping (pH Partitioning)

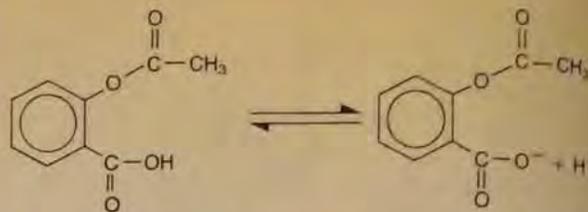
Because the ionization of drugs is pH dependent, when the pH of the fluid on one side of a membrane differs from the pH of the fluid on the other side, drug molecules will tend to accumulate on the side where the pH most favors their ionization. Accordingly, since acidic drugs tend to ionize in basic media, and since basic drugs tend to ionize in acidic media, *when there is a pH gradient between two sides of a membrane,*

- *Acidic drugs will accumulate on the alkaline side.*
- *Basic drugs will accumulate on the acidic side.*

The process whereby a drug accumulates on the side of a membrane where the pH most favors its ionization is referred to as *ion trapping* or *pH partitioning*. Figure 4-6 shows the steps of ion trapping using aspirin as an example.

Because ion trapping can influence the movement of drugs throughout the body, the process is not simply of academic interest. Rather, ion trapping has practical clinical implications. Knowledge of ion trapping helps us understand drug absorption as well as the movement of drugs to sites of action, metabolism, and excretion. Understanding of ion trapping can be put to practical use when we need to actively influence drug movement. Poisoning is the principal example: By manipulating urinary pH, we can employ ion trapping to draw toxic substances from the blood into the urine, thereby accelerating their removal.

A Ionization of aspirin, a weak acid



B Ionization of amphetamine, a weak base

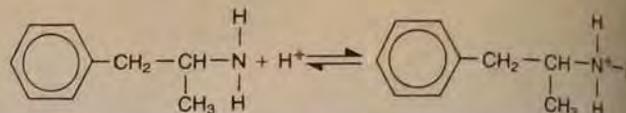


Figure 4-5 • Ionization of weak acids (A) and weak bases (B).

The extent of ionization of weak acids (A) and weak bases (B) depends on the pH of their surroundings. The ionized (charged) forms of acids and bases are not lipid soluble and hence do not readily cross membranes. Note that acids ionize by giving up a proton and that bases ionize by taking on a proton.

ABSORPTION

Absorption is defined as *the movement of a drug from its site of administration into the blood*. The rate of absorption determines how *soon* effects will begin. The *amount* of absorption helps determine how *intense* effects will be.

Factors Affecting Drug Absorption

The rate at which a drug undergoes absorption is influenced by the physical and chemical properties of the drug itself and by physiologic and anatomic factors at the absorption site.

Rate of Dissolution. Before a drug can be absorbed, it must first dissolve. Hence, the rate of dissolution helps determine the rate of absorption. Drugs in formulations that allow rapid dissolution have a faster onset than drugs formulated for slow dissolution.

Surface Area. The surface area available for absorption is a major determinant of the rate of absorption. The larger the surface area, the faster absorption will be. For this reason, orally administered drugs are usually absorbed from the small intestine rather than from the stomach. (Recall that the small intestine, because of its lining of microvilli, has an extremely large surface area, whereas the surface area of the stomach is relatively small.)

Blood Flow. Drugs are absorbed most rapidly from sites where blood flow is high. Why? Because blood containing newly absorbed drug will be replaced rapidly by drug-free blood, thereby maintaining a large gradient between the concentration of drug outside the blood and the concentration of drug in the blood. The greater the concentration gradient, the more rapid absorption will be.

Lipid Solubility. As a rule, highly lipid-soluble drugs are absorbed more rapidly than drugs whose lipid solubility is low. Why? Because lipid-soluble drugs can readily cross the

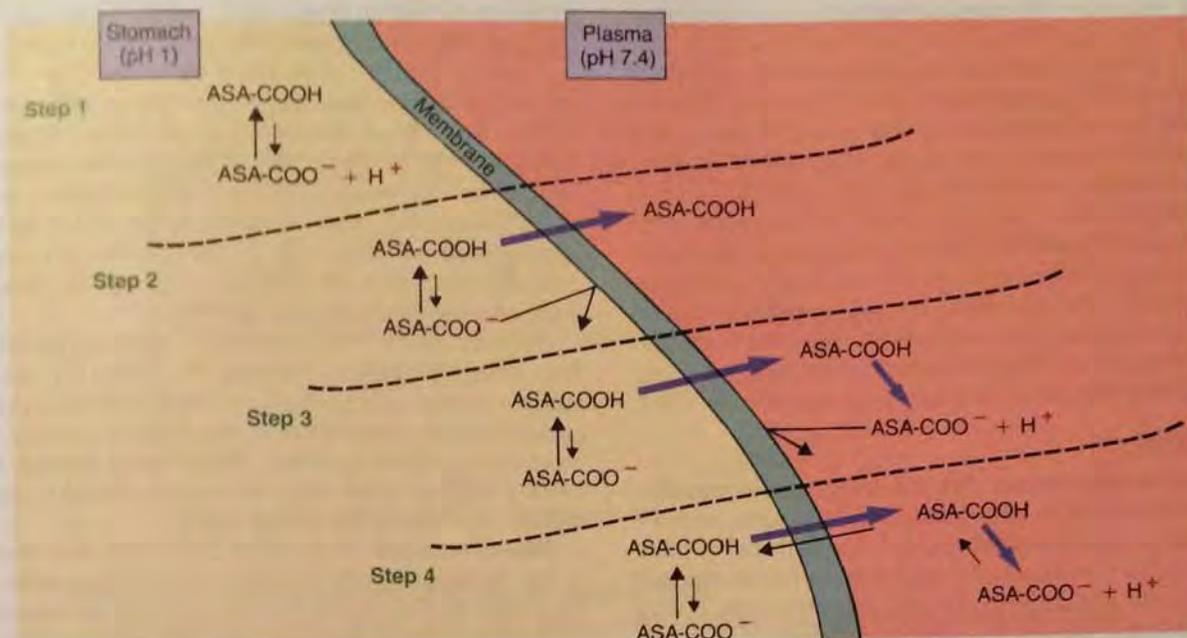


Figure 4-6 ■ Ion trapping of drugs.

This figure demonstrates ion trapping using aspirin as an example. Because aspirin is an acidic drug, it will be nonionized in acid media and ionized in alkaline media. As indicated, ion trapping causes molecules of orally administered aspirin to move from the acidic (pH 1) environment of the stomach to the more alkaline (pH 7.4) environment of the plasma, thereby causing aspirin to accumulate in the blood. In the figure, aspirin (acetylsalicylic acid) is depicted as ASA with its COOH (carboxylic acid) group attached.

Step 1: Once ingested, ASA dissolves in the stomach contents, after which some ASA molecules give up a proton and become ionized. However, most of the ASA in the stomach remains nonionized. Why? Because the stomach is acidic, and acidic drugs don't ionize in acidic media.

Step 2: Because most ASA molecules in the stomach are nonionized (and therefore lipid soluble), most ASA molecules in the stomach can readily cross the membranes that separate the stomach lumen from the plasma. Because of the concentration gradient that exists between the stomach and the plasma, nonionized ASA molecules will begin moving into the plasma. (Note that, because of their charge, ionized ASA molecules cannot leave the stomach.)

Step 3: As the nonionized ASA molecules enter the relatively alkaline environment of the plasma, most give up a proton (H⁺) and become negatively charged ions. ASA molecules that become ionized in the plasma cannot diffuse back into the stomach.

Step 4: As the nonionized ASA molecules in the plasma become ionized, more nonionized molecules will pass from the stomach to the plasma to replace them. This movement occurs because the laws of diffusion demand equal concentrations of diffusible substances on both sides of a membrane. Because only the nonionized form of ASA is able to diffuse across the membrane, it is this form that the laws of diffusion will attempt to equilibrate. Nonionized ASA will continue to move from the stomach to the plasma until the amount of ionized ASA in plasma has become large enough to prevent conversion of newly arrived nonionized molecules into the ionized form. Equilibrium will then be established between the plasma and the stomach. At equilibrium, there will be equal amounts of **nonionized** ASA in the stomach and plasma. However, on the plasma side, the amount of ionized ASA will be much larger than on the stomach side. Because there are equal concentrations of nonionized ASA on both sides of the membrane but a much higher concentration of ionized ASA in the plasma, the total concentration of ASA in plasma will be much higher than in the stomach.

membranes that separate them from the blood, whereas drugs of low lipid solubility cannot.

pH Partitioning. pH partitioning can influence drug absorption. Absorption will be enhanced when the difference between the pH of plasma and the pH at the site of administration is such that drug molecules will have a greater tendency to be ionized in the plasma.

Characteristics of Commonly Used Routes of Administration

The routes of administration that are used most commonly fall into two major groups: *enteral* (via the gastrointestinal [GI] tract) and *parenteral*. The literal definition of *parenteral* is *outside the GI tract*. However, in common parlance, the term *parenteral* is used to mean *by injection*. The principal

parenteral routes are *intravenous*, *subcutaneous*, and *intramuscular*.

For each of the major routes of administration—oral (PO), intravenous (IV), intramuscular (IM), and subcutaneous (subQ)—the pattern of drug absorption (ie, the rate and extent of absorption) is unique. Consequently, the route by which a drug is administered will significantly affect both the onset and the intensity of effects. Why do patterns of absorption differ between routes? Because the barriers to absorption associated with each route are different. In the discussion below, we examine these barriers and their influence on absorption pattern. In addition, as we discuss each major route, we will consider its clinical advantages and disadvantages. The distinguishing characteristics of the four major routes are summarized in Table 4-1.

Intravenous

Barriers to Absorption. When a drug is administered IV, there are no barriers to absorption. Why? Because, with IV administration, absorption is bypassed. Recall that absorption is defined as the movement of a drug from its site of administration into the blood. Since IV administration puts a drug directly into the blood, all barriers are bypassed.

Absorption Pattern. Intravenous administration results in “absorption” that is both instantaneous and complete. Intravenous “absorption” is instantaneous in that drug enters the blood directly. “Absorption” is complete in that virtually all of the administered dose reaches the blood.

Advantages. Rapid Onset. Intravenous administration results in rapid onset of action. Although rapid onset is not always important, it has obvious benefit in emergencies.

Control. Because the entire dose is administered directly into the blood, we have precise control over levels of drug in the blood. This contrasts with the other major routes of ad-

ministration, and especially with oral administration (see below), in which the amount absorbed is less predictable.

Permits Use of Large Fluid Volumes. The IV route is the only parenteral route that permits the use of large volumes of fluid. Some drugs that require parenteral administration are poorly soluble in water, and hence must be dissolved in a large volume. Because of the physical limitations presented by soft tissues (eg, muscle, subcutaneous tissue), injection of large volumes at these sites is not feasible. In contrast, the amount of fluid that can be infused into a vein, although limited, is nonetheless relatively big.

Permits Use of Irritant Drugs. Certain drugs, because of their irritant properties, can only be given IV. A number of anticancer drugs, for example, are very chemically reactive. If present in high concentrations, these agents can cause severe local injury. However, when administered through a freely flowing IV line, these drugs are rapidly diluted in the blood, thereby minimizing the risk of injury.

Disadvantages. High Cost, Difficulty, and Inconvenience. Intravenous administration is expensive, difficult, and inconvenient. The cost of IV administration sets and their set-up charges can be substantial. Also, setting up an IV line takes time and special training. Because of the difficulty involved, most patients are unable to self-administer IV drugs, and therefore must depend on a healthcare professional. Because patients are tethered to lines and bottles, their mobility is limited. In contrast, oral administration is easy, convenient, and cheap.

Irreversibility. More important than cost or convenience, IV administration can be *dangerous*. Once a drug has been injected, there is no turning back: The drug is in the body and cannot be retrieved. Hence, if the dose is excessive, avoiding harm may be impossible.

TABLE 4-1 ■ Properties of Major Routes of Drug Administration

Route	Barriers to Absorption	Absorption Pattern	Advantages	Disadvantages
Parenteral				
Intravenous (IV)	None (absorption is bypassed)	Instantaneous	Rapid onset, and hence ideal for emergencies Precise control over drug levels Permits use of large fluid volumes Permits use of irritant drugs	Irreversible Expensive Inconvenient Difficult to do, and hence poorly suited for self-administration Risk of fluid overload, infection, and embolism Drug must be water soluble
Intramuscular (IM)	Capillary wall (easy to pass)	Rapid with water-soluble drugs Slow with poorly soluble drugs	Permits use of poorly soluble drugs Permits use of depot preparations	Possible discomfort Inconvenient Potential for injury
Subcutaneous (subQ)	Same as IM	Same as IM	Same as IM	Same as IM
Enteral				
Oral (PO)	Epithelial lining of GI tract; capillary wall	Slow and variable	Easy Convenient Inexpensive Ideal for self-medication Potentially reversible, and hence safer than parenteral routes	Variability Inactivation of some drugs by gastric acid and digestive enzymes Possible nausea and vomiting from local irritation Patient must be conscious and cooperative

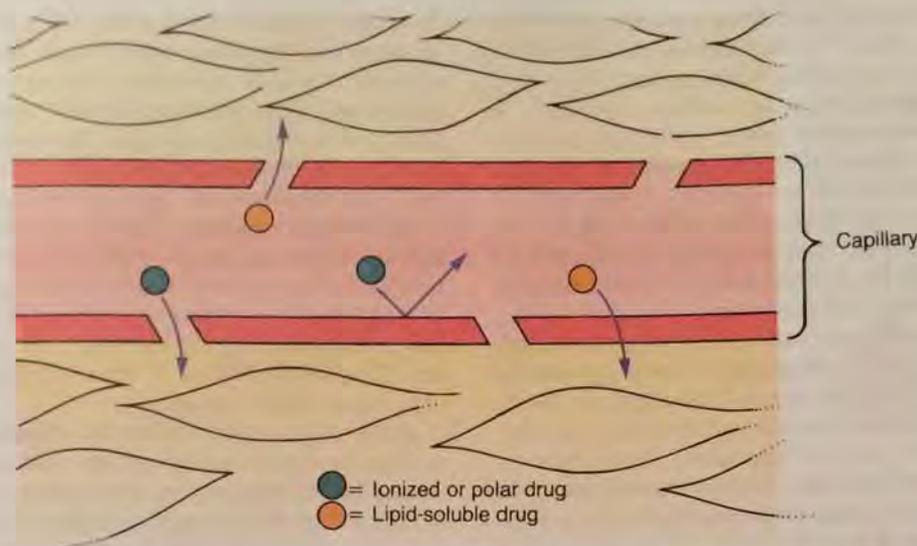


Figure 4-7 = Drug movement at typical capillary beds.

In most capillary beds, "large" gaps exist between the cells that compose the capillary wall. Drugs and other molecules can pass freely into and out of the bloodstream through these gaps. As illustrated, lipid-soluble compounds can also pass directly through the cells of the capillary wall.

To minimize risk, IV drugs should be injected slowly (over 1 minute or more). Because all of the blood in the body is circulated about once every minute, by injecting a drug over a 1-minute interval, we cause it to be diluted in the largest volume of blood possible. By doing so, we can avoid drug concentrations that are unnecessarily high—or even dangerously high.

Performing IV injections slowly has the additional advantage of reducing the risk of toxicity to the central nervous system (CNS). When a drug is injected into the antecubital vein of the arm, it takes about 15 seconds to reach the brain. Consequently, if the dose is sufficient to cause CNS toxicity, signs of toxicity may become apparent 15 seconds after starting the injection. If the injection is being done slowly (eg, over a 1-minute interval), only 25% of the total dose will have been administered when signs of toxicity appear. If administration is discontinued immediately, adverse effects will be much less than they would have been had the entire dose been given.

Fluid Overload. When drugs are administered in a large volume, fluid overload can occur. This can be a significant problem for patients with hypertension, kidney disease, or heart failure.

Infection. Infection can occur from injecting a contaminated drug. Fortunately, the risk of infection is much lower today than it was before the development of modern techniques for sterilizing drugs intended for IV use.

Embolism. Intravenous administration carries a risk of embolism (blood vessel blockage at a site distant from the point of administration). Embolism can be caused in several ways. First, insertion of an IV needle can injure the venous wall, leading to formation of a thrombus (clot); embolism can result if the clot breaks loose and becomes lodged in another vessel. Second, injection of hypotonic or hypertonic fluids can destroy red blood cells; the debris from these cells can produce embolism.

Lastly, injection of drugs that are not fully dissolved can cause embolism. Particles of undissolved drug are like small grains of sand, which can become embedded in blood vessels and cause blockage. Because of the risk of embolism, you should check IV solutions prior to administration to ensure that

drugs are in solution. If the fluid is cloudy or contains particles, the drug is not dissolved and must not be administered.

The Importance of Reading Labels. Not all formulations of the same drug are appropriate for IV administration. Accordingly, it is essential to read the label before giving a drug IV. Two examples illustrate why this is so important. The first is insulin. Seven types of insulin are now available (eg, regular insulin, insulin aspart, NPH insulin). Some of these formulations can be given IV; others cannot. Regular insulin, for example, is formulated as a clear liquid, and is safe for IV use. In contrast, NPH insulin is formulated as a particulate suspension. This suspension is safe for subQ use, but its particles could be fatal if given IV. By checking the label, inadvertent IV injection of particulate insulin can be avoided.

Epinephrine provides our second example of why you should read the label before giving a drug IV. Epinephrine, which stimulates the cardiovascular system, can be injected by several routes (IM, IV, subQ, intracardiac, intraspinal). Be aware, however, that a solution prepared for use by one route will differ in concentration from a solution prepared for use by other routes. For example, whereas solutions intended for *subcutaneous* administration are *concentrated*, solutions intended for *intravenous* use are *dilute*. If a solution prepared for subQ use were to be inadvertently administered IV, the result could prove *fatal*. (Intravenous administration of concentrated epinephrine could overstimulate the heart and blood vessels, causing severe hypertension, cerebral hemorrhage, stroke, and death.) The take-home message is that simply giving the *right drug* is not sufficient; you must also be sure that the formulation and concentration are *appropriate for the intended route*.

Intramuscular

Barriers to Absorption. When a drug is injected IM, the only barrier to absorption is the *capillary wall*. In capillary beds that serve muscles and most other tissues, there are "large" spaces between the cells that compose the capillary wall (Fig. 4-7). Drugs can pass through these spaces with

ease, and need not cross cell membranes to enter the bloodstream. Accordingly, like IV administration, IM administration presents no significant barrier to absorption.

Absorption Pattern. Drugs administered IM may be absorbed rapidly or slowly. The rate of absorption is determined largely by two factors: (1) water solubility of the drug and (2) blood flow to the site of injection. Drugs that are highly soluble in water will be absorbed rapidly (within 10 to 30 minutes), whereas drugs that are poorly soluble will be absorbed slowly. Similarly, absorption will be rapid from sites where blood flow is high, and slow where blood flow is low.

Advantages. The IM route can be used for parenteral administration of *poorly soluble drugs*. Recall that drugs must be dissolved if they are to be administered IV. Consequently, the IV route cannot be used for poorly soluble compounds. In contrast, since little harm will come from depositing a suspension of undissolved drug in the interstitial space of muscle tissue, the IM route is acceptable for drugs whose water solubility is poor.

A second advantage of the IM route is that we can use it to administer *depot preparations* (preparations from which the drug is absorbed slowly over an extended time). Depending on the depot formulation, the effects of a single injection may persist for days, weeks, or even months. For example, *benzathine penicillin G*, a depot preparation of penicillin, can release therapeutically effective amounts of penicillin for a month following a single IM injection. In contrast, a single IM injection of penicillin G itself would be absorbed and excreted in less than 1 day. The obvious advantage of depot preparations is that they can greatly reduce the number of injections required during long-term therapy.

Disadvantages. The major drawbacks of IM administration are discomfort and inconvenience. Intramuscular injection of some preparations can be painful. Also, IM injections can cause local tissue injury and possibly nerve damage (if the injection is done improperly). Lastly, because of bleeding risk, IM injections cannot be used for patients receiving anticoagulant therapy. Like all other forms of parenteral administration, IM injections are less convenient than oral administration.

Subcutaneous

The pharmacokinetics of subQ administration are nearly identical to those of IM administration. As with IM administration, there are no significant barriers to absorption: Once a drug has been injected subQ, it readily enters the blood by passing through the spaces between cells of the capillary wall. As with IM administration, blood flow and drug solubility are the major determinants of how fast absorption takes place. Because of the similarities between subQ and IM administration, these routes have similar advantages (suitability for poorly soluble drugs and depot preparations) and similar drawbacks (discomfort, inconvenience, potential for injury).

Oral

In the discussion below, the abbreviation PO is used in reference to oral administration. This abbreviation stands for *per os*, a Latin phrase meaning *by way of the mouth*.

Barriers to Absorption. Following oral administration, drugs may be absorbed from the stomach, the intestine, or both. In either case, there are two barriers to cross: (1) the layer of *epithelial cells* that lines the GI tract, and (2) the *capillary wall*.

Because the walls of the capillaries that serve the GI tract offer no significant resistance to absorption, the major barrier to absorption is the GI epithelium. To cross this layer of tightly packed cells, drugs must pass *through* cells rather than between them. For some drugs, intestinal absorption may be *reduced* by *P-glycoprotein*, a transporter that can pump certain drugs *out* of epithelial cells back into the intestinal lumen.

Absorption Pattern. Because of multiple factors, the rate and extent of drug absorption following oral administration can be *highly variable*. Factors that can influence absorption include (1) solubility and stability of the drug, (2) gastric and intestinal pH, (3) gastric emptying time, (4) food in the gut, (5) coadministration of other drugs, and (6) special coatings on the drug preparation.

Drug Movement Following Absorption. Before proceeding, we need to quickly review what happens to drugs following their absorption from the GI tract. As depicted in Figure 4-8, drugs absorbed from all sites along the GI tract (except the oral mucosa and the distal segment of the rectum) must pass through the liver (via the portal blood) before they can reach the general circulation. For many drugs, this passage is uneventful: they go through the liver, enter the inferior vena cava, and eventually reach the general circulation. Other drugs undergo extensive hepatic metabolism. And still others may undergo *enterohepatic recirculation*, a repeating cycle in which a drug moves from the liver into the duodenum (via the bile duct) and then back to the liver (via the portal blood). This cycle is discussed further under *Enterohepatic Recirculation*.

Advantages. Oral administration is easy, convenient, and inexpensive. (By inexpensive, we don't mean that oral drugs themselves are inexpensive, but rather there is no cost for the administration process.) Because of its relative ease, oral administration is the preferred route for self-medication.

Although absorption of oral drugs can be highly variable, this route is still *safer than injection*. With oral administration, there is no risk of fluid overload, infection, or embolism. Furthermore, since oral administration is potentially reversible, whereas injections are not, oral administration is safer. Recall that with parenteral administration there is no turning back: Once a drug has been injected, there is little we can do to prevent absorption and subsequent effects. Therefore, when giving drugs parenterally, we must live with the consequences of our mistakes. In contrast, if need be, there are steps we can take to prevent absorption following inappropriate oral administration. For example, we can decrease absorption by giving activated charcoal, a compound that adsorbs (soaks up) drugs while they are still in the GI tract; once drugs are adsorbed onto the charcoal, they cannot be absorbed into the bloodstream. Our ability to prevent the absorption of orally administered drugs gives PO medications a safety factor that is unavailable with drugs given by injection.

Disadvantages. Variability. The major disadvantage of PO therapy is that absorption can be highly variable. That is, a drug administered to patient A may be absorbed rapidly and completely, whereas the same drug given to patient B may be absorbed slowly and incompletely. This variability makes it difficult to control the concentration of a drug at its sites of action, and therefore makes it difficult to control the onset, intensity, and duration of responses.

Inactivation. Oral administration can lead to inactivation of certain drugs. Penicillin G, for example, can't be taken orally because it would be destroyed by stomach acid. Simi-

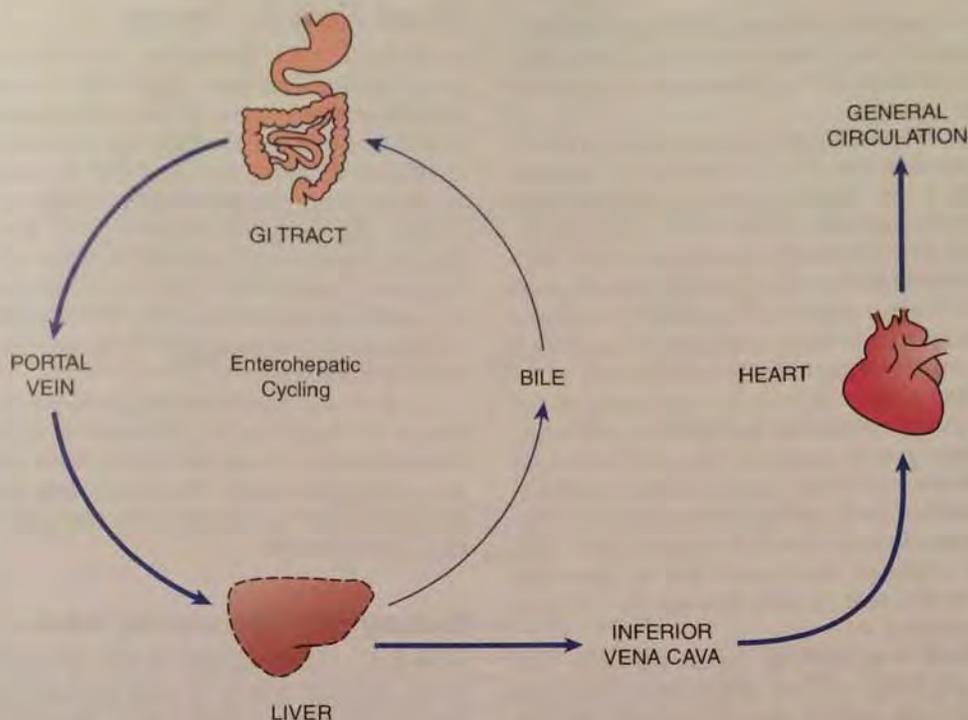


Figure 4-8 • Movement of drugs following GI absorption.

All drugs absorbed from sites along the GI tract—stomach, small intestine, and large intestine (but not the oral mucosa or distal rectum)—must go through the liver, via the portal vein, on their way to the heart and then the general circulation. For some drugs, passage is uneventful. Others undergo extensive hepatic metabolism. And still others undergo *enterohepatic recirculation*, a repeating cycle in which a drug moves from the liver into the duodenum (via the bile duct) and then back to the liver (via the portal blood). As discussed in the text under *Enterohepatic Recirculation*, the process is limited to drugs that have first undergone hepatic glucuronidation.

larly, insulin can't be taken orally because it would be destroyed by digestive enzymes. Other drugs (eg, nitroglycerin) undergo extensive inactivation as they pass through the liver, a phenomenon known as the "first-pass effect" (see below under *Special Considerations in Drug Metabolism*).

Patient Requirements. Oral drug administration requires a conscious, cooperative patient. Drugs cannot be administered PO to comatose individuals or to individuals who, for whatever reason (eg, psychosis, seizure, obstinacy, nausea), are unable or unwilling to swallow medication.

Local Irritation. Some oral preparations cause local irritation of the GI tract, which can result in discomfort, nausea, and vomiting.

Comparing Oral Administration with Parenteral Administration

Because of ease, convenience, and relative safety, *oral administration is generally preferred to parenteral administration*. However, there are situations in which parenteral administration may be superior. These are

- Emergencies that require rapid onset of drug action.
- Situations in which plasma drug levels must be tightly controlled. (Because of variable absorption, oral administration does not permit tight control of drug levels.)
- Treatment with drugs that would be destroyed by gastric acidity, digestive enzymes, or hepatic enzymes if given orally (eg, insulin, penicillin G, nitroglycerin).

- Treatment with drugs that would cause severe local injury if administered by mouth (eg, certain anticancer agents).
- Treating a systemic disorder with drugs that cannot cross membranes (eg, quaternary ammonium compounds).
- Treating conditions for which the prolonged effects of a depot preparation might be desirable.
- Treating patients who cannot or will not take drugs orally.

Pharmaceutical Preparations for Oral Administration

There are several kinds of "packages" (formulations) into which a drug can be put for oral administration. Three such formulations—*tablets*, *enteric-coated preparations*, and *sustained-release preparations*—are discussed below.

Before we discuss drug formulations, it will be helpful to define two terms: *chemical equivalence* and *bioavailability*. Drug preparations are considered *chemically equivalent* if they contain the same amount of the identical chemical compound (drug). Preparations are considered equal in *bioavailability* if the drug they contain is absorbed at the same rate and to the same extent. Please note that it is possible for two formulations of the same drug to be chemically equivalent while differing in bioavailability.

Tablets. A tablet is a mixture of a drug plus binders and fillers, all of which have been compressed together. Tablets made by different manufacturers can differ in their rates of

disintegration and dissolution, causing differences in bioavailability. As a result, two tablets that contain the same amount of the same drug can differ with respect to onset and intensity of effects.

Enteric-Coated Preparations. Enteric-coated preparations consist of drugs that have been covered with a material designed to dissolve in the intestine but not the stomach. Materials used for enteric coatings include fatty acids, waxes, and shellac. Because enteric-coated preparations release their contents into the intestine and not the stomach, these preparations are employed for two general purposes: (1) to protect drugs from acid and pepsin in the stomach and (2) to protect the stomach from drugs that can cause gastric discomfort.

The primary disadvantage of enteric-coated preparations is that absorption can be even more variable than with standard tablets. Because gastric emptying time can vary from minutes up to 12 hours, and because enteric-coated preparations cannot be absorbed until they leave the stomach, variations in gastric emptying time can alter time of onset. Furthermore, enteric coatings sometimes fail to dissolve, thereby allowing medication to pass through the GI tract without being absorbed at all.

Sustained-Release Preparations. Sustained-release formulations are capsules filled with tiny spheres that contain the actual drug; the individual spheres have coatings that dissolve at variable rates. Because some spheres dissolve more slowly than others, drug is released steadily throughout the day. The primary advantage of sustained-release preparations is that they permit a reduction in the number of daily doses. These formulations have the additional advantage of producing relatively steady drug levels over an extended time (much like giving a drug by infusion). The major disadvantages of sustained-release formulations are high cost and the potential for variable absorption.

Additional Routes of Administration

Drugs can be administered by a number of routes in addition to those already discussed. Drugs can be applied *topically* for local therapy of the skin, eyes, ears, nose, mouth, and vagina. In a few cases, topical agents (eg, nitroglycerin, nicotine, testosterone, estrogen) are formulated for *transdermal* absorption into the systemic circulation. Some drugs are *inhaled* to elicit local effects in the lung, especially in the treatment of asthma. Other inhalational agents (eg, volatile anesthetics, oxygen) are used for their systemic effects. *Rectal suppositories* may be employed for local effects or for effects throughout the body. *Vaginal suppositories* may be employed to treat local disorders. For management of some conditions, drugs must be given by *direct injection into a specific site* (eg, heart, joints, nerves, CNS). The unique characteristics of these routes are addressed throughout the book as we discuss specific drugs that employ them.

DISTRIBUTION

Distribution is defined as *the movement of drugs throughout the body*. Drug distribution is determined by three major factors: blood flow to tissues, the ability of a drug to exit the vascular system, and, to a lesser extent, the ability of a drug to enter cells.

Blood Flow to Tissues

In the first phase of distribution, drugs are carried by the blood to the tissues and organs of the body. The rate at which drugs are delivered to a particular tissue is determined by blood flow to that tissue. Since most tissues are well perfused, regional blood flow is rarely a limiting factor in drug distribution.

There are two pathologic conditions—abscesses and tumors—in which low regional blood flow can affect drug therapy. An abscess is a pus-filled pocket of infection that has no internal blood vessels. Because abscesses lack a blood supply, antibiotics cannot reach the bacteria within. Accordingly, if drug therapy is to be effective, the abscess must first be surgically drained.

Solid tumors have a limited blood supply. Although blood flow to the outer regions of tumors is relatively high, blood flow becomes progressively lower toward the core. As a result, we cannot achieve high drug levels deep inside tumors. Limited blood flow is a major reason why solid tumors are resistant to drug therapy.

Exiting the Vascular System

After a drug has been delivered to an organ or tissue via the blood, the next step is to exit the vasculature. Since most drugs do not produce their effects within the blood, the ability to leave the vascular system is an important determinant of drug actions. Exiting the vascular system is also necessary for drugs to undergo metabolism and excretion. Drugs in the vascular system leave the blood at capillary beds.

Typical Capillary Beds

Most capillary beds offer no resistance to the departure of drugs. Why? Because, in most tissues, drugs can leave the vasculature simply by passing through pores in the capillary wall. Since drugs pass *between* capillary cells rather than *through* them, movement into the interstitial space is not impeded. The exit of drugs from a typical capillary bed is depicted in Figure 4-7.

The Blood-Brain Barrier

The term *blood-brain barrier* (BBB) refers to the unique anatomy of capillaries in the CNS. As shown in Figure 4-9, there are *tight junctions* between the cells that compose the walls of most capillaries in the CNS. These junctions are so tight that they prevent drug passage. Consequently, in order to leave the blood and reach sites of action within the brain, a drug must be able to pass *through* cells of the capillary wall. Only drugs that are *lipid soluble* or have a *transport system* can cross the BBB to a significant degree.

Recent evidence indicates that, in addition to tight junctions, the BBB has another protective component: *P-glycoprotein*. As noted earlier, P-glycoprotein is a transporter that pumps a variety of drugs out of cells. In capillaries of the CNS, P-glycoprotein pumps drugs back into the blood, and thereby limits their access to the brain.

The presence of the blood-brain barrier is a mixed blessing. The good news is that the barrier protects the brain from injury by potentially toxic substances. The bad news is that the barrier can be a significant obstacle to therapy of CNS disorders. The barrier can, for example, impede access of antibiotics to CNS infections.

The blood-brain barrier is not fully developed at birth. As a result, newborns have heightened sensitivity to medicines

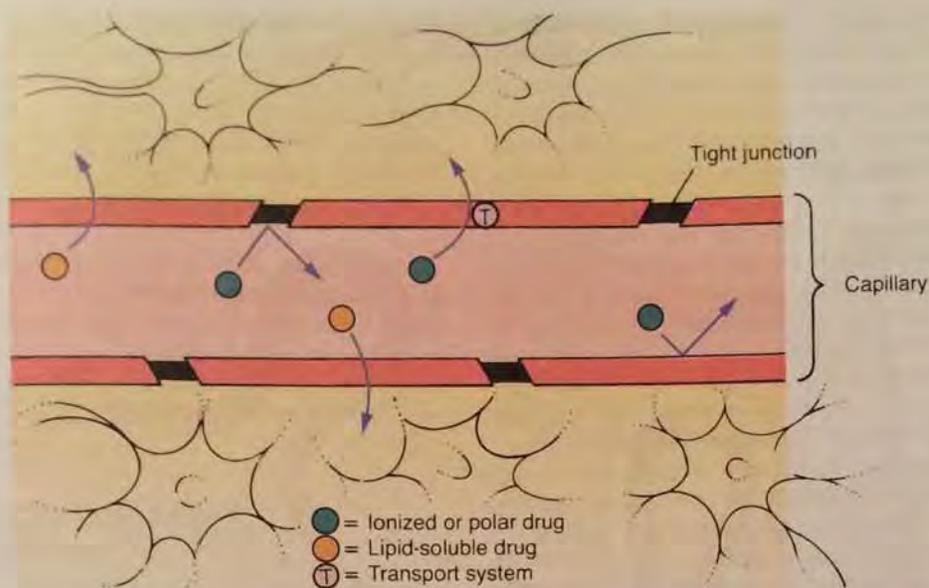


Figure 4-9 ■ Drug movement across the blood-brain barrier.

Tight junctions between cells that compose the walls of capillaries in the CNS prevent drugs from passing between cells to exit the vascular system. Consequently, in order to reach sites of action within the brain, a drug must pass directly through cells of the capillary wall. To do this, the drug must be lipid soluble or be able to use an existing transport system.

that act on the brain. Likewise, neonates are especially vulnerable to CNS poisons.

Placental Drug Transfer

The membranes of the placenta separate the maternal circulation from the fetal circulation (Fig. 4-10). *The membranes of the placenta do NOT constitute an absolute barrier to the passage of drugs.* The same factors that determine the movement of drugs across other membranes determine the movement of drugs across the placenta. Accordingly, lipid-soluble, nonionized compounds readily pass from the maternal bloodstream into the blood of the fetus. In contrast, compounds that are ionized, highly polar, or protein bound (see below) are largely excluded—as are drugs that are substrates for P-glycoprotein, a transporter that can pump a variety of drugs out of placental cells into the maternal blood.

Drugs that have the ability to cross the placenta can cause serious harm. Some compounds can cause birth defects, ranging from low birth weight to mental retardation to gross malformations. (Recall the thalidomide experience.) If a pregnant woman is a habitual user of opioids (eg, heroin), her child will be born drug dependent, and hence will need treatment with a heroin substitute to prevent withdrawal. The use of respiratory depressants (anesthetics and analgesics) during delivery can depress respiration in the neonate. Accordingly, infants exposed to respiratory depressants must be monitored until breathing has normalized.

Protein Binding

Drugs can form reversible bonds with various proteins in the body. Of all the proteins with which drugs can bind, *plasma albumin* is the most important, being the most abundant protein in plasma. Like other proteins, albumin is a large molecule, having a molecular weight of 69,000. Be-

cause of its size, *albumin always remains in the bloodstream:* Albumin is too large to squeeze through pores in the capillary wall, and no transport system exists by which it might leave.

Figure 4-11A depicts the binding of drug molecules to albumin. Note that the drug molecules are much smaller than albumin. (The molecular mass of the average drug is about 300 to 500 compared with 69,000 for albumin.) As indicated by the two-way arrows, binding between albumin and drugs is *reversible*. Hence, drugs may be *bound* or *unbound* (free).

Even though a drug can bind albumin, only some molecules will be bound at any moment. The percentage of drug molecules that are bound is determined by the strength of the attraction between albumin and the drug. For example, the attraction between albumin and warfarin (an anticoagulant) is strong, causing nearly all (99%) of the warfarin molecules in plasma to be bound, leaving only 1% free. For gentamicin (an antibiotic), the ratio of bound to free is quite different; since the attraction between gentamicin and albumin is relatively weak, less than 10% of the gentamicin molecules in plasma are bound, leaving more than 90% free.

An important consequence of protein binding is restriction of drug distribution. Because albumin is too large to leave the bloodstream, drug molecules that are bound to albumin cannot leave either (Fig. 4-11B). As a result, bound molecules cannot reach their sites of action, metabolism, or excretion.

In addition to restricting drug distribution, protein binding can be a source of drug interactions. As suggested by Figure 4-11A, each molecule of albumin has only a few sites to which drug molecules can bind. Because the number of binding sites is limited, drugs with the ability to bind albumin will

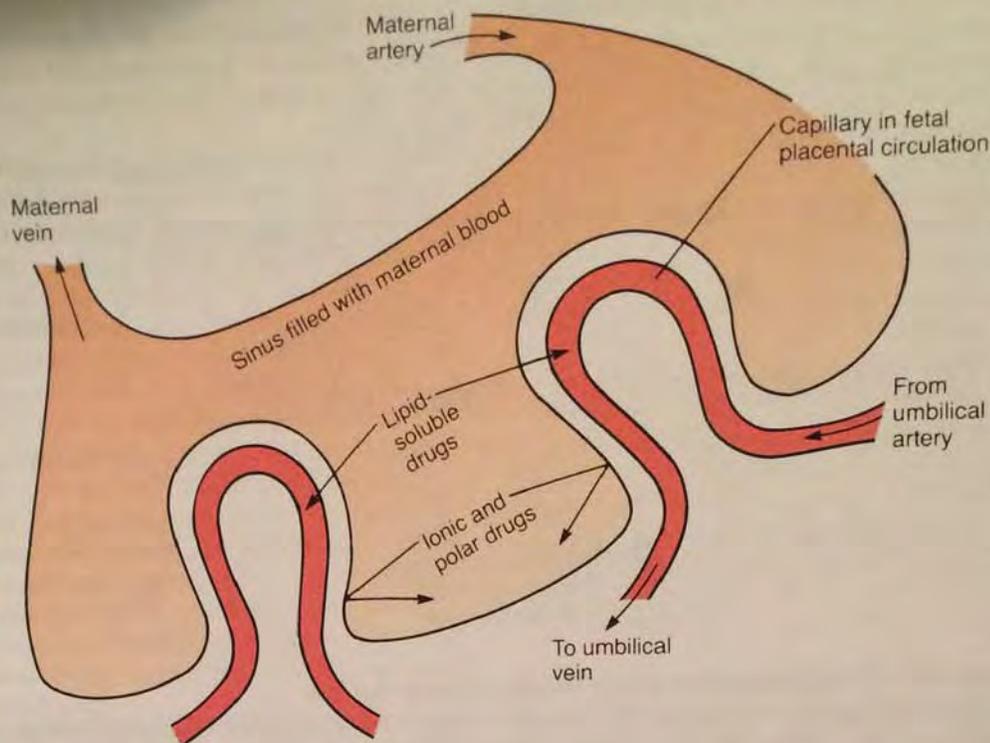


Figure 4-10 ■ Placental drug transfer.

To enter the fetal circulation, drugs must cross membranes of the maternal and fetal vascular systems. Lipid-soluble drugs can readily cross these membranes and enter the fetal blood, whereas ions and polar molecules are prevented from reaching the fetal blood.

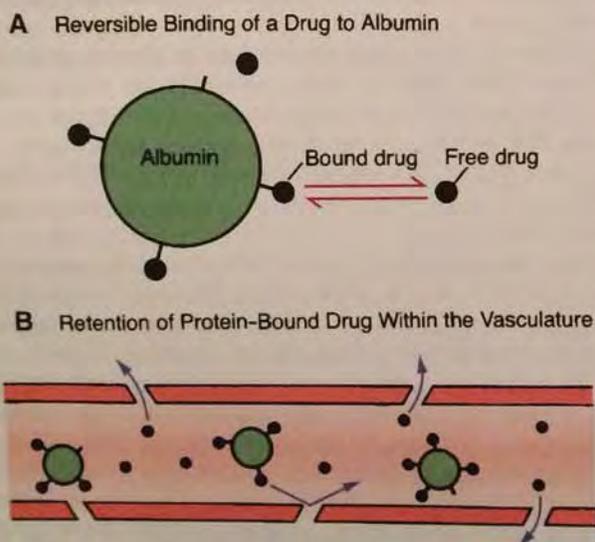


Figure 4-11 ■ Protein binding of drugs.

A, Albumin is the most prevalent protein in plasma and the most important of the proteins to which drugs bind. **B**, Only unbound (free) drug molecules can leave the vascular system. Bound molecules are too large to fit through the pores in the capillary wall.

compete with one another for those sites. As a result, one drug can displace another from albumin, causing the free concentration of the displaced drug to rise. By increasing levels of free drug, competition for binding can increase the intensity of drug responses. Toxicity can result.

Entering Cells

Some drugs must enter cells to reach their sites of action, and practically all drugs must enter cells to undergo metabolism and excretion. The factors that determine the ability of a drug to cross cell membranes are the same factors that determine the passage of drugs across all other membranes, namely, lipid solubility, the presence of a transport system, or both.

As discussed in Chapter 5, many drugs produce their effects by binding with receptors located on the external surface of the cell membrane. Obviously, these drugs do not need to cross the cell membrane to act.

METABOLISM

Drug metabolism, also known as *biotransformation*, is defined as the enzymatic alteration of drug structure. Most drug metabolism takes place in the liver.

Hepatic Drug-Metabolizing Enzymes

Most drug metabolism that takes place in the liver is performed by the *hepatic microsomal enzyme system*, also known as the *P450 system*. The term *P450* refers to *cytochrome P450*, a key component of this enzyme system.

It is important to appreciate that cytochrome P450 is not a single molecular entity, but rather a group of 12 closely related enzyme families. Three of the cytochrome P450 (CYP) families—designated CYP1, CYP2, and CYP3—metabolize drugs. The other nine families metabolize endogenous compounds (eg, steroids, fatty acids). Each of the three P450

families that metabolize drugs is itself composed of multiple forms, each of which metabolizes only certain drugs. To identify the individual forms of cytochrome P450, we use designations such as CYP1A2, CYP2D6, and CYP3A4, indicating specific members of the CYP1, CYP2, and CYP3 families, respectively. I mention this nomenclature only so that it will be familiar when you come across it in your reading. This information is not intended for memorization.

Hepatic microsomal enzymes are capable of catalyzing a wide variety of reactions using drugs as substrates. Some of these reactions are illustrated in Figure 4-12. As these examples indicate, drug metabolism doesn't always result in the breakdown of drugs into smaller molecules; drug metabolism can also result in the synthesis of a molecule that is larger than the parent drug.

Therapeutic Consequences of Drug Metabolism

Drug metabolism has six possible consequences of therapeutic significance:

- Accelerated renal excretion of drugs
- Drug inactivation
- Increased therapeutic action
- Activation of "prodrugs"
- Increased toxicity
- Decreased toxicity

The reactions shown in Figure 4-12 illustrate these outcomes.

Accelerated Renal Drug Excretion. *The most important consequence of drug metabolism is promotion of renal drug excretion.* As discussed below under *Renal Drug Excretion*, the kidney, which is the major organ of drug excretion, is unable to excrete drugs that are highly lipid soluble. Hence, by converting lipid-soluble drugs into more hydrophilic (water-soluble) forms, metabolic conversion can accelerate renal excretion of many agents. For certain highly lipid-soluble drugs (eg, thiopental), complete renal excretion would take years were it not for their conversion into more hydrophilic forms.

What kinds of metabolic transformations enhance excretion? Two important mechanisms are shown in Figure 4-12, panels 1A and 1B. In panel 1A, a simple structural change (addition of a hydroxyl group) converts pentobarbital into a more polar (less lipid-soluble) form. In panel 1B, a highly lipophilic drug (phenytoin) is converted into a highly hydrophilic form by undergoing *glucuronidation*, a process in which a hydrophilic glucose derivative (glucuronic acid) is attached to phenytoin. As a result of glucuronidation, phenytoin is rendered much more water soluble, and hence can be rapidly excreted by the kidneys.

It should be noted that not all glucuronides are excreted by the kidneys. In many cases, glucuronidated drugs are secreted into the bile and then transported to the duodenum (via the bile duct), after which they can undergo excretion in the feces. However, in some cases, secretion into the bile can result in *enterohepatic recirculation* (see below).

Drug Inactivation. Drug metabolism can convert pharmacologically active compounds to inactive forms. This process is illustrated by the conversion of procaine (a local anesthetic) into *para*-aminobenzoic acid (PABA), an inactive metabolite (see Fig. 4-12, panel 2).

Increased Therapeutic Action. Metabolism can increase the effectiveness of some drugs. This concept is illustrated by the conversion of codeine into morphine (see Fig. 4-12, panel 3). The analgesic activity of morphine is so much greater than that of codeine that formation of morphine may account for virtually all the pain relief that occurs following codeine administration.

Activation of Prodrugs. A *prodrug* is a compound that is pharmacologically inactive as administered and then undergoes conversion to its active form within the body. Activation of a prodrug is illustrated by the metabolic conversion of prazepam into desmethyldiazepam (see Fig. 4-12, panel 4). (Prazepam is a close relative of diazepam, a drug familiar to us under the trade name Valium.)

Increased or Decreased Toxicity. By converting drugs into inactive forms, metabolism can decrease toxicity. Conversely, metabolism can increase the potential for harm by converting relatively safe compounds into forms that are toxic. Increased toxicity is illustrated by the conversion of acetaminophen [Tylenol, others] into a hepatotoxic metabolite (see Fig. 4-12, panel 5). It is this product of metabolism, and not acetaminophen itself, that causes injury when acetaminophen is taken in overdose.

Special Considerations in Drug Metabolism

Several factors can influence the rate at which drugs are metabolized. These must be accounted for in drug therapy.

Age. The drug-metabolizing capacity of infants is limited. The liver does not develop its full capacity to metabolize drugs until about 1 year after birth. During the time prior to hepatic maturation, infants are especially sensitive to drugs, and care must be taken to avoid injury.

Induction of Drug-Metabolizing Enzymes. Some drugs act on the liver to increase rates of drug metabolism. For example, when phenobarbital is administered for several days, it can cause the drug-metabolizing capacity of the liver to double. Phenobarbital increases metabolism by causing the liver to synthesize drug-metabolizing enzymes. This process of stimulating enzyme synthesis is known as *induction*.

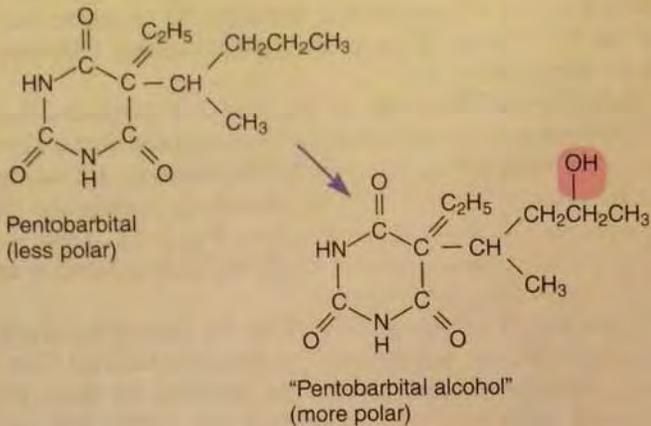
Induction of drug-metabolizing enzymes can have two therapeutic consequences. First, by stimulating the liver to produce more drug-metabolizing enzymes, a drug can increase the rate of its own metabolism, thereby necessitating an increase in its dosage to maintain therapeutic effects. Second, induction of drug-metabolizing enzymes can accelerate the metabolism of other drugs used concurrently, necessitating an increase in their dosages.

First-Pass Effect. The term *first-pass effect* refers to the rapid hepatic inactivation of certain oral drugs. As discussed earlier, when oral drugs are absorbed from the GI tract, they are carried directly to the liver via the hepatic portal vein. If the capacity of the liver to metabolize a drug is extremely high, that drug can be completely inactivated on its first pass through the liver. As a result, no therapeutic effects can occur. To circumvent the first-pass effect, a drug that undergoes rapid hepatic metabolism is often administered parenterally. This permits the drug to temporarily bypass the liver, thereby allowing it to reach therapeutic levels in the systemic blood.

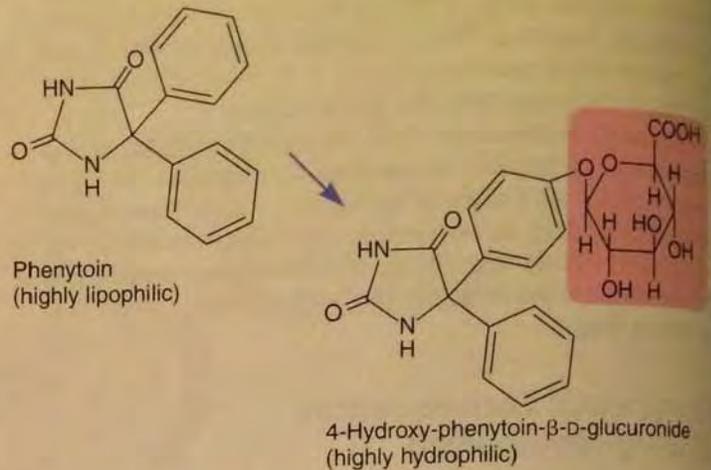
Nitroglycerin is the classic example of a drug that undergoes such rapid hepatic metabolism that it is largely without

1. PROMOTION OF RENAL DRUG EXCRETION

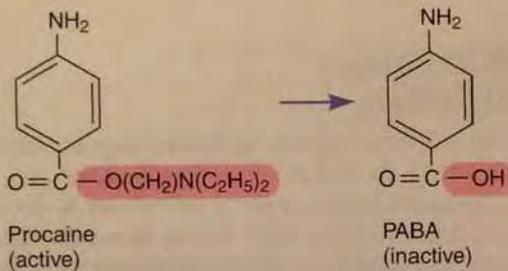
A. Increasing Polarity



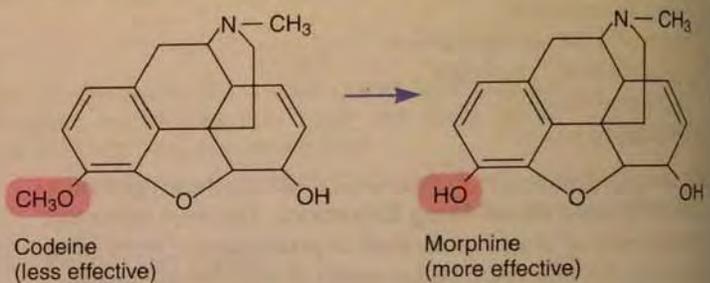
B. Glucuronidation



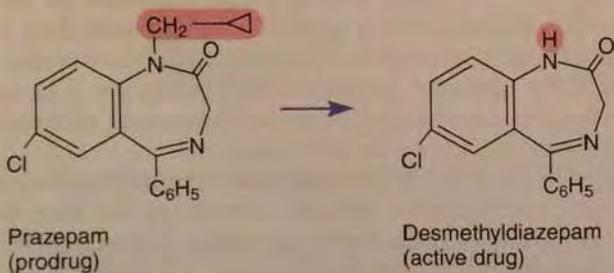
2. INACTIVATION OF DRUGS



3. INCREASED EFFECTIVENESS OF DRUGS



4. ACTIVATION OF PRODRUGS



5. INCREASED DRUG TOXICITY

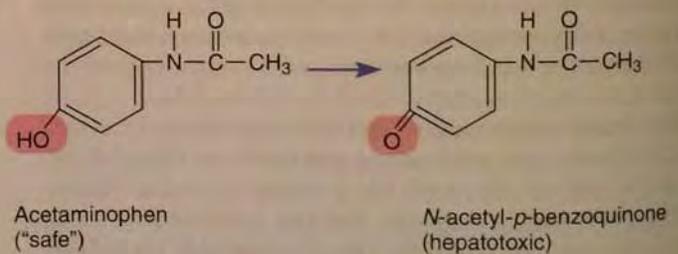


Figure 4-12 ■ Therapeutic consequences of drug metabolism. (See text for details.)

effect following oral administration. However, when administered sublingually (under the tongue), nitroglycerin is very active. Sublingual administration is effective because it permits nitroglycerin to be absorbed directly into the systemic circulation. Once in the circulation, the drug is carried to its sites of action prior to passage through the liver. Hence, therapeutic action can be exerted before the drug is exposed to hepatic enzymes.

Nutritional Status. Hepatic drug-metabolizing enzymes require a number of cofactors to function. In the malnourished patient, these cofactors may be deficient, causing drug metabolism to be compromised.

Competition Between Drugs. When two drugs are metabolized by the same metabolic pathway, they may compete with each other for metabolism, and may thereby decrease the rate at which one or both agents are metabolized. If metabolism is depressed enough, a drug can accumulate to dangerous levels.

Enterohepatic Recirculation

As noted earlier and depicted in Figure 4-8, enterohepatic recirculation is a repeating cycle in which a drug is transported from the liver into the duodenum (via the bile duct)

and then back to the liver (via the portal blood). It is important to note, however, that only certain drugs can participate. Specifically, the process is limited to drugs that have undergone *glucuronidation* (see Fig. 4-12, panel 1B). Following glucuronidation, these drugs can enter the bile and then pass to the duodenum. Once there, they can be hydrolyzed by intestinal beta-glucuronidase, an enzyme that breaks the bond between the original drug and the glucuronide moiety, thereby releasing free drug. Because the free drug is more lipid soluble than the glucuronidated form, the free drug can undergo reabsorption across the intestinal wall, followed by transport back to the liver, where the cycle can start again. Because of enterohepatic recycling, drugs can remain in the body much longer than they otherwise would.

Do all glucuronidated drugs undergo extensive recycling? No. Glucuronidated drugs that are more stable to hydrolysis will be excreted intact in the feces, without significant recirculation.

EXCRETION

Drug excretion is defined as *the removal of drugs from the body*. Drugs and their metabolites can exit the body in urine, bile, sweat, saliva, breast milk, and expired air. The most important organ for drug excretion is the kidney.

Renal Drug Excretion

The kidneys account for the majority of drug excretion. When the kidneys are healthy, they serve to limit the duration of action of many drugs. Conversely, if renal failure occurs, both the duration and intensity of drug responses may increase.

Steps in Renal Drug Excretion

Urinary excretion is the net result of three processes: (1) glomerular filtration, (2) passive tubular reabsorption, and (3) active tubular secretion (Fig. 4-13).

Glomerular Filtration. Renal excretion begins at the glomerulus of the kidney tubule. The glomerulus consists of a capillary network surrounded by Bowman's capsule; small pores perforate the capillary walls. As blood flows through the glomerular capillaries, fluids and small molecules—including drugs—are forced through the pores of the capillary wall. This process, called glomerular filtration, moves drugs from the blood into the tubular urine. Blood cells and large molecules (eg, proteins) are too big to pass through the capillary pores and therefore do not undergo filtration. Because large molecules are not filtered, drugs bound to albumin remain behind in the blood.

Passive Tubular Reabsorption. As depicted in Figure 4-13, the vessels that deliver blood to the glomerulus return to proximity with the renal tubule at a point distal to the glomerulus. At this distal site, drug concentrations in the blood are lower than drug concentrations in the tubule. This concentration gradient acts as a driving force to move drugs from the lumen of the tubule back into the blood. Because lipid-soluble drugs can readily cross the membranes that compose the tubular and vascular walls, *drugs that are lipid soluble undergo passive reabsorption from the tubule back into the blood*. In contrast, drugs that are not lipid soluble (ions and polar compounds) remain in the urine to be excreted. By converting

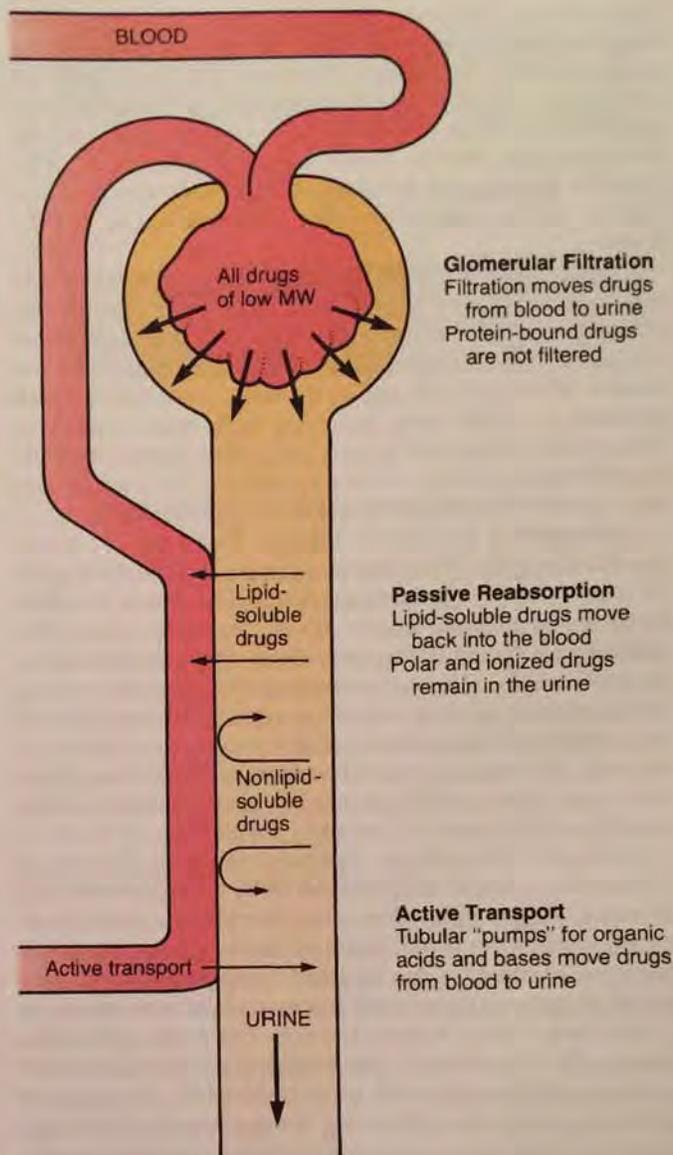


Figure 4-13 ■ Renal drug excretion.

(MW = molecular weight.) (Redrawn from Binns TB [ed]: *Absorption and Distribution of Drugs*. Edinburgh: Churchill Livingstone, 1964.)

lipid-soluble drugs into more polar forms, drug metabolism reduces passive reabsorption of drugs and thereby accelerates their excretion.

Active Tubular Secretion. There are active transport systems in the kidney tubules that pump drugs from the blood to the tubular urine. The tubules have two primary classes of pumps, one for organic acids and one for organic bases. In addition, tubule cells contain P-glycoprotein, which can pump a variety of drugs into the urine. These pumps have a relatively high capacity and play a significant role in excreting certain compounds.

Factors That Modify Renal Drug Excretion

pH-Dependent Ionization. The phenomenon of pH-dependent ionization can be used to accelerate renal excretion of drugs. Recall that passive tubular reabsorption is limited to

lipid-soluble compounds. Because ions are not lipid soluble, drugs that are ionized at the pH of tubular urine will remain in the tubule and be excreted. Consequently, by manipulating urinary pH in such a way as to promote the ionization of a drug, we can decrease passive reabsorption back into the blood, and can thereby hasten the drug's elimination. This principle has been employed to promote the excretion of poisons as well as medications that have been taken in toxic doses.

The treatment of aspirin poisoning provides an example of how manipulation of urinary pH can be put to therapeutic advantage. When children have been exposed to toxic doses of aspirin, they can be treated, in part, by giving an agent that elevates urinary pH (ie, makes the urine more basic). Since aspirin is an acidic drug, and since acids tend to ionize in basic media, elevation of urinary pH causes more of the aspirin molecules in urine to become ionized. As a result, less drug is passively reabsorbed and hence more is excreted.

Competition for Active Tubular Transport. Competition between drugs for active tubular transport can delay renal excretion, thereby prolonging effects. The active transport systems of the renal tubules can be envisioned as motor-driven revolving doors that carry drugs from the plasma into the renal tubules. These "revolving doors" can carry only a limited number of drug molecules per unit of time. Accordingly, if there are too many molecules present, some must wait their turn. Because of competition, if we administer two drugs at the same time, and if both use the same transport system, excretion of each will be delayed by the presence of the other.

Competition for transport has been employed clinically to prolong the effects of drugs that normally undergo rapid renal excretion. For example, when administered alone, penicillin is rapidly cleared from the blood by active tubular transport. Excretion of penicillin can be delayed by concurrent administration of probenecid, an agent that is removed from the blood by the same tubular transport system that pumps penicillin. Hence, if a large dose of probenecid is administered, renal excretion of penicillin will be delayed while the transport system is occupied with moving the probenecid. Years ago, when penicillin was expensive to produce, combined use with probenecid was common. Today penicillin is cheap. As a result, rather than using probenecid to preserve penicillin levels, we simply give penicillin in huge doses.

Age. The kidneys of newborns are not fully developed. Until their kidneys reach full capacity (a few months after birth), infants have a limited capacity to excrete drugs. This must be accounted for when medicating an infant.

Nonrenal Routes of Drug Excretion

In most cases, excretion of drugs by nonrenal routes has minimal clinical significance. However, in certain situations, nonrenal excretion can have important therapeutic and toxicologic consequences.

Breast Milk

Drugs taken by breast-feeding women can undergo excretion into milk. As a result, breast-feeding can expose the nursing infant to drugs. The factors that influence the appearance of drugs in breast milk are the same factors that determine the passage of drugs across membranes. Accordingly, lipid-soluble drugs have ready access to breast milk,

whereas drugs that are polar, ionized, or protein bound cannot enter in significant amounts. Because infants may be harmed by compounds excreted in breast milk, nursing mothers should avoid all drugs. If a woman *must* take medication, she should consult with her prescriber to ensure that the drug will not reach concentrations in her milk high enough to harm her baby.

Other Nonrenal Routes of Excretion

The *bile* is an important route of excretion for certain drugs. Recall that bile is secreted into the small intestine and then leaves the body in the feces. In some cases, drugs entering the intestine in bile may undergo reabsorption back into the portal blood. This reabsorption, referred to as *enterohepatic recirculation*, can substantially prolong a drug's sojourn in the body (see *Special Considerations in Drug Metabolism*).

The *lungs* are the major route by which volatile anesthetics are excreted.

Small amounts of drugs can appear in *sweat* and *saliva*. These routes have little therapeutic or toxicologic significance.

TIME COURSE OF DRUG RESPONSES

To achieve the therapeutic objective, we must control the time course of drug responses. We need to regulate the time at which drug responses start, the time they are most intense, and the time they cease. Because the four pharmacokinetic processes—absorption, distribution, metabolism, and excretion—determine how much drug will be at its sites of action at any given time, these processes are the major determinants of the time course over which drug responses take place. Having discussed the individual processes that contribute to determining the time course of drug action, we can now discuss the time course itself.

Plasma Drug Levels

In most cases, the time course of drug action bears a direct relationship to the concentration of a drug in the blood. Hence, before discussing the time course per se, we need to review several important concepts related to plasma drug levels.

Clinical Significance of Plasma Drug Levels

Clinicians frequently monitor plasma drug levels in efforts to regulate drug responses. When measurements indicate that drug levels are inappropriate, these levels can be adjusted up or down by changing dosage size, dosage timing, or both.

The practice of regulating plasma drug levels in order to control drug responses should seem a bit odd, given that (1) drug responses are related to drug concentrations at sites of action and that (2) the site of action of most drugs is not in the blood. The question arises, "Why adjust plasma levels of a drug when what really matters is the concentration of that drug at its sites of action?" The answer begins with the following observation: More often than not, it is a practical impossibility to measure drug concentrations at sites of action. For example, when a patient with epilepsy takes phenytoin (an antiseizure agent), we cannot routinely draw samples from inside the skull to see if brain levels of the medication are adequate for seizure control. Fortunately, in the case of phen-

ytom and most other drugs, it is not necessary to measure drug concentrations at actual sites of action in order to have an objective basis for adjusting dosage. Experience has shown that, for most drugs, *there is a direct correlation between therapeutic and toxic responses and the amount of drug present in plasma*. Therefore, although we can't usually measure drug concentrations at sites of action, we *can* determine plasma drug concentrations that, in turn, are highly predictive of therapeutic and toxic responses. Accordingly, the dosing objective is commonly spoken of in terms of achieving a specific plasma level of a drug.

Two Plasma Drug Levels Defined

Two plasma drug levels are of special importance: (1) the minimum effective concentration and (2) the toxic concentration. These levels are depicted in Figure 4-14 and defined below.

Minimum Effective Concentration. The minimum effective concentration (MEC) is defined as *the plasma drug level below which therapeutic effects will not occur*. Hence, to be of benefit, a drug must be present in concentrations at or above the MEC.

Toxic Concentration. Toxicity occurs when plasma drug levels climb too high. The plasma level at which toxic effects begin is termed the *toxic concentration*. Doses must be kept small enough so that the toxic concentration is not reached.

Therapeutic Range

As indicated in Figure 4-14, there is a range of plasma drug levels, falling between the MEC and the toxic concentration, that is termed the *therapeutic range*. When plasma levels are within the therapeutic range, there is enough drug present to produce therapeutic responses but not so much that toxicity results. *The objective of drug dosing is to maintain plasma drug levels within the therapeutic range.*

The width of the therapeutic range is a major determinant of the ease with which a drug can be used safely. Drugs that have a narrow therapeutic range are difficult to administer safely. Conversely, drugs that have a wide therapeutic range can be administered safely with relative ease. Acetaminophen, for example, has a relatively wide therapeutic range: The toxic concentration is about 30 times greater than the MEC. Because of this wide therapeutic range, the dosage does not need to be highly precise; a broad range of doses can be employed to produce plasma levels that will be above the MEC and below the toxic concentration. In contrast, lithium (used for bipolar disorder [manic-depressive illness]) has a very narrow therapeutic range: The toxic concentration is only 3 times greater than the MEC. Because toxicity can result from lithium levels that are not much greater than those needed for therapeutic effects, lithium dosing must be done carefully. If lithium had a wider therapeutic range, the drug would be much easier to use.

Understanding the concept of therapeutic range can facilitate patient care. Because drugs with a narrow therapeutic range are more dangerous than drugs with a wide therapeutic range, patients taking drugs with a narrow therapeutic range are the most likely to require intervention for drug-related complications. The nurse who is aware of this fact can focus attention on these patients. In contrast, the nurse who has no basis for predicting which drugs are most likely to produce toxicity has no basis for allocating attention, and therefore is

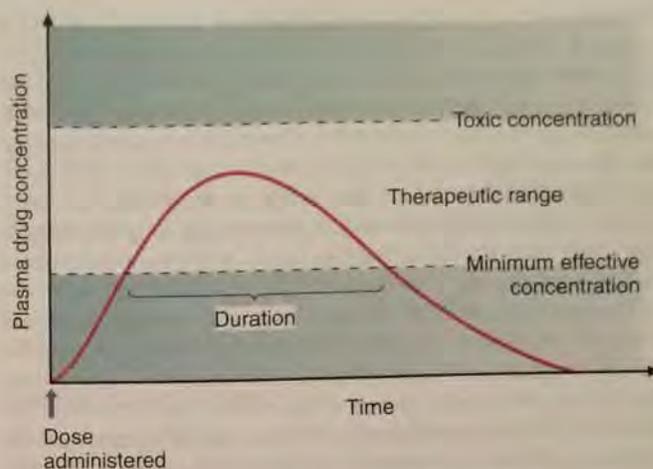


Figure 4-14 • Single-dose time course.

obliged to monitor all patients with equal diligence—a process that is both stressful and inefficient.

However, lest you get the wrong impression, the above advice should not be construed as a license to be lax about patients taking drugs that have a wide therapeutic range. Even these drugs can cause harm. Hence, although patients receiving drugs with a narrow therapeutic range should be monitored most closely, common sense dictates that patients receiving safer drugs must not be neglected.

Single-Dose Time Course

Figure 4-14 shows how plasma drug levels change over time after a single dose of an oral medication. Drug levels rise as the medicine undergoes absorption. Drug levels then decline as metabolism and excretion eliminate the drug from the body.

Because responses cannot occur until plasma drug levels have reached the MEC, there is a latent period between drug administration and onset of effects. The extent of this delay is determined by the rate of absorption.

The duration of effects is determined largely by the combination of metabolism and excretion. As long as drug levels remain above the MEC, therapeutic responses will be maintained; when levels fall below the MEC, benefits will cease. Since metabolism and excretion are the processes most responsible for causing plasma drug levels to fall, these processes are the primary determinants of how long drug effects will persist.

Drug Half-Life

Before proceeding to the topic of multiple dosing, we need to discuss the concept of half-life. When a patient ceases drug use, the combination of metabolism and excretion will cause the amount of drug in the body to decline. The half-life of a drug is an index of just how rapidly that decline occurs.

Drug half-life is defined as *the time required for the amount of drug in the body to decrease by 50%*. A few drugs have half-lives that are extremely short—on the order of minutes. In contrast, the half-lives of some drugs exceed 1 week. Drugs with short half-lives leave the body quickly. Drugs with long half-lives leave slowly.

Note that, in our definition of half-life, a *percentage*—not a specific *amount*—of drug is lost during one half-life. That is, the half-life does not specify, for example, that 2 gm or 18 mg will leave the body in a given time. Rather, the half-life tells us that, no matter what the amount of drug in the body may be, half (50%) will leave during a specified period of time (the half-life). The actual amount of drug that is lost during one half-life depends on just how much drug is present: The more drug that is in the body, the larger the amount lost during one half-life.

The concept of half-life is best understood through an example. Morphine provides a good illustration. The half-life of morphine is approximately 3 hours. By definition, this means that body stores of morphine will decrease by 50% every 3 hours—regardless of how much morphine is in the body. If there is 50 mg of morphine in the body, 25 mg (50% of 50 mg) will be lost in 3 hours; if there is only 2 mg of morphine in the body, only 1 mg (50% of 2 mg) will be lost in 3 hours. Note that, in both cases, morphine levels drop by 50% during an interval of one half-life. However, the actual *amount* lost is larger when total body stores of the drug are higher.

The half-life of a drug determines the dosing interval (ie, how much time separates each dose). For drugs with a short half-life, the dosing interval must be correspondingly short. If a long dosing interval were used, drug levels would fall below the MEC between doses, and therapeutic effects would be lost. Conversely, if a drug has a long half-life, a long time can separate doses without loss of benefits.

Drug Levels Produced with Repeated Doses

Multiple dosing leads to drug accumulation. When a patient takes a single dose of a drug, plasma levels simply go up and then come back down. In contrast, when a patient takes repeated doses of a drug, the process is more complex and results in drug accumulation. The factors that determine the rate and extent of accumulation are considered below.

The Process by Which Plateau Drug Levels Are Achieved

Administering repeated doses will cause a drug to build up in the body until a *plateau* (steady level) has been achieved. What causes drug levels to reach plateau? To begin with, common sense tells us that, if a second dose of a drug is administered before all of the prior dose has been eliminated, total body stores of that drug will be higher after the second dose than after the initial dose. As succeeding doses are administered, drug levels will climb even higher. The drug will continue to accumulate until a state has been achieved in which the amount of drug eliminated between doses equals the amount administered. *When the amount of drug eliminated between doses equals the dose administered, average drug levels will remain constant and plateau will have been reached.*

The process by which multiple dosing produces a plateau is illustrated in Figure 4-15. The drug in this figure is a hypothetical agent with a half-life of exactly 1 day. The regimen consists of a 2-gm dose administered once daily. For the purpose of illustration, we assume that absorption takes

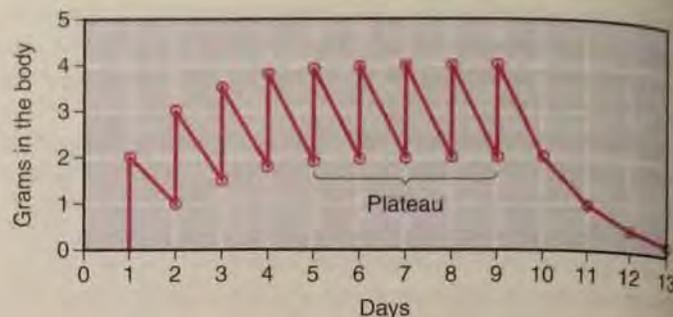


Figure 4-15 = Drug accumulation with repeated administration.

This figure illustrates the accumulation of a hypothetical drug during repeated administration. The drug has a half-life of 1 day. The dosing schedule is 2 gm given once a day on days 1 through 9. Note that plateau is reached at about the beginning of day 5 (ie, after four half-lives). Note also that, when administration is discontinued, it takes about 4 days (four half-lives) for most (94%) of the drug to leave the body.

place instantly. Upon giving the first 2-gm dose (day 1 in the figure), total body stores go from zero to 2 gm. Within one half-life (1 day), body stores drop by 50%—from 2 gm down to 1 gm. At the beginning of day 2, the second 2-gm dose is given, causing body stores to rise from 1 gm up to 3 gm. Over the next day (one half-life), body stores again drop by 50%, this time from 3 gm down to 1.5 gm. When the third dose is given, body stores go from 1.5 gm up to 3.5 gm. Over the next half-life, stores drop by 50% down to 1.75 gm. When the fourth dose is given, drug levels climb to 3.75 gm and, between doses, levels again drop by 50%, this time to approximately 1.9 gm. When the fifth dose is given (at the beginning of day 5), drug levels go up to about 3.9 gm. This process of accumulation continues until body stores reach 4 gm. When total body stores of this drug are 4 gm, 2 gm will be lost each day (ie, over one half-life). Since a 2-gm dose is being administered each day, when body stores reach 4 gm, the amount lost between doses will equal the dose administered. At this point, body stores will simply alternate between 4 gm and 2 gm; average body stores will be stable, and plateau will have been reached. Note that the reason that plateau is finally reached is that the actual amount of drug lost between doses gets larger each day. That is, although 50% of total body stores is lost each day, the *amount* in grams grows progressively larger because total body stores are getting larger day by day. Plateau is reached when the amount lost between doses grows to be as large as the amount administered.

Time to Plateau

When a drug is administered repeatedly in the same dose, *plateau will be reached in approximately four half-lives.* For the hypothetical agent illustrated in Figure 4-15, total body stores approached their peak near the beginning of day 5, or approximately 4 full days after treatment began. Because the half-life of this drug is 1 day, reaching plateau in 4 days is equivalent to reaching plateau in four half-lives.

As long as dosage remains constant, the time required to reach plateau is independent of dosage size. Put another

way, the time required to reach plateau when giving repeated large doses of a particular drug is identical to the time required to reach plateau when giving repeated small doses of that drug. Referring to the drug in Figure 4-15, just as it took four half-lives (4 days) to reach plateau when a dose of 2 gm was administered daily, it would also take four half-lives to reach plateau if a dose of 4 gm were administered daily. It is true that the *height* of the plateau would be greater if a 4-gm dose were given, but the time required to reach plateau would not be altered by the increase in dosage. To confirm this statement, substitute a dose of 4 gm in the exercise we just went through and see when plateau is reached.

Techniques for Reducing Fluctuations in Drug Levels

As we can see in Figure 4-15, when a drug is administered repeatedly, its level will fluctuate between doses. The highest level is referred to as the *peak concentration*, and the lowest level is referred to as the *trough concentration*. The acceptable height of the peaks and troughs will depend upon the drug's therapeutic range: The peaks must be kept below the toxic concentration, and the troughs must be kept above the MEC. If there is not much difference between the toxic concentration and the MEC, then fluctuations must be kept to a minimum.

Three techniques can be employed to reduce fluctuations in drug levels. One technique is to *administer drugs by continuous infusion*. With this procedure, plasma levels can be kept nearly constant. Another is to *administer a depot preparation*, which releases the drug slowly and steadily. The third is to *reduce both the size of each dose and the dosing interval* (keeping the total daily dose constant). For example, rather than giving the drug from Figure 4-15 in 2-gm doses once every 24 hours, we could give this drug in 1-gm doses every 12 hours. With this altered dosing schedule, the total daily dose would remain unchanged, as would total body stores at plateau. However, instead of fluctuating over a range of 2 gm between doses, levels would fluctuate over a range of 1 gm.

Loading Doses Versus Maintenance Doses

As discussed above, if we administer a drug in repeated doses of *equal size*, an interval equivalent to about four half-lives is required to achieve plateau. For drugs whose half-lives are long, achieving plateau could take days or even weeks. When plateau must be achieved more quickly, a large initial dose can be administered. This large initial dose is called a *loading dose*. After high drug levels have been established with a loading dose, plateau can be maintained by giving smaller doses. These smaller doses are referred to as *maintenance doses*.

The claim that use of a loading dose will shorten the time to plateau may appear to contradict an earlier statement,

which said that the time to plateau is not affected by dosage size. However, there is no contradiction. For any *specified dosage*, it will always take about four half-lives to reach plateau. When a loading dose is administered followed by maintenance doses, we have not reached plateau *for the loading dose*. Rather, we have simply used the loading dose to rapidly produce a drug level equivalent to the plateau level for a smaller dose. If we wished to achieve plateau level for the loading dose, we would be obliged to either administer repeated doses equivalent to the loading dose for a period of four half-lives or administer a dose even larger than the original loading dose. Think about it.

Decline from Plateau

When drug administration is discontinued, most (94%) of the drug in the body will be eliminated over an interval equal to about four half-lives. This statement can be validated with simple arithmetic. Let's consider a patient who has been taking morphine. In addition, let's assume that, at the time dosing ceased, the total body store of morphine was 40 mg. Within one half-life after drug withdrawal, morphine stores will decline by 50%—down to 20 mg. During the second half-life, stores will again decline by 50%, dropping from 20 mg to 10 mg. During the third half-life, the level will decline once more by 50%—from 10 mg down to 5 mg. During the fourth half-life, the level will again decline by 50%—from 5 mg down to 2.5 mg. Hence, over a period of four half-lives, total body stores of morphine will drop from an initial level of 40 mg down to 2.5 mg, an overall decline of 94%. Most of the drug in the body will be cleared within four half-lives.

The time required for drugs to leave the body is important when toxicity develops. Let's consider the elimination of digitoxin (a drug once used for heart failure). Digitoxin, true to its name, is a potentially dangerous drug with a narrow therapeutic range. In addition, the half-life of digitoxin is prolonged—about 7 days. What will be the consequence of digitoxin overdose? Toxic levels of the drug will remain in the body for a long time: Since digitoxin has a half-life of 7 days, and since four half-lives are required for most of the drug to be cleared from the body, it could take weeks for digitoxin stores to fall to a safe level. During the time that excess drug remains in the body, significant effort will be required to keep the patient alive. If digitoxin had a shorter half-life, body stores would decline more rapidly, thereby making management of overdose less difficult. (Because of its long half-life and potential for toxicity, digitoxin has been replaced by digoxin, a drug with identical actions but a much shorter half-life.)

It is important to note that the concept of half-life does not apply to the elimination of all drugs. A few agents, most notably ethanol (alcohol), leave the body at a *constant rate*, regardless of how much is present. The implications of this kind of decline for ethanol are discussed in Chapter 38.

KEY POINTS

- Pharmacokinetics consists of four basic processes: absorption, distribution, metabolism, and excretion.
- Pharmacokinetic processes determine the concentration of a drug at its sites of action, and thereby determine the intensity and time course of responses.
- To move around the body, drugs must cross membranes, either by (1) passing through pores, (2) undergoing transport, or (3) penetrating the membrane directly.
- P-glycoprotein—found in the liver, kidney, placenta, intestine, and brain capillaries—can transport a variety of drugs out of cells.
- To cross membranes, most drugs must dissolve directly into the lipid bilayer of the membrane. Accordingly, lipid-soluble drugs can cross membranes easily, whereas drugs that are polar or ionized cannot.
- Acidic drugs ionize in basic (alkaline) media, whereas basic drugs ionize in acidic media.
- Absorption is defined as the movement of a drug from its site of administration into the blood.
- Absorption is enhanced by rapid drug dissolution, high lipid solubility of the drug, a large surface area for absorption, and high blood flow at the site of administration.
- Intravenous administration has several advantages: rapid onset, precise control over the amount of drug entering the blood, suitability for use with large volumes of fluid, and suitability for irritant drugs.
- Intravenous administration has several disadvantages: high cost; difficulty; inconvenience; danger because of irreversibility; and the potential for fluid overload, infection, and embolism.
- Intramuscular administration has two advantages: suitability for insoluble drugs and suitability for depot preparations.
- Intramuscular administration has two disadvantages: inconvenience and the potential for discomfort.
- Subcutaneous administration has the same advantages and disadvantages as IM administration.
- Oral administration has the advantages of ease, convenience, economy, and safety.
- The principal disadvantages of oral administration are high variability and possible inactivation by stomach acid, digestive enzymes, and liver enzymes (because oral drugs must pass through the liver before reaching the general circulation).
- Enteric-coated oral formulations are designed to release their contents in the small intestine—not in the stomach.
- Sustained-release oral formulations are designed to release their contents slowly, thereby permitting a longer interval between doses.
- Distribution is defined as the movement of drugs throughout the body.
- In most tissues, drugs can easily leave the vasculature through spaces between the cells that compose the capillary wall.
- The term *blood-brain barrier* refers to the presence of tight junctions between the cells that compose capillary walls in the CNS. Because of this barrier, drugs must pass through the cells of the capillary wall (rather than between them) in order to reach the CNS.
- The membranes of the placenta do not constitute an absolute barrier to the passage of drugs. The same factors that determine drug movements across all other membranes determine the movement of drugs across the placenta.
- Many drugs bind reversibly to plasma albumin. While bound to albumin, drug molecules cannot leave the vascular system.
- Drug metabolism (biotransformation) is defined as the enzymatic alteration of drug structure.
- Most drug metabolism takes place in the liver and is catalyzed by the cytochrome P450 system of enzymes.
- The most important consequence of drug metabolism is promotion of renal drug excretion (by converting lipid-soluble drugs into more hydrophilic forms).
- Other consequences of drug metabolism are conversion of drugs to less active (or inactive) forms, conversion of drugs to more active forms, conversion of prodrugs to their active forms, and conversion of drugs to more toxic or less toxic forms.
- Some drugs can induce (stimulate) synthesis of hepatic drug-metabolizing enzymes, and can thereby accelerate their own metabolism and the metabolism of other drugs.
- The term *first-pass effect* refers to the rapid inactivation of some oral drugs as they pass through the liver after being absorbed.
- Enteroleptatic recirculation is a repeating cycle in which a drug undergoes glucuronidation in the liver, transport to the duodenum via the bile, hydrolytic release of free drug by intestinal enzymes, followed by transport in the portal blood back to the liver, where the cycle can begin again.
- Most drugs are excreted by the kidneys.
- Renal drug excretion has three steps: glomerular filtration, passive tubular reabsorption, and active tubular secretion.
- Drugs that are highly lipid soluble undergo extensive passive reabsorption back into the blood, and therefore cannot be excreted by the kidney (until they are converted to more polar forms by the liver).
- Drugs can be excreted into breast milk, thereby posing a threat to the nursing infant.
- For most drugs, there is a direct correlation between the level of drug in plasma and the intensity of therapeutic and toxic effects.
- The minimum effective concentration (MEC) is defined as the plasma drug level below which therapeutic effects will not occur.
- The therapeutic range of a drug lies between the MEC and the toxic concentration.
- Drugs with a wide therapeutic range are relatively easy to use safely, whereas drugs with a narrow therapeutic range are difficult to use safely.
- The half-life of a drug is defined as the time required for the amount of drug in the body to decline by 50%.
- Drugs that have a short half-life must be administered more frequently than drugs that have a long half-life.

- When drugs are administered repeatedly, their levels will gradually rise and then reach a steady plateau.
- The time required to reach plateau is equivalent to about four half-lives.
- The time required to reach plateau is independent of dosage size, although the height of the plateau will be higher with larger doses.
- If plasma drug levels fluctuate too much between doses, the fluctuations could be reduced by (1) giving smaller doses at shorter intervals (keeping the total daily dose the same), (2) using a continuous infusion, or (3) using a depot preparation.

- For a drug with a long half-life, it may be necessary to use a loading dose to achieve plateau quickly.
- When drug administration is discontinued, most (94%) of the drug in the body will be eliminated over four half-lives.

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Dose-Response Relationships**Basic Features of the Dose-Response Relationship****Maximal Efficacy and Relative Potency****Drug-Receptor Interactions****Introduction to Drug Receptors****The Four Primary Receptor Families****Receptors and Selectivity of Drug Action****Theories of Drug-Receptor Interaction****Agonists, Antagonists, and Partial Agonists****Regulation of Receptor Sensitivity****Drug Responses That Do Not Involve Receptors****Interpatient Variability in Drug Responses****The Therapeutic Index**

Pharmacodynamics is defined as the study of the biochemical and physiologic effects of drugs and the molecular mechanisms by which those effects are produced. In short, pharmacodynamics is the study of what drugs do to the body and how they do it.

In order to participate rationally in achieving the therapeutic objective, nurses need a basic understanding of pharmacodynamics. You must know about drug actions in order to educate patients about their medications, make PRN decisions, and evaluate patients for drug responses, both beneficial and harmful. You also need to understand drug actions when conferring with prescribers about drug therapy: If you believe a patient is receiving inappropriate medication or is being denied a required drug, you will need to support that conviction with arguments based at least in part on knowledge of pharmacodynamics.

DOSE-RESPONSE RELATIONSHIPS

The dose-response relationship (ie, the relationship between the size of an administered dose and the intensity of the response produced) is a fundamental concern in therapeutics. Dose-response relationships determine the minimum amount of drug we can use, the maximum response a drug can elicit, and how much we need to increase the dosage in order to produce the desired increase in response.

Basic Features of the Dose-Response Relationship

The basic characteristics of dose-response relationships are illustrated in Figure 5-1. Part *A* shows dose-response data plotted on *linear* coordinates. Part *B* shows the same data

plotted on *semilogarithmic* coordinates (ie, the scale on which dosage is plotted is logarithmic rather than linear). The most obvious and important characteristic revealed by these curves is that the dose-response relationship is *graded*. That is, as the dosage increases, the response becomes progressively larger. Because drug responses are graded, therapeutic effects can be adjusted to fit the needs of each patient. To tailor treatment to a particular patient, all we need do is raise or lower the dosage until a response of the desired intensity is achieved. If drug responses were *all-or-nothing* instead of graded, drugs could produce only one intensity of response. If that response were too strong or too weak for a particular patient, there would be nothing we could do to adjust the intensity to better suit the patient. Clearly, the graded nature of the dose-response relationship is essential for successful drug therapy.

As indicated in Figure 5-1, the dose-response relationship can be viewed as having three phases. Phase 1 (Fig. 5-1*B*) occurs at low doses. The curve is flat during this phase because doses are too low to elicit a measurable response. During phase 2, an increase in dose elicits a corresponding increase in the response. This is the phase during which the dose-response relationship is graded. As the dose goes higher, we eventually reach a point where an increase in dose is unable to elicit a further increase in response. At this point, the curve flattens out into phase 3.

Maximal Efficacy and Relative Potency

Dose-response curves reveal two characteristic properties of drugs: *maximal efficacy* and *relative potency*. Curves that reflect these properties are shown in Figure 5-2.

Maximal Efficacy

Maximal efficacy is defined as *the largest effect that a drug can produce*. Maximal efficacy is indicated by the *height* of the dose-response curve.

The concept of maximal efficacy is illustrated by the dose-response curves for meperidine [Demerol] and pentazocine [Talwin], two morphine-like pain relievers (Fig. 5-2*A*). As you can see, the curve for pentazocine levels off at a maximum height below that of the curve for meperidine. This tells us that the maximum degree of pain relief we can achieve with pentazocine is smaller than the maximum degree of pain relief we can achieve with meperidine. Put another way, no matter how much pentazocine we administer, we can never produce the degree of pain relief that we can with meperidine. Accordingly, we would say that meperidine has greater maximal efficacy than pentazocine.

Despite what intuition might tell us, a drug with very high maximal efficacy is not always more desirable than a drug with lower efficacy. Recall that we want to match the intensity of the response to the patient's needs. This may be

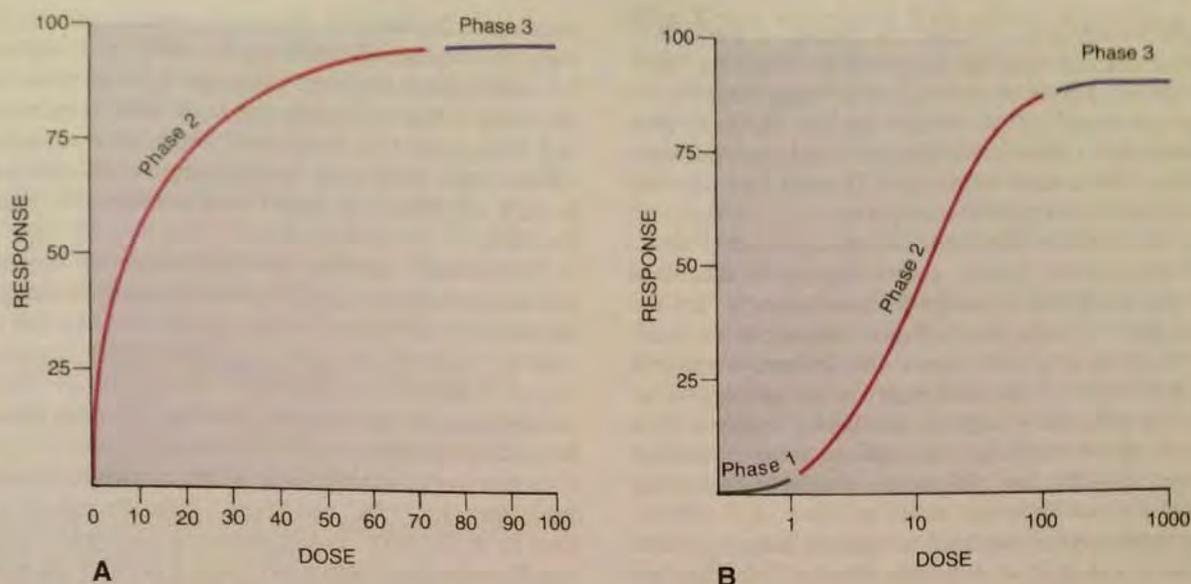


Figure 5-1 ■ Basic components of the dose-response curve.

A, A dose-response curve with dose plotted on a linear scale. **B**, The same dose-response relationship shown in **A** but with the dose plotted on a logarithmic scale. Note the three phases of the dose-response curve: **Phase 1**, The curve is relatively flat; doses are too low to elicit a significant response. **Phase 2**, The curve climbs upward as bigger doses elicit correspondingly bigger responses. **Phase 3**, The curve levels off; bigger doses are unable to elicit a further increase in response. (Phase 1 is not indicated in **A** because very low doses cannot be shown on a linear scale.)

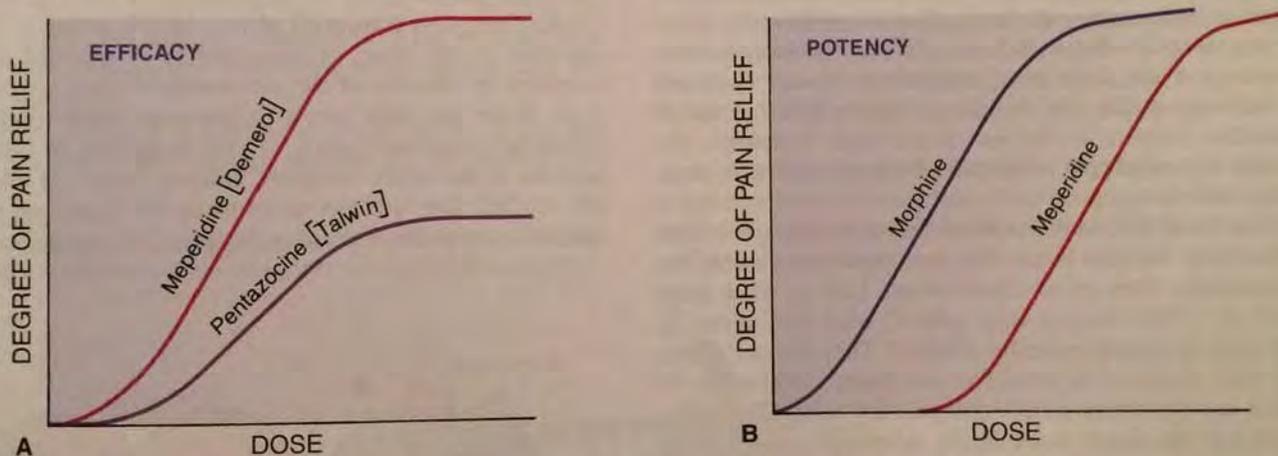


Figure 5-2 ■ Dose-response curves demonstrating efficacy and potency.

A, Efficacy, or "maximal efficacy," is an index of the maximal response a drug can produce. The efficacy of a drug is indicated by the height of its dose-response curve. In this example, meperidine has greater efficacy than pentazocine. Efficacy is an important quality in a drug. **B**, Potency is an index of how much drug must be administered to elicit a desired response. In this example, achieving pain relief with meperidine requires higher doses than with morphine. We would say that morphine is more potent than meperidine. Note that, if administered in sufficiently high doses, meperidine can produce just as much pain relief as morphine. Potency is usually not an important quality in a drug.

difficult to do with a drug that produces extremely intense responses. For example, certain diuretics (eg, furosemide) have such high maximal efficacy that they can cause dehydration. If we only want to mobilize a modest volume of water, a diuretic with lower maximal efficacy (eg, hydrochlorothiazide) would be preferred. Similarly, if a patient has a mild headache, we would not select a powerful analgesic (eg, morphine) for relief. Rather, we would select an analgesic with lower maximal efficacy, such as aspirin. Put

another way, it is neither appropriate nor desirable to hunt squirrels with a cannon.

Relative Potency

The term *potency* refers to the amount of drug we must give to elicit an effect. Potency is indicated by the relative position of the dose-response curve along the *x* (dose) axis.

The concept of potency is illustrated by the curves in Figure 5-2B. These curves plot doses for two analgesics—

morphine and meperidine—versus the degree of pain relief achieved. As you can see, for any particular degree of pain relief, the required dose of meperidine is larger than the required dose of morphine. Because morphine produces pain relief at lower doses than meperidine, we would say that morphine is more potent than meperidine. That is, a potent drug is one that produces its effects at low doses.

Potency is rarely an important characteristic of a drug. The fact that morphine is more potent than meperidine does not mean that morphine is a superior medicine. In fact, the only consequence of morphine's greater potency is that morphine can be given in smaller doses. The difference between providing pain relief with morphine versus meperidine is much like the difference between purchasing candy with a dime instead of two nickels; although the dime is smaller (more potent) than the two nickels, the purchasing power of the dime and the two nickels is identical.

Although potency is usually of no clinical concern, it can be important if a drug is so lacking in potency that doses become inconveniently large. For example, if a drug were of extremely low potency, we might need to administer that drug in huge doses multiple times a day to achieve beneficial effects. In this case, an alternative drug with higher potency would be desirable. Fortunately, it is rare for a drug to be so lacking in potency that doses of inconvenient magnitude need be given.

It is important to note that the potency of a drug implies nothing about its maximal efficacy! Potency and efficacy are completely independent qualities. Drug A can be more effective than drug B even though drug B may be more potent. Also, drugs A and B can be equally effective even though one may be more potent. As we saw in Figure 5-2B, although meperidine happens to be less potent than morphine, the maximal degree of pain relief that we can achieve with these drugs is identical.

A final comment on the word *potency* is in order. In everyday parlance, we tend to use the word *potent* to express the pharmacologic concept of effectiveness. That is, when most people say, "This drug is very potent," what they mean is, "This drug produces powerful effects." They do not mean, "This drug produces its effects at low doses." In pharmacology, we use the words *potent* and *potency* with the specific meanings given above. Accordingly, whenever you see those words in this book, they will refer only to the dosage needed to produce effects—never to the maximal effects a drug can produce.

DRUG-RECEPTOR INTERACTIONS

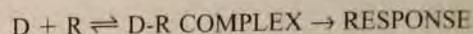
Introduction to Drug Receptors

Drugs are not "magic bullets"—they are simply chemicals. Being chemicals, the only way drugs can produce their effects is by interacting with other chemicals. Receptors are the special "chemicals" in the body that most drugs interact with to produce effects.

We can define a receptor as *any functional macromolecule in a cell to which a drug binds to produce its effects.* Under this broad definition, many cellular components could be considered drug receptors, since drugs bind to many cellular components (eg, enzymes, ribosomes, tubulin) to produce their effects. However, although the formal definition of a re-

ceptor encompasses all functional macromolecules, the term *receptor* is generally reserved for what is arguably the most important group of macromolecules through which drugs act: the body's own receptors for hormones, neurotransmitters, and other regulatory molecules. The other macromolecules to which drugs bind, such as enzymes and ribosomes, can be thought of simply as target molecules, rather than as true receptors.

The general equation for the interaction between drugs and their receptors is as follows (where D = drug and R = receptor):



As suggested by the equation, binding of a drug to its receptor is usually *reversible*.

A receptor is analogous to a light switch, in that it has two configurations: "ON" and "OFF." Like the switch, a receptor must be in the "ON" configuration to influence cellular function. Receptors are activated ("turned on") by interaction with other molecules. Under physiologic conditions, receptor activity is regulated by endogenous compounds (neurotransmitters, hormones, other regulatory molecules). When a drug binds to a receptor, all that it can do is mimic or block the actions of endogenous regulatory molecules. By doing so, the drug will either increase or decrease the rate of the physiologic activity normally controlled by that receptor.

An illustration should help clarify the receptor concept. Let's consider receptors for norepinephrine (NE) in the heart. Cardiac output is controlled in part by NE acting at specific receptors in the heart. Norepinephrine is supplied to those receptors by neurons of the autonomic nervous system (Fig. 5-3). When the body needs to increase cardiac output, the following events take place: (1) the firing rate of autonomic neurons to the heart increases, causing increased release of NE; (2) NE then binds to receptors on the heart; and (3) as a consequence of the interaction between NE and its receptors,

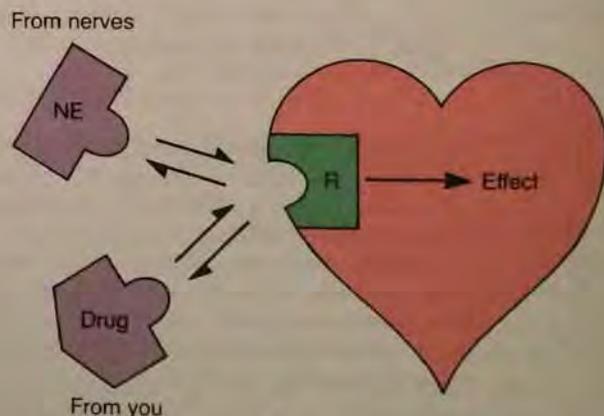


Figure 5-3 • Interaction of drugs with receptors for norepinephrine.

Under physiologic conditions, cardiac output can be increased by the binding of norepinephrine (NE) to receptors (R) on the heart. Norepinephrine is supplied to these receptors by nerves. These same receptors can be acted on by drugs, which can either mimic the actions of endogenous NE (and thereby increase cardiac output) or block the actions of endogenous NE (and thereby reduce cardiac output).

both the rate and force of cardiac contractions increase, thereby increasing cardiac output. When the demand for cardiac output subsides, the autonomic neurons reduce their firing rate, binding of NE to its receptors diminishes, and cardiac output returns to resting levels.

The same cardiac receptors whose function is regulated by endogenous NE can also serve as receptors for drugs. That is, just as endogenous molecules can bind to these receptors, so can compounds that enter the body as drugs. The binding of drugs to these receptors can have one of two effects: (1) drugs can *mimic* the action of endogenous NE (and thereby increase cardiac output), or (2) drugs can *block* the action of endogenous NE (and thereby prevent stimulation of the heart by autonomic neurons).

Several important properties of receptors and drug-receptor interactions are illustrated by this example:

- The receptors through which drugs act are normal points of control of physiologic processes.
- Under physiologic conditions, receptor function is regulated by molecules supplied by the body.
- All that drugs can do at receptors is mimic or block the action of the body's own regulatory molecules.
- Because drug action is limited to mimicking or blocking the body's own regulatory molecules, drugs cannot give cells new functions. Rather, drugs can only alter the rate of pre-existing processes. In other words, drugs cannot make the body do anything that it is not already capable of doing.*
- Drugs produce their therapeutic effects by helping the body use its pre-existing capabilities to the patient's best advantage. Put another way, medications simply help the body help itself.
- In theory, it should be possible to synthesize drugs that can alter the rate of any biologic process for which receptors exist.

*The only exception to this rule is gene therapy. By inserting genes into cells, we actually can make them do something they were previously incapable of.

The Four Primary Receptor Families

Although the body has many different receptors, they comprise only four primary families: cell membrane-embedded enzymes, ligand-gated ion channels, G protein-coupled receptor systems, and transcription factors. These families are depicted in Figure 5-4. In the discussion below, the term *ligand-binding domain* refers to the specific region of the receptor where binding of drugs and endogenous regulatory molecules takes place.

Cell Membrane-Embedded Enzymes. As shown in Figure 5-4, receptors of this type span the cell membrane. The ligand-binding domain is located on the cell surface, and the enzyme's catalytic site is inside. Binding of an endogenous regulatory molecule or agonist drug (one that mimics the action of the endogenous regulatory molecule) activates the enzyme, thereby increasing its catalytic activity. Responses to activation of these receptors occur in seconds. Insulin is a good example of an endogenous ligand that acts through this type of receptor.

Ligand-Gated Ion Channels. Like membrane-embedded enzymes, ligand-gated ion channels span the cell membrane. The function of these receptors is to regulate flow of ions into and out of cells. Each ligand-gated channel is specific for a particular ion (eg, Na^+ , Ca^{++}). As shown in Figure 5-4, the ligand-binding domain is on the cell surface. When an endogenous ligand or agonist drug binds the receptor, the channel opens, allowing ions to flow inward or outward. (The direction of flow is determined by the concentration gradient of the ion across the membrane.) Responses to activation of a ligand-gated ion channel are extremely fast, usually occurring in milliseconds. Several neurotransmitters, including acetylcholine and gamma-aminobutyric acid (GABA), act through this type of receptor.

G Protein-Coupled Receptor Systems. G protein-coupled receptor systems have three components: the receptor itself, G protein (so named because it binds GTP), and an effector (typically an ion channel or an enzyme). These systems work

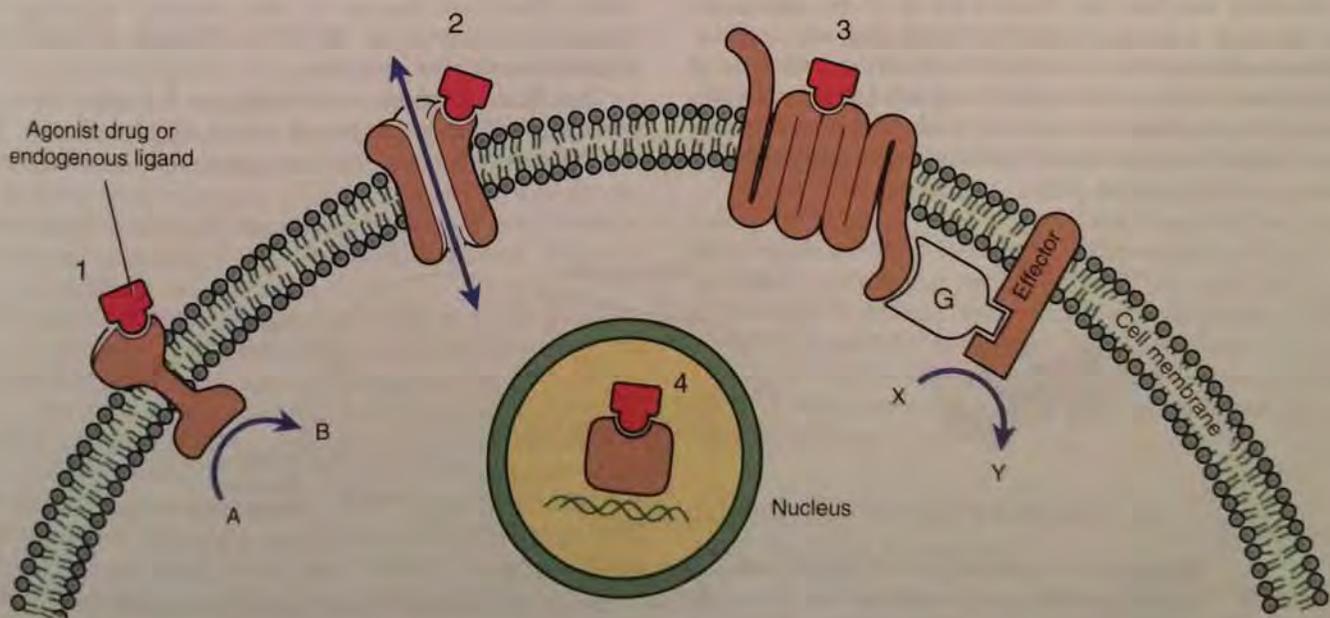


Figure 5-4 • The four primary receptor families.

1, Cell membrane-embedded enzyme. 2, Ligand-gated ion channel. 3, G protein-coupled receptor system (G = G protein). 4, Transcription factor. (See text for details.)

as follows: binding of an endogenous ligand or agonist drug activates the receptor, which in turn activates G protein, which in turn activates the effector. Responses to activation of this type of system develop rapidly. Numerous endogenous ligands—including NE, serotonin, histamine, and many peptide hormones—act through G protein-coupled receptor systems.

As shown in Figure 5-4, the receptors that couple to G proteins are serpentine structures that traverse the cell membrane 7 times. For some of these receptors, the ligand-binding domain is on the cell surface. For others, the ligand-binding domain is located in a pocket accessible from the cell surface.

Transcription Factors. Transcription factors differ from other receptors in two ways: (1) transcription factors are found *within* the cell rather than on the surface, and (2) responses to activation of these receptors are *delayed*. Transcription factors are situated on DNA in the cell nucleus. Their function is to regulate protein synthesis. Activation of these receptors by endogenous ligands or by agonist drugs stimulates transcription of messenger RNA molecules, which then act as templates for synthesis of specific proteins. The entire process—from activation of the transcription factor through completion of protein synthesis—may take hours or even days. Because transcription factors are intracellular, they can be activated only by ligands that are sufficiently lipid soluble to cross the cell membrane. Endogenous ligands that act through transcription factors include thyroid hormone and all of the steroid hormones (eg, progesterone, testosterone, cortisol).

Receptors and Selectivity of Drug Action

In Chapter 1 we noted that selectivity is a highly desirable characteristic of a drug, in that the more selective a drug is, the fewer side effects it will produce. Selective drug action is possible, in large part, because drugs act through specific receptors.

The body employs many different kinds of receptors to regulate its sundry physiologic activities. There are receptors for each neurotransmitter (eg, NE, acetylcholine, dopamine); there are receptors for each hormone (eg, progesterone, insulin, thyrotropin); and there are receptors for all of the other molecules the body uses to regulate physiologic processes (eg, histamine, prostaglandins, leukotrienes). As a rule, each type of receptor participates in the regulation of just a few processes.

Selective drug action is made possible by the existence of many types of receptors, each regulating just a few processes.

Common sense tells us that, if a drug interacts with only one type of receptor, and if that receptor type regulates just a few processes, then the effects of the drug will be limited. Conversely, intuition also tells us that, if a drug interacts with several different receptor types, then that drug is likely to elicit a wide variety of responses.

How can a drug interact with one receptor type and not with others? In some important ways, a receptor is analogous to a lock and a drug is analogous to a key for that lock: Just as only keys with the proper profile can fit a particular lock, only those drugs with the proper size, shape, and physical properties can bind to a particular receptor.

The binding of acetylcholine (a neurotransmitter) to its receptor illustrates the lock-and-key analogy (Fig. 5-5). To bind with its receptor, acetylcholine must have a shape that is complementary to the shape of the receptor. In addition, acetylcholine must possess positive charges that are positioned so as to permit their interaction with corresponding negative sites on the receptor. If acetylcholine lacked these properties, it would be unable to interact with the receptor.

Like the acetylcholine receptor, all other receptors impose specific requirements on the molecules with which they will interact. Because receptors have such specific requirements, it is possible to synthesize drugs that interact with just one receptor type to the exclusion of all others. Such medications tend to elicit selective responses.

Even though a drug is selective for only one type of receptor, is it possible for that drug to produce nonselective effects? Yes: If a single receptor type is responsible for regulating several physiologic processes, then drugs that interact with that receptor will also influence several processes. For example, in addition to modulating perception of pain, morphine receptors help regulate other processes, including respiration and motility of the bowel. Consequently, although morphine is selective for one class of receptor, the drug can still produce a variety of effects. In clinical practice, it is common for morphine to cause respiratory depression and constipation along with reduction of pain. Note that morphine produces these varied effects not because it lacks receptor selectivity, but because the receptor for which morphine is selective helps regulate a variety of processes.

One final comment on selectivity: *Selectivity does not guarantee safety.* A compound can be highly selective for a particular receptor and still be dangerous. For example, at-

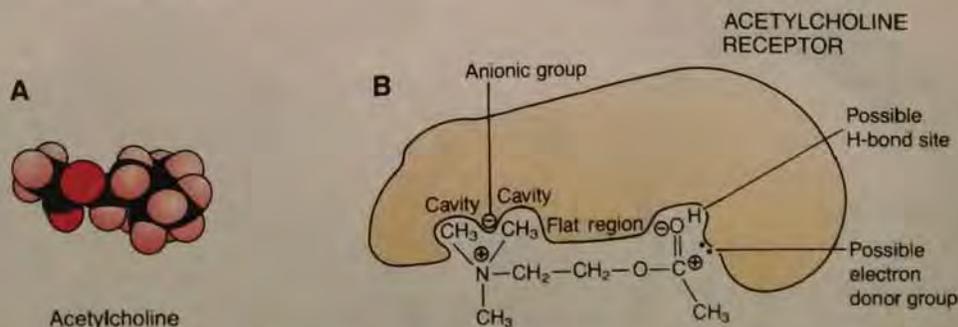


Figure 5-5 • Interaction of acetylcholine with its receptor.

A. Three-dimensional model of the acetylcholine molecule. **B.** Binding of acetylcholine to its receptor. Note how the shape of acetylcholine closely matches the shape of the receptor. Note also how the positive charges on acetylcholine align with the negative sites on the receptor. (Modified from Goldstein A, Aronow L, Sumner MK: *Principles of Drug Action: The Basis of Pharmacology*, 2nd ed. New York: John Wiley & Sons, 1974.)

though botulinum toxin is highly selective for one type of receptor, the compound is anything but safe: Botulinum toxin can cause paralysis of the muscles of respiration, resulting in death from respiratory arrest.

Theories of Drug-Receptor Interaction

In the discussion below, we consider two theories of drug-receptor interaction: (1) the simple occupancy theory and (2) the modified occupancy theory. These theories help explain dose-response relationships and the ability of drugs to mimic or block the actions of endogenous regulatory molecules.

Simple Occupancy Theory

The simple occupancy theory of drug-receptor interaction states that (1) the intensity of the response to a drug is proportional to the number of receptors occupied by that drug and that (2) a maximal response will occur when *all* available receptors have been occupied. This relationship between receptor occupancy and the intensity of the response is depicted in Figure 5-6.

Although certain aspects of dose-response relationships can be explained by the simple occupancy theory, other important phenomena cannot. Specifically, there is nothing in this theory to explain why one drug should be more potent than another. In addition, this theory cannot explain how one drug can have higher maximal efficacy than another. That is, according to this theory, two drugs acting at the same receptor should produce the same maximal effect, providing that their dosages were high enough to produce 100% receptor occupancy. However, we have already seen this is not true. As illustrated in Figure 5-2A, there is a dose of pentazocine above which no further increase in response can be elicited. Presumably, all receptors are occupied when the dose-response curve levels off. However, at 100% receptor occupancy, the response elicited by pentazocine is less than that elicited by morphine. Simple occupancy theory cannot account for this difference.

Modified Occupancy Theory

The modified occupancy theory of drug-receptor interaction explains certain observations that cannot be accounted for with the simple occupancy theory. The simple occupancy theory assumes that all drugs acting at a particular receptor are identical with respect to (1) the ability to bind to the receptor and (2) the ability to influence receptor function once binding has taken place. The modified occupancy theory is based on different assumptions.

The modified theory ascribes two qualities to drugs: *affinity* and *intrinsic activity*. The term *affinity* refers to the strength of the attraction between a drug and its receptor. *Intrinsic activity* refers to the ability of a drug to activate the receptor following binding. *Affinity and intrinsic activity are independent properties.*

Affinity. As noted, the term *affinity* refers to the strength of the attraction between a drug and its receptor. Drugs with high affinity are strongly attracted to their receptors. Conversely, drugs with low affinity are weakly attracted.

The affinity of a drug for its receptors is reflected in its *potency*. Because they are strongly attracted to their receptors, drugs with high affinity can bind to their receptors when present in low concentrations. Because they bind to receptors at

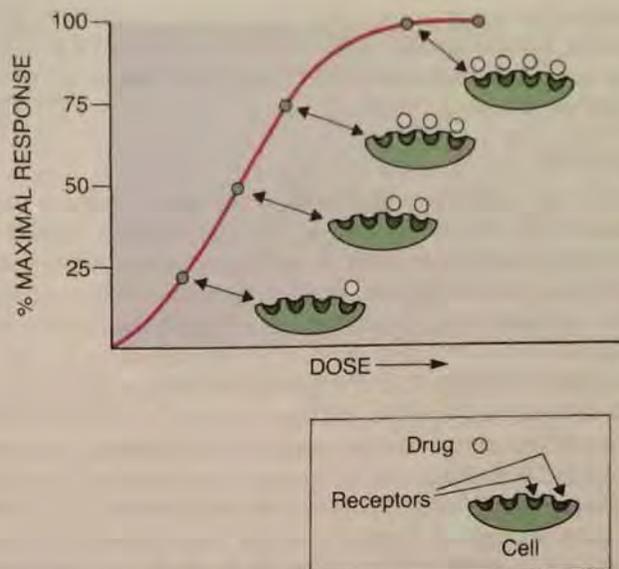


Figure 5-6 • Model of simple occupancy theory.

The simple occupancy theory states that the intensity of response to a drug is proportional to the number of receptors occupied; maximal response is reached with 100% receptor occupancy. Because the hypothetical cell in this figure has only four receptors, maximal response is achieved when all four receptors are occupied. (**Note:** Real cells have thousands of receptors.)

low concentrations, drugs with high affinity are effective in low doses. That is, *drugs with high affinity are very potent*. Conversely, drugs with low affinity must be present in high concentrations to bind to their receptors. Accordingly, these drugs are less potent.

Intrinsic Activity. The term *intrinsic activity* refers to the ability of a drug to activate a receptor upon binding. Drugs with high intrinsic activity cause intense receptor activation. Conversely, drugs with low intrinsic activity cause only slight activation.

The intrinsic activity of a drug is reflected in its *maximal efficacy*. Drugs with high intrinsic activity have high maximal efficacy. That is, by causing intense receptor activation, they are able to cause intense responses. Conversely, if intrinsic activity is low, maximal efficacy will be low as well.

It should be noted that, under the modified occupancy theory, the intensity of the response to a drug is still related to the number of receptors occupied. The wrinkle added by the modified theory is that intensity is also related to the ability of the drug to activate receptors once binding has occurred. Under the modified theory, two drugs can occupy the same number of receptors but produce effects of different intensity; the drug with greater intrinsic activity will produce the more intense response.

Agonists, Antagonists, and Partial Agonists

As noted, when drugs bind to receptors they can do one of two things: they can either *mimic* the action of endogenous regulatory molecules or they can *block* the action of endogenous regulatory molecules. Drugs that mimic the body's own regulatory molecules are called *agonists*. Drugs that block the

actions of endogenous regulators are called *antagonists*. Like agonists, *partial agonists* also mimic the actions of endogenous regulatory molecules, but they produce responses of intermediate intensity.

Agonists

Agonists are molecules that activate receptors. Because neurotransmitters, hormones, and all other endogenous regulators of receptor function activate the receptors to which they bind, all of these compounds are considered agonists. When drugs act as agonists, they simply bind to receptors and mimic the actions of the body's own regulatory molecules.

In terms of the modified occupancy theory, an agonist is a drug that has both *affinity* and *high intrinsic activity*. Affinity allows the agonist to bind to receptors, while intrinsic activity allows the bound agonist to "activate" or "turn on" receptor function.

Many therapeutic agents produce their effects by functioning as agonists. Dobutamine, for example, is a drug that mimics the action of NE at receptors on the heart, thereby causing heart rate and force of contraction to increase. The insulin that we administer as a drug mimics the actions of endogenous insulin at receptors. Norethindrone, a component of many oral contraceptives, acts by "turning on" receptors for progesterone.

It is important to note that agonists do not necessarily make physiologic processes go faster; receptor activation by these compounds can also make a process go slower. For example, there are receptors on the heart that, when *activated* by acetylcholine (the body's own agonist for these receptors), will cause heart rate to *decrease*. Drugs that mimic the action of acetylcholine at these receptors will also decrease heart rate. Because such drugs produce their effects by causing receptor activation, they would be called agonists—even though they cause heart rate to decline.

Antagonists

Antagonists produce their effects by preventing receptor activation by endogenous regulatory molecules and drugs. Antagonists have virtually no effects of their own on receptor function.

In terms of the modified occupancy theory, an antagonist is a drug with affinity for a receptor but with no intrinsic activity. Affinity allows the antagonist to bind to receptors, but lack of intrinsic activity prevents the bound antagonist from causing receptor activation.

Although antagonists do not cause receptor activation, they most certainly *do* produce pharmacologic effects. Antagonists produce their effects by *preventing the activation of receptors by agonists*. Antagonists can produce beneficial effects by blocking the actions of endogenous regulatory molecules or by blocking the actions of drugs. (The ability of antagonists to block the actions of drugs is employed most commonly to treat overdose.)

It is important to note that the response to an antagonist is determined by how much *agonist* is present. Because antagonists act by preventing receptor activation, *if there is no agonist present, administration of an antagonist will have no observable effect*; the drug will bind to its receptors but nothing will happen. On the other hand, if receptors are undergoing activation by agonists, administration of an antagonist will

shut the process down, resulting in an observable response. This is an important concept, so please think about it.

Many therapeutic agents produce their effects by acting as receptor antagonists. Antihistamines, for example, suppress allergy symptoms by binding to receptors for histamine, thereby preventing activation of these receptors by histamine released in response to allergens. The use of antagonists to treat drug toxicity is illustrated by naloxone, an agent that blocks receptors for morphine and related opioids; by preventing activation of opioid receptors, naloxone can completely reverse all symptoms of opioid overdose.

Noncompetitive Versus Competitive Antagonists. Antagonists can be subdivided into two major classes: (1) noncompetitive antagonists and (2) competitive antagonists. Most antagonists are competitive.

Noncompetitive (Insurmountable) Antagonists. Noncompetitive antagonists bind *irreversibly* to receptors. The effect of irreversible binding is equivalent to reducing the total number of receptors available for activation by an agonist. Because the intensity of the response to an agonist is proportional to the total number of receptors occupied, and because noncompetitive antagonists decrease the number of receptors available for activation, noncompetitive antagonists *reduce the maximal response* that an agonist can elicit. If sufficient antagonist is present, agonist effects will be blocked completely. Dose-response curves illustrating inhibition by a noncompetitive antagonist are shown in Figure 5-7A.

Because the binding of noncompetitive antagonists is irreversible, inhibition by these agents cannot be overcome, no matter how much agonist may be available. Because inhibition by noncompetitive antagonists cannot be reversed, these agents are rarely used therapeutically. (Recall from Chapter 1 that reversibility is one of the properties of an ideal drug.)

Although noncompetitive antagonists bind irreversibly, this does not mean that their effects last forever. Cells are constantly breaking down "old" receptors and synthesizing new ones. Consequently, the effects of noncompetitive antagonists wear off as the receptors to which they are bound are replaced. Since the life cycle of a receptor can be relatively short, the effects of noncompetitive antagonists may subside in a few days.

Competitive (Surmountable) Antagonists. Competitive antagonists bind *reversibly* to receptors. As their name implies, competitive antagonists produce receptor blockade by competing with agonists for receptor binding. If an agonist and a competitive antagonist have equal affinity for a particular receptor, then the receptor will be occupied by whichever agent—agonist or antagonist—is present in the highest concentration. If there are more antagonist molecules present than agonist molecules, antagonist molecules will occupy the receptors and receptor activation will be blocked. Conversely, if agonist molecules outnumber the antagonists, receptors will be occupied mainly by the agonist and little inhibition will occur.

Because competitive antagonists bind reversibly to receptors, the inhibition they cause is *surmountable*. In the presence of sufficiently high amounts of agonist, agonist molecules will occupy all receptors and inhibition will be completely overcome. The dose-response curves shown in

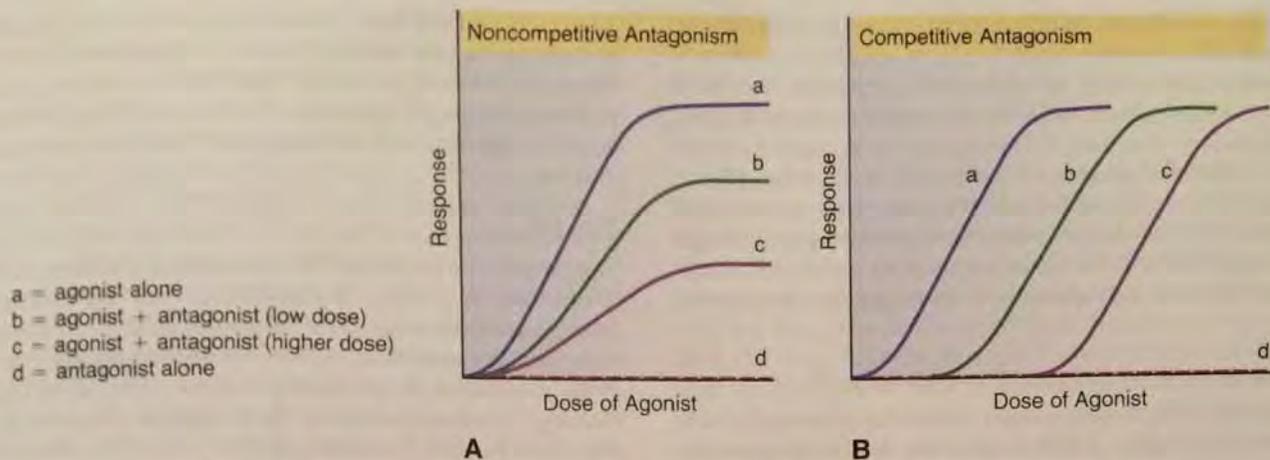


Figure 5-7 • Dose-response curves in the presence of competitive and noncompetitive antagonists.

A, Effect of a noncompetitive antagonist on the dose-response curve of an agonist. Note that noncompetitive antagonists decrease the maximal response achievable with an agonist. **B**, Effect of a competitive antagonist on the dose-response curve of an agonist. Note that the maximal response achievable with the agonist is not reduced. Competitive antagonists simply increase the amount of agonist required to produce any given intensity of response.

Figure 5-7B illustrate the process of overcoming the effects of a competitive antagonist with large doses of an agonist.

Partial Agonists

A partial agonist is an agonist that has only moderate intrinsic activity. As a result, *the maximal effect that a partial agonist can produce is lower than that of a full agonist*. Pentazocine is an example of a partial agonist. As the curves in Figure 5-2A indicate, the degree of pain relief that can be achieved with pentazocine is much lower than the relief that can be achieved with meperidine (a full agonist).

Partial agonists are interesting in that they can act as *antagonists* as well as *agonists*. For example, when pentazocine is administered by itself, it occupies opioid receptors and produces moderate relief of pain. In this situation, the drug is acting as an agonist. However, if a patient is already taking meperidine (a full agonist at opioid receptors) and is then given a large dose of pentazocine, pentazocine will occupy the opioid receptors and prevent their activation by meperidine. As a result, rather than experiencing the high degree of pain relief that meperidine can produce, the patient will experience only the limited relief that pentazocine can produce. In this situation, pentazocine is acting as both an agonist (producing moderate pain relief) and an antagonist (blocking the higher degree of relief that could have been achieved with meperidine by itself).

Regulation of Receptor Sensitivity

Receptors are dynamic components of the cell. In response to continuous activation or continuous inhibition, the number of receptors on the cell surface can change, as can their sensitivity to agonist molecules (drugs and endogenous ligands). For example, when the receptors of a cell are continually exposed to an *agonist*, the cell usually becomes less responsive. When this occurs, the cell is said to be *desensitized* or *refractory*, or

to have undergone *down-regulation*. Several mechanisms may be responsible, including destruction of receptors by the cell and modification of receptors such that they respond less fully. Continuous exposure to antagonists has the opposite effect, causing the cell to become *hypersensitive* (also referred to as *supersensitive*). One mechanism that can cause hypersensitivity is synthesis of more receptors.

DRUG RESPONSES THAT DO NOT INVOLVE RECEPTORS

Although the effects of most drugs result from drug-receptor interactions, some drugs do not act through receptors. Rather, they act through simple physical or chemical interactions with other small molecules.

Common examples of “receptorless drugs” include antacids, antiseptics, saline laxatives, and chelating agents. Antacids neutralize gastric acidity by direct chemical interaction with stomach acid. The antiseptic action of ethyl alcohol results from precipitating bacterial proteins. Magnesium sulfate, a powerful laxative, acts by retaining water in the intestinal lumen through an osmotic effect. Dimercaprol, a chelating agent, prevents toxicity from heavy metals (eg, arsenic, mercury) by forming complexes with these compounds. All of these pharmacologic effects are the result of simple physical or chemical interactions, and not interactions with cellular receptors.

INTERPATIENT VARIABILITY IN DRUG RESPONSES

The dose required to produce a therapeutic response can vary substantially from patient to patient. Why? Because people differ from one another. In this section we consider interpatient variation as a general issue. The specific kinds of differ-

ences that underlie variability in drug responses are discussed in Chapter 8.

In order to promote the therapeutic objective, you must be alert to interpatient variation in drug responses. Because of interpatient variation, it is not possible to predict exactly how an individual patient will respond to medication. Hence, each patient must be evaluated to determine his or her actual response. The nurse who appreciates the reality of interpatient variability will be better prepared to anticipate, evaluate, and respond appropriately to each patient's therapeutic needs.

Measurement of Interpatient Variability

An example of how interpatient variability is measured will facilitate discussion. Let's assume we've just developed a drug that suppresses production of stomach acid, and now want to evaluate variability in patient responses. To make this evaluation, we must first define a specific *therapeutic objective* or *endpoint*. Because our drug reduces gastric acidity, an appropriate endpoint is elevation of gastric pH to a value of 5.

Having defined a therapeutic endpoint, we can now perform our study. Subjects for the study are 100 people with gastric hyperacidity. We begin our experiment by giving each subject a low initial dose (100 mg) of our drug. Next we measure gastric pH to determine how many individuals achieved the therapeutic goal of pH 5. Let's assume that only two people responded to the initial dose. To the remaining 98 subjects, we give an additional 20-mg dose and again determine whose gastric pH rose to 5. Let's assume that six more responded to this dose (120 mg total). We continue the experiment, administering doses in 20-mg increments, until all 100 subjects have responded with the desired elevation in pH.

The data from our hypothetical experiment are plotted in Figure 5-8. The plot is called a *frequency distribution*

curve. We can see from the curve that a wide range of doses is required to produce the desired response in all subjects. For some subjects, a dose of only 100 mg was sufficient to produce the target response. For other subjects, the therapeutic endpoint was not achieved until the dose totaled 240 mg.

The ED₅₀

The dose at the middle of the frequency distribution curve is termed the *ED₅₀* (Fig. 5-8B). (*ED₅₀* is an abbreviation for *average effective dose*.) The *ED₅₀* is defined as *the dose that is required to produce a defined therapeutic response in 50% of the population*. In the case of our new drug, the *ED₅₀* was 170 mg—the dose needed to elevate gastric pH to a value of 5 in 50 of the 100 people tested.

The *ED₅₀* can be considered a "standard" dose and, as such, is frequently the dose selected for initial treatment. After evaluating a patient's response to this "standard" dose, we can then adjust subsequent doses up or down to meet the patient's needs.

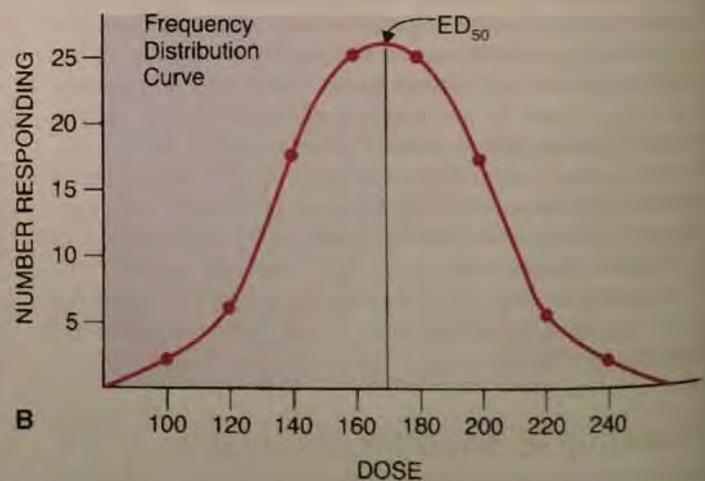
Clinical Implications of Interpatient Variability

Interpatient variation has four important clinical consequences. As a nurse you should be aware of these implications:

- *The initial dose of a drug is necessarily an approximation. Subsequent doses must be "fine tuned" based on the patient's response.* Because initial doses are approximations, it would be wise not to challenge the prescriber if the initial dose differs by a small amount (eg, 10% to 20%) from recommended doses in a drug reference. Rather, you should administer the medication as prescribed and evaluate the response. Dosage adjustments can then be made as needed. Of course, if the prescriber's order calls for a dose that differs from the recommended dose by a large amount, that order should be challenged.

Dose of Drug (mg)	Number of Subjects Responding at Each Dose
100	2
120	6
140	17
160	25
180	25
200	17
220	6
240	2

A



B

Figure 5-8 ■ Interpatient variation in drug responses.

A, Data from tests of a hypothetical acid suppressant in 100 patients. The goal of the study is to determine the dosage required by each patient to elevate gastric pH to 5. Note the wide variability in doses needed to produce the target response for the 100 subjects. **B**, Frequency distribution curve for the data in **A**. The dose at the middle of the curve is termed the *ED₅₀*—the dose that will produce a predefined intensity of response in 50% of the population.

- When given an average effective dose (ED_{50}), some patients will be undertreated, whereas others will have received more drug than they need. Accordingly, when therapy is initiated with a dose equivalent to the ED_{50} , it is especially important to evaluate the response. Patients who fail to respond may need an increase in dosage. Conversely, patients who show signs of toxicity will need a dosage reduction.
- Because drug responses are not completely predictable, you must look at the patient (and not the Physicians' Desk Reference) to determine if too much or too little medication has been administered. In other words, dosage should be adjusted on the basis of the patient's response and not just on the basis of what some reference says is supposed to work. For example, although many postoperative patients receive adequate pain relief with an "average" dose of morphine, this dose is not appropriate for everyone: An average dose may be effective for some patients, ineffective for others, and toxic for still others. Clearly, dosage must be adjusted on the basis of the patient's response, and must not be given in blind compliance with the dosage recommended in a book.
- Because of variability in responses, nurses, patients, and other concerned individuals must evaluate actual responses and be prepared to inform the prescriber about these responses so that proper adjustments in dosage can be made.

THE THERAPEUTIC INDEX

The therapeutic index is a measure of a drug's safety. The therapeutic index, determined using laboratory animals, is defined as the ratio of a drug's LD_{50} to its ED_{50} . (The LD_{50} ,

or average lethal dose, is the dose that is lethal to 50% of the animals treated.) A large (or high) therapeutic index indicates that a drug is relatively safe. Conversely, a small (or low) therapeutic index indicates that a drug is relatively unsafe.

The concept of therapeutic index is illustrated by the frequency distribution curves in Figure 5-9. Part A of the figure shows curves for therapeutic and lethal responses to drug "X." Part B shows equivalent curves for drug "Y." As you can see in Figure 5-9A, the average lethal dose (100 mg) for drug X is much larger than the average therapeutic dose (10 mg). Because this drug's lethal dose is much larger than its therapeutic dose, common sense tells us that the drug should be relatively safe. The safety of this drug is reflected in its high therapeutic index, which is 10. In contrast, drug Y is unsafe. As shown in Figure 5-9B, the average lethal dose for drug Y (20 mg) is only twice the average therapeutic dose (10 mg). Hence, for drug Y, a dose only twice the ED_{50} could be lethal to 50% of those treated. Clearly, drug Y is not safe. This lack of safety is reflected in its low therapeutic index.

The curves for drug Y illustrate a phenomenon that is even more important than the therapeutic index. As you can see, there is *overlap* between the curve for therapeutic effects and the curve for lethal effects. This overlap tells us that the high doses needed to produce therapeutic effects in some people may be large enough to cause death. The message here is that, if a drug is to be truly safe, the highest dose required to produce therapeutic effects must be substantially lower than the lowest dose required to produce death.

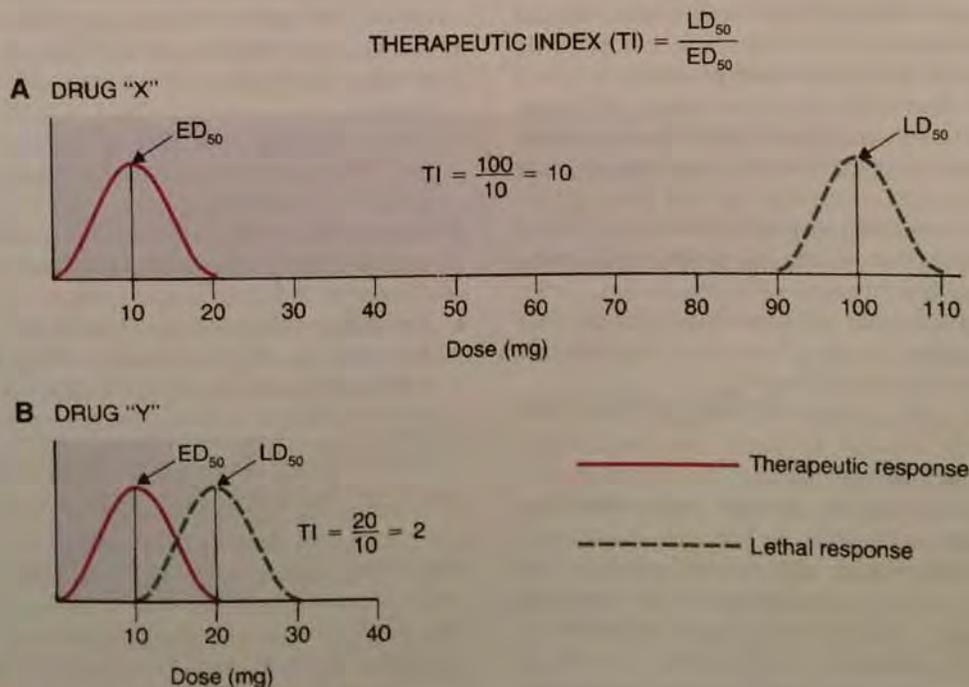


Figure 5-9 • The therapeutic index.

A, Frequency distribution curves indicating the ED_{50} and LD_{50} for drug "X." Because its LD_{50} is much greater than its ED_{50} , drug X is relatively safe. B, Frequency distribution curves indicating the ED_{50} and LD_{50} for drug "Y." Because its LD_{50} is very close to its ED_{50} , drug Y is not very safe. Also note the overlap between the effective-dose curve and the lethal-dose curve.

- Pharmacodynamics is the study of the biochemical and physiologic effects of drugs and the molecular mechanisms by which those effects are produced.
- For most drugs, the dose-response relationship is graded. That is, the response gets more intense with increasing dosage.
- Maximal efficacy is defined as the biggest effect a drug can produce.
- Although efficacy is important, there are situations in which a drug with relatively low efficacy is preferable to a drug with very high efficacy.
- A potent drug is simply a drug that produces its effects at low doses. As a rule, potency is not important.
- Potency and efficacy are independent qualities. Drug A can be more effective than drug B even though drug B may be more potent. Also, drugs A and B can be equally effective, although one may be more potent than the other.
- A receptor can be defined as any functional macromolecule in a cell to which a drug binds to produce its effects.
- Binding of drugs to their receptors is almost always reversible.
- The receptors through which drugs act are normal points of control for physiologic processes.
- Under physiologic conditions, receptor function is regulated by molecules supplied by the body.
- All that drugs can do at receptors is mimic or block the action of the body's own regulatory molecules.
- Because drug action is limited to mimicking or blocking the body's own regulatory molecules, drugs cannot give cells new functions. Rather, drugs can only alter the rate of pre-existing processes.
- Receptors make selective drug action possible.
- There are four primary families of receptors: cell membrane-embedded enzymes, ligand-gated ion channels, G protein-coupled receptor systems, and transcription factors.
- If a drug interacts with only one type of receptor, and if that receptor type regulates just a few processes, then the effects of the drug will be relatively selective.
- If a drug interacts with only one type of receptor, but that receptor type regulates multiple processes, then the effects of the drug will be nonselective.
- If a drug interacts with multiple receptors, its effects will be nonselective.
- Selectivity does not guarantee safety.
- The term *affinity* refers to the strength of the attraction between a drug and its receptor.
- Drugs with high affinity have high relative potency.
- The term *intrinsic activity* refers to the ability of a drug to activate receptors.
- Drugs with high intrinsic activity have high maximal efficacy.
- Agonists are molecules that activate receptors.
- In terms of the modified occupancy theory, agonists have both affinity and high intrinsic activity. Affinity allows them to bind to receptors, while intrinsic activity allows them to activate the receptor after binding.
- Antagonists are drugs that prevent receptor activation by endogenous regulatory molecules and by other drugs.
- In terms of the modified occupancy theory, antagonists have affinity for receptors but no intrinsic activity. Affinity allows the antagonist to bind to receptors, but lack of intrinsic activity prevents the bound antagonist from causing receptor activation.
- Antagonists have no observable effects in the absence of agonists.
- Partial agonists have only moderate intrinsic activity. Hence their maximal efficacy is lower than that of full agonists.
- Partial agonists can act as agonists (if there is no full agonist present) and as antagonists (if a full agonist is present).
- Continuous exposure of cells to agonists can result in receptor desensitization (aka refractoriness or down-regulation), whereas continuous exposure to antagonists can result in hypersensitivity (aka supersensitivity).
- Some drugs act through simple physical or chemical interactions with other small molecules rather than through receptors.
- The ED_{50} is defined as the dose required to produce a defined therapeutic response in 50% of the population.
- An average effective dose (ED_{50}) is perfect for some people, insufficient for others, and excessive for still others.
- The initial dose of a drug is necessarily an approximation. Subsequent doses must be "fine tuned" based on the patient's response.
- Because drug responses are not completely predictable, you must look at the patient (and not a reference book) to determine if dosage is appropriate.
- The therapeutic index—defined as the $LD_{50}:ED_{50}$ ratio—is a measure of a drug's safety. Drugs with a high therapeutic index are safe. Drugs with a low therapeutic index are not safe.

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Drug Interactions

Drug-Drug Interactions

Consequences of Drug-Drug Interactions

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Impact of Food on Drug Action

Timing of Drug Administration with Respect to Meals

Drug-Supplement Interactions

In this chapter we consider the interactions of drugs with other drugs, with foods, and with dietary supplements. Our principal focus is on the mechanisms and clinical consequences of drug-drug interactions and drug-food interactions. Drug-supplement interactions are discussed briefly here and at greater length in Chapter 108.

DRUG-DRUG INTERACTIONS

Drug-drug interactions can occur whenever a patient takes two or more drugs. Some interactions are both intended and desired, as when we combine drugs to treat hypertension. In contrast, some interactions are both unintended and undesired, as when we precipitate malignant hyperthermia in a patient receiving halothane and succinylcholine. Some adverse interactions are well known, and hence generally avoidable. Others are yet to be documented.

Drug interactions occur because patients frequently take more than one drug. They may take multiple drugs to treat a single disorder. They may have multiple disorders that require treatment with different drugs. They may take over-the-counter drugs in addition to prescription medicines. And they may take caffeine, nicotine, alcohol, and other drugs that have nothing to do with illness.

Our objective in this chapter is to establish an overview of drug interactions, emphasizing the basic mechanisms by which drugs can interact. We will not attempt to catalog the huge number of specific interactions that are known. For information on interactions of specific drugs, you can refer to the chapters in which those drugs are discussed.

Consequences of Drug-Drug Interactions

When two drugs interact, there are three possible outcomes: (1) one drug may intensify the effects of the other, (2) one drug may reduce the effects of the other, or (3) the combination may produce a new response not seen with either drug alone.

Intensification of Effects

When a patient is taking two medications, one drug may intensify the effects of the other. This type of interaction is often termed *potentiative*. Potentiative interactions may be beneficial or detrimental. A potentiative interaction that enhances therapeutic effects is clearly beneficial. Conversely, a potentiative interaction that intensifies adverse effects is clearly detrimental. Examples of beneficial and detrimental potentiative interactions follow.

Increased Therapeutic Effects. The interaction between sulbactam and ampicillin represents a beneficial potentiative interaction. When administered alone, ampicillin undergoes rapid inactivation by bacterial enzymes. Sulbactam inhibits those enzymes, and thereby prolongs and intensifies ampicillin's therapeutic effects.

Increased Adverse Effects. The interaction between aspirin and warfarin represents a potentially detrimental potentiative interaction. Warfarin is an anticoagulant used to suppress formation of blood clots. Unfortunately, if the dosage of warfarin is too high, the patient is at risk of spontaneous bleeding. Accordingly, for therapy to be safe and effective, the dosage must be high enough to suppress clot formation but not so high that bleeding occurs. Like warfarin, aspirin also suppresses clotting. As a result, if aspirin and warfarin are taken concurrently, the risk of bleeding is significantly increased. Clearly, potentiative interactions such as this are undesirable.

Reduction of Effects

Interactions that result in reduced drug effects are often termed *inhibitory*. As with potentiative interactions, inhibitory interactions can be beneficial or detrimental. Inhibitory interactions that reduce toxicity are beneficial. Conversely, inhibitory interactions that reduce therapeutic effects are detrimental. Examples follow.

Reduced Therapeutic Effects. The interaction between propranolol and albuterol represents a detrimental inhibitory interaction. Albuterol is taken by people with asthma to dilate the bronchi. Propranolol, a drug for cardiovascular disorders, can act in the lung to block the effects of albuterol. Hence, if propranolol and albuterol are taken together, propranolol can reduce albuterol's therapeutic effects. Inhibitory actions such as this, which can result in therapeutic failure, are clearly detrimental.

Reduced Adverse Effects. The use of naloxone to treat morphine overdose is an excellent example of a beneficial inhibitory interaction. When administered in excessive dosage, morphine can produce coma and profound respiratory depression; death can result. Naloxone, a drug that blocks morphine's actions, can completely reverse all symptoms of toxicity. The benefits of such an inhibitory interaction are obvious.

Creation of a Unique Response

Rarely, the combination of two drugs produces a new response not seen with either agent alone. To illustrate, let's consider the combination of alcohol with disulfiram [Antabuse], a drug used to treat alcoholism. When alcohol and disulfiram are combined, a host of unpleasant and dangerous responses can result. These effects do not occur when disulfiram or alcohol is used alone.

Basic Mechanisms of Drug-Drug Interactions

Drugs can interact through four basic mechanisms: (1) direct chemical or physical interaction, (2) pharmacokinetic interaction, (3) pharmacodynamic interaction, and (4) combined toxicity.

Direct Chemical or Physical Interactions

Some drugs, because of their physical or chemical properties, can undergo direct interaction with other drugs. Direct physical and chemical interactions usually render both drugs inactive.

Direct interactions occur most commonly when drugs are combined in IV solutions. Frequently, but not always, the interaction produces a precipitate. If a precipitate appears when drugs are mixed together, that solution should be discarded. Keep in mind, however, that direct drug interactions may not always leave visible evidence. Hence you cannot rely on simple inspection to reveal all direct interactions. Because drugs can interact in solution, *never combine two or more drugs in the same container unless it has been established that a direct interaction will not occur.*

The same kinds of interactions that can take place when drugs are mixed together in a bottle can also occur when drugs are mixed together in the patient. However, since drugs are diluted in body water following administration, and since dilution decreases chemical interactions, significant interactions within the patient are much less likely than in a bottle.

Pharmacokinetic Interactions

Drug interactions can affect all four of the basic pharmacokinetic processes. That is, when two drugs are taken together, one may alter the absorption, distribution, metabolism, or excretion of the other.

Altered Absorption. Drug absorption may be enhanced or reduced by drug interactions. In some cases, these interactions have great clinical significance. There are several mechanisms by which one drug can alter the absorption of another:

- By elevating gastric pH, antacids can decrease the ionization of basic drugs in the stomach, thereby increasing the ability of basic drugs to cross membranes and be absorbed. Antacids have the opposite effect on acidic drugs.

- Laxatives can reduce absorption of other oral drugs by accelerating their passage through the intestine.
- Drugs that depress peristalsis (eg, morphine, atropine) prolong drug transit time in the intestine, thereby increasing the time for absorption.
- Drugs that induce vomiting can decrease absorption of oral drugs.
- Cholestyramine and certain other adsorbent drugs, which are administered orally but do not undergo absorption, can adsorb other drugs onto themselves, thereby preventing absorption of the other drugs into the blood.
- Drugs that reduce regional blood flow can reduce absorption of other drugs from that region. For example, when epinephrine is injected together with a local anesthetic (as is often done), the epinephrine causes local vasoconstriction, thereby reducing regional blood flow and delaying absorption of the anesthetic.

Altered Distribution. There are two principal mechanisms by which one drug can alter the distribution of another: (1) competition for protein binding and (2) alteration of extracellular pH.

Competition for Protein Binding. When two drugs bind to the same site on plasma albumin, coadministration of those drugs produces competition for binding. As a result, binding of one or both agents is reduced, causing plasma levels of free drug to rise. In theory, the increase in free drug can intensify effects. However, since the newly freed drug usually undergoes rapid elimination, the increase in plasma levels of free drug is rarely sustained or significant.

Alteration of Extracellular pH. Because of the pH partitioning effect (see Chapter 4), a drug with the ability to change extracellular pH can alter the distribution of other drugs. For example, if a drug were to increase extracellular pH, that drug would increase the ionization of acidic drugs in extracellular fluids (ie, plasma and interstitial fluid). As a result, acidic drugs would be drawn from within cells (where the pH was below that of the extracellular fluid) into the extracellular space. Hence, the alteration in pH would change drug distribution.

The ability of drugs to alter pH and thereby alter the distribution of other drugs can be put to practical use in the management of poisoning. For example, symptoms of aspirin toxicity can be reduced with sodium bicarbonate, a drug that elevates extracellular pH. By increasing the pH outside cells, bicarbonate causes aspirin to move from intracellular sites into the interstitial fluid and plasma, thereby minimizing injury to cells.

Altered Metabolism. Altered metabolism is one of the most important—and most complex—mechanisms by which drugs interact. Some drugs *increase* the metabolism of other drugs, and some drugs *decrease* the metabolism of other drugs. Drugs that increase the metabolism of other drugs do so by inducing synthesis of hepatic drug-metabolizing enzymes. Drugs that decrease the metabolism of other drugs do so by inhibiting those enzymes.

As we discussed in Chapter 4, the majority of drug metabolism is catalyzed by the cytochrome P450 (CYP) group of enzymes, which is composed of a large number of isozymes (closely related enzymes). Of all the isozymes in the P450 group, five are responsible for the metabolism of most drugs. These five isozymes of CYP are designated CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Table 6-1 lists major drugs that are metabolized by each isozyme, and indicates drugs that can inhibit or induce those isozymes.

Induction of CYP Isozymes. Drugs that stimulate the synthesis of CYP isozymes are referred to as *inducing agents*. The classic example of an inducing agent is phenobarbital, a member of the barbiturate family. By increasing the synthesis of specific CYP isozymes, phenobarbital and other inducing

TABLE 6-1 ■ Drugs That Are Important Substrates, Inhibitors, or Inducers of Specific CYP Isozymes

CYP	Substrates	Inhibitors	Inducers	
CYP1A2	CNS Drugs: amitriptyline, clomipramine, clozapine, desipramine, duloxetine, fluvoxamine, haloperidol, imipramine, methadone, ramelteon, rasagiline, ropinirole, tacrine Others: theophylline, tizanidine, warfarin	Acyclovir Ciprofloxacin Ethinyl estradiol Fluvoxamine Isoniazid Norfloxacin Oral contraceptives Zafirlukast Zileuton	Carbamazepine Phenobarbital Phenytoin Primidone Rifampin Ritonavir Tobacco St. John's wort	
CYP2C9	Diazepam, phenytoin, ramelteon, voriconazole, warfarin	Amiodarone Azole antifungals Efavirenz Fenofibrate Fluorouracil Fluoxetine	Fluvastatin Fluvoxamine Gemfibrozil Isoniazid Leflunomide Zafirlukast	Aprepitant Carbamazepine Phenobarbital Phenytoin Primidone Rifampin Rifapentine Ritonavir St. John's wort
CYP2C19	Citalopram, clopidogrel, methadone, phenytoin, thioridazine, voriconazole	Chloramphenicol Cimetidine Esomeprazole Etravirine Felbamate Fluconazole Fluoxetine	Fluvoxamine Isoniazid Ketoconazole Lansoprazole Modafinil Omeprazole Ticlopidine Voriconazole	Carbamazepine Phenobarbital Phenytoin St. John's wort Tipranavir/ ritonavir
CYP2D6	CNS Drugs: amitriptyline, atomoxetine, clozapine, desipramine, donepezil, doxepin, duloxetine, fentanyl, haloperidol, iloperidone, imipramine, meperidine, nortriptyline, propoxyphene, tetrabenazine, thioridazine, tramadol, trazodone Antidysrhythmic Drugs: flecainide, mexiletine, propafenone Beta Blocker: metoprolol Opioids: codeine, dextromethorphan, hydrocodone	Amiodarone Cimetidine Darifenacin Darunavir/ritonavir Duloxetine Fluoxetine Methadone	Paroxetine Propoxyphene Propranolol Quinidine Ritonavir Sertraline Tipranavir/ritonavir	Not an inducible enzyme
CYP3A4	Antibacterials/Antifungals: clarithromycin, erythromycin, ketoconazole, itraconazole, rifabutin, telithromycin, voriconazole Anticancer Drugs: busulfan, dasatinib, doxorubicin, erlotinib, etoposide, ixabepilone, lapatinib, paclitaxel, pazopanib, romidepsin, sunitinib, tamoxifen, vinblastine, vincristine Calcium Channel Blockers: amlodipine, felodipine, isradipine, nifedipine, nimodipine, nisoldipine, verapamil Drugs for HIV Infections: amprenavir, darunavir, etravirine, indinavir, maraviroc, nelfinavir, ritonavir, saquinavir, tipranavir Drugs for Erectile Dysfunction: sildenafil, tadalafil, vardenafil Drugs for Urge Incontinence: darifenacin, fesoterodine, solifenacin, tolterodine Immunosuppressants: cyclosporine, everolimus, sirolimus, tacrolimus Opioids: alfentanil, alfuzosin, fentanyl, methadone, oxycodone Sedative-Hypnotics: alprazolam, eszopiclone, midazolam, ramelteon, triazolam	Amiodarone Amprenavir Aprepitant Atazanavir Azole antifungals Chloramphenicol Cimetidine Clarithromycin Conivaptan Cyclosporine Darunavir/ritonavir Delavirdine Diltiazem Dronedarone Erythromycin Fluvoxamine Fosamprenavir Grapefruit juice	Indinavir Isoniazid Methylprednisolone Nefazodone Nelfinavir Nicardipine Nifedipine Norfloxacin Pazopanib Prednisone Quinine Ritonavir Saquinavir Synergid Telithromycin Tipranavir/ritonavir Verapamil	Amprenavir Aprepitant Bosentan Carbamazepine Dexamethasone Efavirenz Ethosuximide Etravirine Garlic supplements Nevirapine Oxcarbazepine Phenobarbital Phenytoin Primidone Rifabutin Rifampin Rifapentine Ritonavir St. John's wort

CNS = central nervous system, HIV = human immunodeficiency virus.

Continued

TABLE 6-1 ■ Drugs That Are Important Substrates, Inhibitors, or Inducers of Specific CYP Isozymes—cont'd

CYP	Substrates	Inhibitors	Inducers
CYP3A4— cont'd	<p><i>Statins:</i> atorvastatin, lovastatin, simvastatin</p> <p><i>Antidysrhythmic Drugs:</i> disopyramide, dronedarone, lidocaine, quinidine</p> <p><i>Others:</i> aprepitant, bosentan, cinacalcet, cisapride, colchicine, conivaptan, dihydroergotamine, dronabinol, eplerenone, ergotamine, estrogens, ethosuximide, fluticasone, guanfacine, iloperidone, ondansetron, oral contraceptives, pimozide, ranolazine, saxagliptin, sertraline, silodosin, tiagabine, tolvaptan, trazodone, warfarin</p>	(See p. 61)	(See p. 61)

agents can stimulate their own metabolism as well as that of other drugs.

Inducing agents can increase the rate of drug metabolism by as much as two- to threefold. This increase develops over 7 to 10 days. Rates of metabolism return to normal 7 to 10 days after the inducing agent has been withdrawn.

When an inducing agent is taken with another medicine, dosage of the other medicine may need adjustment. For example, if a woman taking oral contraceptives were to begin taking phenobarbital, induction of drug metabolism by phenobarbital would accelerate metabolism of the contraceptive, thereby lowering its level. If drug metabolism is increased enough, protection against pregnancy would be lost. To maintain contraceptive efficacy, dosage of the contraceptive should be increased. Conversely, when a patient *discontinues* an inducing agent, dosages of other drugs may need to be *lowered*. If dosage is not reduced, drug levels may climb dangerously high as rates of hepatic metabolism decline to their baseline (noninduced) values.

Inhibition of CYP Isozymes. If drug A inhibits the metabolism of drug B, then levels of drug B will rise. The result may be beneficial or harmful. The interaction of ketoconazole (an antifungal drug) with cisapride* (a GI stimulant) and cyclosporine (an expensive immunosuppressant) provides an interesting case in point. Ketoconazole inhibits CYP3A4, the CYP isozyme that metabolizes cisapride and cyclosporine. If ketoconazole is combined with either drug, that drug's level will rise. In the case of cisapride, the result can be a fatal cardiac dysrhythmia—a clearly undesirable outcome. However, in the case of cyclosporine, inhibition of CYP3A4 allows us to achieve therapeutic drug levels at lower doses, thereby greatly reducing the cost of treatment—a clearly beneficial result.

Although inhibition of drug metabolism can be beneficial, as a rule inhibition has undesirable results. That is, in most cases, when an inhibitor increases the level of another drug, the outcome is toxicity. Accordingly, when a patient is taking an inhibitor along with his or her other medicines, you should be alert for possible adverse effects. Unfortunately, since the number of possible interactions of this type is large, keeping track is a challenge.

Altered Renal Excretion. Drugs can alter all three phases of renal excretion: filtration, reabsorption, and active secretion. By doing so, one drug can alter the renal excretion of

another. Glomerular filtration can be decreased by drugs that reduce cardiac output: A reduction in cardiac output decreases renal blood flow, which decreases drug filtration at the glomerulus, which in turn decreases the rate of drug excretion. By altering urinary pH, one drug can alter the ionization of another, and thereby increase or decrease the extent to which that drug undergoes passive tubular reabsorption. Lastly, competition between two drugs for active tubular secretion can decrease the renal excretion of both agents.

Interactions That Involve P-Glycoprotein. As we discussed in Chapter 4 (Pharmacokinetics), P-glycoprotein (PGP) is a transmembrane protein that transports a wide variety of drugs *out* of cells, including cells of the intestinal epithelium, placenta, blood-brain barrier, liver, and kidney tubules. Like P450 isozymes, PGP is subject to induction and inhibition by drugs. In fact (and curiously), most of the drugs that induce or inhibit P450 have the same impact on PGP. Drugs that *induce* PGP can have the following impact on other drugs:

- *Reduced absorption*—by increasing drug export from cells of the intestinal epithelium into the intestinal lumen
- *Reduced fetal drug exposure*—by increasing drug export from placental cells into the maternal blood
- *Reduced brain drug exposure*—by increasing drug export from cells of brain capillaries into the blood
- *Increased drug elimination*—by increasing drug export from liver into the bile and from renal tubular cells into the urine

Drugs that inhibit PGP will have opposite effects.

Pharmacodynamic Interactions

By influencing pharmacodynamic processes, one drug can alter the effects of another. Pharmacodynamic interactions are of two basic types: (1) interactions in which the interacting drugs act at the *same* site and (2) interactions in which the interacting drugs act at *separate* sites. Pharmacodynamic interactions may be potentiative or inhibitory, and can be of great clinical significance.

Interactions at the Same Receptor. Interactions that occur at the same receptor are almost always *inhibitory*. Inhibition occurs when an antagonist drug blocks access of an agonist drug to its receptor. These agonist-antagonist interactions are described in Chapter 5. There are many agonist-antagonist interactions of clinical importance. Some reduce

*In the United States, cisapride [Propulsid] availability is restricted.

therapeutic effects and are therefore undesirable. Others reduce toxicity and are of obvious benefit. The interaction between naloxone and morphine noted above is an example of a beneficial inhibitory interaction: By blocking access of morphine to its receptors, naloxone can reverse all symptoms of morphine overdose.

Interactions Resulting from Actions at Separate Sites. Even though two drugs have different mechanisms of action and act at separate sites, if both drugs influence the same physiologic process, then one drug can alter responses produced by the other. Interactions resulting from effects produced at different sites may be potentiative or inhibitory.

The interaction between morphine and diazepam [Valium] illustrates a potentiative interaction resulting from concurrent use of drugs that act at separate sites. Morphine and diazepam are central nervous system (CNS) depressants, but these drugs do not share the same mechanism of action. Hence, when these agents are administered together, the ability of each to depress CNS function reinforces the depressant effects of the other. This potentiative interaction can result in profound CNS depression.

The interaction between two diuretics—hydrochlorothiazide and spironolactone—illustrates how the effects of a drug acting at one site can counteract the effects of a second drug acting at a different site. Hydrochlorothiazide acts on the distal convoluted tubule of the nephron to increase excretion of potassium. Acting at a different site in the kidney, spironolactone works to decrease renal excretion of potassium. Consequently, when these two drugs are administered together, the potassium-sparing effects of spironolactone tend to balance the potassium-wasting effects of hydrochlorothiazide, leaving renal excretion of potassium at about the same level it would have been had no drugs been given at all.

Combined Toxicity

Common sense tells us that, if drug A and drug B are both toxic to the same organ, then taking them together will cause more injury than if they were not combined. For example, when we treat tuberculosis with isoniazid and rifampin, both of which are hepatotoxic, we cause more liver injury than we would using just one of the drugs. As a rule, drugs with overlapping toxicity are not used together. Unfortunately, when treating tuberculosis, the combination is essential, and hence can't be avoided.

Clinical Significance of Drug-Drug Interactions

From the foregoing it should be clear that drug interactions have the potential to affect the outcome of therapy. As a result of drug-drug interactions, the intensity of responses may be increased or reduced. Interactions that increase therapeutic effects or reduce toxicity are desirable. Conversely, interactions that reduce therapeutic effects or increase toxicity are detrimental.

Common sense tells us that the risk of a serious drug interaction is proportional to the number of drugs that a patient is taking. That is, the more drugs the patient receives, the greater the risk of a detrimental interaction. Because the average hospitalized patient receives 6 to 10 drugs, interactions are common. Be alert for them.

Interactions are especially important for drugs that have a narrow therapeutic range. For these agents, an interaction that produces a modest increase in drug levels can cause toxicity. Conversely, an interaction that produces a modest decrease in drug levels can cause therapeutic failure.

Although a large number of important interactions have been documented, many more are yet to be identified. There-

fore, if a patient develops unusual symptoms, it is wise to suspect that a drug interaction may be the cause—especially since yet another drug might be given to control the new symptoms.

Minimizing Adverse Drug-Drug Interactions

We can minimize adverse interactions in several ways. The most obvious is to minimize the number of drugs a patient receives. Indiscriminate use of multiple-drug therapy does not constitute good treatment—and increases the risk of undesired interactions. A second and equally important way to avoid detrimental interactions is to take a thorough drug history. A history that identifies all drugs the patient is taking allows the prescriber to adjust the regimen accordingly. Please note, however, that patients taking illicit drugs or over-the-counter preparations may fail to report such drug use. You should be aware of this possibility and make a special effort to ensure that the patient's drug use profile is complete. Additional measures for reducing adverse interactions include adjusting the dosage when an inducer of metabolism is added to or deleted from the regimen, adjusting the timing of administration to minimize interference with absorption, monitoring for early signs of toxicity when combinations of toxic agents cannot be avoided, and being especially vigilant when the patient is taking a drug with a narrow therapeutic range.

DRUG-FOOD INTERACTIONS

Drug-food interactions are both important and poorly understood. They are important because they can result in toxicity or therapeutic failure. They are poorly understood because research has been largely lacking.

Impact of Food on Drug Absorption

Decreased Absorption. Food frequently decreases the rate of drug absorption, and occasionally decreases the extent of absorption. Reducing the rate of absorption merely delays the onset of effects; peak effects are not lowered. In contrast, reducing the extent of absorption reduces the intensity of peak responses.

The interaction between calcium-containing foods and tetracycline antibiotics is a classic example of food reducing drug absorption. Tetracyclines bind with calcium to form an insoluble and nonabsorbable complex. Hence, if tetracyclines are administered with milk products or calcium supplements, absorption is reduced and antibacterial effects may be lost.

High-fiber foods can reduce absorption of some drugs. For example, absorption of digoxin [Lanoxin], used for cardiac disorders, is reduced significantly by wheat bran, rolled oats, and sunflower seeds. Since digoxin has a narrow therapeutic range, reduced absorption can result in therapeutic failure.

Increased Absorption. With some drugs, food increases the extent of absorption. When this occurs, peak effects are heightened. For example, a high-calorie meal more than doubles the absorption of saquinavir [Invirase], a drug for

HIV infection. If saquinavir is taken without food, absorption may be insufficient for antiviral activity.

Impact of Food on Drug Metabolism: The Grapefruit Juice Effect

Grapefruit juice can inhibit the metabolism of certain drugs, thereby raising their blood levels. The effect is quite remarkable. In one study, coadministration of grapefruit juice produced a 406% increase in blood levels of felodipine [Plendil], a calcium channel blocker used for hypertension. In addition to felodipine and other calcium channel blockers, grapefruit juice can increase blood levels of lovastatin [Mevacor], cyclosporine [Sandimmune], midazolam [Versed], and many other drugs (Table 6-2). This effect is *not* seen with other citrus juices, including orange juice.

Grapefruit juice raises drug levels mainly by inhibiting metabolism. Specifically, grapefruit juice inhibits CYP3A4, an isozyme of cytochrome P450 found in the liver and the intestinal wall. Inhibition of the *intestinal* isozyme is much greater than inhibition of the liver isozyme. By inhibiting CYP3A4, grapefruit juice decreases the intestinal metabo-

lism of many drugs (see Table 6-2), and thereby increases the amount available for absorption. As a result, blood levels of these drugs rise, causing peak effects to be more intense. Since inhibition of CYP3A4 in the liver is minimal, grapefruit juice does not usually affect metabolism of drugs after they have been absorbed. Importantly, grapefruit juice has little or no effect on drugs administered IV. Why? Because, with IV administration, intestinal metabolism is not involved. Inhibition of CYP3A4 is dose dependent: The more grapefruit juice the patient drinks, the greater the inhibition.

What's in grapefruit juice that can inhibit CYP3A4? Four compounds have been identified. Two of them—*bergapten* and *6',7'-dihydroxybergamottin*—are furanocoumarins. The other two—*naringin* and *naringenin*—are flavonoids.

Inhibition of CYP3A4 persists after grapefruit juice is consumed. Therefore, a drug needn't be administered concurrently with grapefruit juice for an interaction to occur. Put another way, metabolism can still be inhibited even if a patient drinks grapefruit juice in the morning but waits until later in the day to take his or her medicine. In fact, when grapefruit

TABLE 6-2 ■ Some Drugs Whose Levels Can Be Increased by Grapefruit Juice

Drug	Indications	Potential Consequences of Increased Drug Levels
<i>Dihydropyridine CCBs</i> : amlodipine, felodipine, nifedipine, nimodipine, nisoldipine	Hypertension; angina pectoris	Toxicity: flushing, headache, tachycardia, hypotension
<i>Nondihydropyridine CCBs</i> : diltiazem, verapamil	Hypertension; angina pectoris	Toxicity: bradycardia, AV heart block, hypotension, constipation
<i>Statins</i> : lovastatin, simvastatin (minimal effect on atorvastatin, fluvastatin, pravastatin, or rosuvastatin)	Cholesterol reduction	Toxicity: headache, GI disturbances, liver and muscle toxicity
Amiodarone	Cardiac dysrhythmias	Toxicity
Caffeine	Prevents sleepiness	Toxicity: restlessness, insomnia, convulsions, tachycardia
Carbamazepine	Seizures; bipolar disorder	Toxicity: ataxia, drowsiness, nausea, vomiting, tremor
Buspirone	Anxiety	Drowsiness, dysphoria
Triazolam	Anxiety; insomnia	Increased sedation
Midazolam	Induction of anesthesia; conscious sedation	Increased sedation
Saquinavir	HIV infection	Increased therapeutic effect
Cyclosporine	Prevents rejection of organ transplants	Increased therapeutic effects; if levels rise too high, renal and hepatic toxicity will occur
Sirolimus and tacrolimus	Prevent rejection of organ transplants	Toxicity
<i>SSRIs</i> : fluoxetine, fluvoxamine, sertraline	Depression	Toxicity: serotonin syndrome
Pimozide	Tourette's syndrome	Toxicity: QT prolongation resulting in a life-threatening ventricular dysrhythmia
Praziquantel	Schistosomiasis	Toxicity
Dextromethorphan	Cough	Toxicity
Sildenafil	Erectile dysfunction	Toxicity

AV = atrioventricular, CCBs = calcium channel blockers, GI = gastrointestinal, HIV = human immunodeficiency virus, SSRIs = selective serotonin reuptake inhibitors.

juice is consumed on a regular basis, inhibition can persist up to 3 days after the last glass.

The effects of grapefruit juice vary considerably among patients. Why? Because levels of CYP3A4 show great individual variation. In patients with very little CYP3A4, inhibition by grapefruit juice may be sufficient to stop metabolism completely. As a result, large increases in drug levels may occur. Conversely, in patients with lots of CYP3A4, metabolism may continue more or less normally, despite inhibition by grapefruit juice.

The clinical consequences of inhibition may be good or bad. As indicated in Table 6-2, by elevating levels of certain drugs, grapefruit juice can increase the risk of serious toxicity, an outcome that is obviously bad. On the other hand, by increasing levels of two other drugs—saquinavir and cyclosporine—grapefruit juice can intensify therapeutic effects, an outcome that is clearly good.

What should patients do if the drugs they are taking can be affected by grapefruit juice? Unless a predictable effect is known, prudence dictates avoiding grapefruit juice entirely.

Impact of Food on Drug Toxicity

Drug-food interactions sometimes increase toxicity. The most dramatic example is the interaction between monoamine oxidase (MAO) inhibitors (a family of antidepressants) and foods rich in tyramine (eg, aged cheeses, yeast extracts, Chianti wine). If an MAO inhibitor is combined with these foods, blood pressure can rise to a life-threatening level. To avoid disaster, patients taking MAO inhibitors must be warned about the consequences of consuming tyramine-rich foods, and must be given a list of foods to strictly avoid (see Chapter 32). Other drug-food combinations that can increase toxicity include the following:

- Theophylline (an asthma medicine) plus caffeine, which can result in excessive CNS excitation
- Potassium-sparing diuretics (eg, spironolactone) plus salt substitutes, which can result in dangerously high potassium levels
- Aluminum-containing antacids (eg, Maalox) plus citrus beverages (eg, orange juice), which can result in excessive absorption of aluminum

Impact of Food on Drug Action

Although most drug-food interactions concern drug absorption or drug metabolism, food may also (rarely) have a direct impact on drug action. For example, foods rich in vitamin K (eg, broccoli, Brussels sprouts, cabbage) can reduce the effects of warfarin, an anticoagulant. How? As discussed in Chapter 52, warfarin acts by inhibiting vitamin K-dependent clotting factors. Accordingly, when vitamin K is more abun-

dant, warfarin is less able to inhibit the clotting factors, and therapeutic effects decline.

Timing of Drug Administration with Respect to Meals

Administration of drugs at the appropriate time with respect to meals is an important part of drug therapy. As discussed, the absorption of some drugs can be significantly decreased by food, and hence these drugs should be administered on an empty stomach. Conversely, the absorption of other drugs can be increased by food, and hence these drugs should be administered with meals.

Many drugs cause stomach upset when taken without food. If food does not reduce their absorption, then these drugs should definitely be administered with meals. However, if food does reduce their absorption, then we have a difficult choice: We can administer them with food and thereby reduce stomach upset (good news), but also reduce absorption (bad news)—or, we can administer them without food and thereby improve absorption (good news), but also increase stomach upset (bad news). Unfortunately, the correct choice is not obvious. The best solution may be to select an alternative drug that doesn't upset the stomach.

When the medication order says to administer a drug "with food" or "on an empty stomach," just what does this mean? To administer a drug with food means to administer it with or shortly after a meal. To administer a drug on an empty stomach means to administer it either 1 hour before a meal or 2 hours after.

Medication orders frequently fail to indicate when a drug should be administered with respect to meals. As a result, inappropriate administration may occur. If you are uncertain about when to give a drug, ask the prescriber if it should be taken on an empty stomach or with food, and if there are any foods or beverages to avoid.

DRUG-SUPPLEMENT INTERACTIONS

Dietary supplements (herbal medicines and other nonconventional remedies) are used widely, creating the potential for frequent and significant interactions with conventional drugs. Of greatest concern are interactions that reduce beneficial responses to conventional drugs and interactions that increase toxicity. How do these interactions occur? Through the same pharmacokinetic and pharmacodynamic mechanisms by which conventional drugs interact with each other. Unfortunately, reliable information about dietary supplements is largely lacking, including information on interactions with conventional agents. Interactions that *have* been well documented are discussed as appropriate throughout this text. Dietary supplements and their interactions are discussed at length in Chapter 108.

KEY POINTS

- Some drug-drug interactions are intended and beneficial; others are unintended and detrimental.
- Drug-drug interactions may result in intensified effects, diminished effects, or an entirely new effect.
- Potentiative interactions are beneficial when they increase therapeutic effects and detrimental when they increase adverse effects.
- Inhibitory interactions are beneficial when they decrease adverse effects and detrimental when they decrease beneficial effects.
- Because drugs can interact in solution, never combine two or more drugs in the same container unless you are certain that a direct interaction will not occur.
- Drug interactions can result in increased or decreased absorption.
- Competition for protein binding rarely results in a sustained or significant increase in plasma levels of free drug.
- Drugs that induce hepatic drug-metabolizing enzymes can accelerate the metabolism of other drugs.
- When an inducing agent is added to the regimen, it may be necessary to increase the dosages of other drugs. Conversely, when an inducing agent is discontinued, dosages of other drugs may need to be reduced.
- A drug that inhibits the metabolism of other drugs will increase their levels. Sometimes the result is beneficial, but usually it's detrimental.
- Drugs that act as antagonists at a particular receptor will diminish the effects of drugs that act as agonists at that receptor. The result may be beneficial (if the antagonist prevents toxic effects of the agonist) or detrimental (if the antagonist prevents therapeutic effects of the agonist).
- Drugs that are toxic to the same organ should not be combined (if at all possible).
- We can help reduce the risk of adverse interactions by minimizing the number of drugs the patient is given and by taking a thorough drug history.
- Food may reduce the rate or extent of drug absorption. Reducing the extent of absorption reduces peak therapeutic responses; reducing the rate of absorption merely delays the onset of effects.
- For some drugs, food may increase the extent of absorption.
- Grapefruit juice can inhibit the intestinal metabolism of certain drugs, thereby increasing their absorption, which in turn increases their blood levels.
- Foods may increase drug toxicity. The combination of an MAO inhibitor with tyramine-rich food is the classic example.
- When the medication order says to administer a drug on an empty stomach, this means administer it either 1 hour before a meal or 2 hours after.
- Conventional drugs can interact with dietary supplements. The biggest concerns are increased toxicity and reduced therapeutic effects of the conventional agent.

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Adverse Drug Reactions and Medication Errors

Adverse Drug Reactions

Scope of the Problem

Definitions

Organ-Specific Toxicity

Identifying Adverse Drug Reactions

Adverse Reactions to New Drugs

Ways to Minimize Adverse Drug Reactions

Medication Guides, Boxed Warnings, and REMS

Medication Errors

What's a Medication Error and Who Makes Them?

Types of Medication Errors

Causes of Medication Errors

Ways to Reduce Medication Errors

How to Report a Medication Error

BOX 7-1. Medication Reconciliation

In this chapter we discuss two related issues of drug safety: (1) adverse drug reactions (ADRs), also known as adverse drug events (ADEs), and (2) medication errors, a major cause of ADRs. We begin with ADRs and then discuss medication errors.

ADVERSE DRUG REACTIONS

An ADR, as defined by the World Health Organization, is any noxious, unintended, and undesired effect that occurs at normal drug doses. Note that this definition excludes undesired effects that occur when dosage is excessive (eg, because of accidental poisoning or medication error). Adverse reactions can range in intensity from mildly annoying to life threatening. Fortunately, when drugs are used properly, many ADRs can be avoided, or at least minimized.

Scope of the Problem

Drugs can adversely affect all body systems in varying degrees of intensity. Among the more mild reactions are drowsiness, nausea, itching, and rash. Severe reactions include neutropenia, hepatocellular injury, cardiac dysrhythmias, anaphylaxis, and hemorrhage—all of which can be fatal.

Although ADRs can occur in all patients, some patients are more vulnerable than others. Adverse events are most common in the elderly and the very young. (Patients over 60 account for nearly 50% of all ADR cases.) Severe illness also

increases the risk of an ADR. Likewise, adverse events are more common in patients receiving multiple drugs than in patients taking just one drug.

Some data on ADRs will underscore their significance. Each year in the United States, about 700,000 people visit emergency departments because of ADRs. Among patients already in a hospital, estimates suggest that over 770,000 experience a serious ADR, and about 110,000 die. If these numbers are correct, ADRs would be the fourth leading cause of death, exceeded only by heart disease, cancer, and stroke.

Definitions

Side Effect

A side effect is formally defined as *a nearly unavoidable secondary drug effect produced at therapeutic doses*. Common examples include drowsiness caused by traditional antihistamines and gastric irritation caused by aspirin. Side effects are generally predictable and their intensity is dose dependent. Some side effects develop soon after drug use starts, whereas others may not appear until a drug has been taken for weeks or months.

Toxicity

The formal definition of toxicity is *an adverse drug reaction caused by excessive dosing*. Examples include coma from an overdose of morphine and severe hypoglycemia from an overdose of insulin. Although the formal definition of toxicity includes only those severe reactions that occur when dosage is excessive, in everyday parlance the term *toxicity* has come to mean any severe ADR, regardless of the dose that caused it. For example, when administered in therapeutic doses, many anticancer drugs cause neutropenia (profound loss of neutrophilic white blood cells), thereby putting the patient at high risk of infection. This neutropenia would be called a toxicity even though it was produced when dosage was therapeutic.

Allergic Reaction

An allergic reaction is an immune response. For an allergic reaction to occur, there must be prior sensitization of the immune system. Once the immune system has been sensitized to a drug, re-exposure to that drug can trigger an allergic response. The intensity of allergic reactions can range from mild itching to severe rash to anaphylaxis. (Anaphylaxis is a life-threatening response characterized by bronchospasm, laryngeal edema, and a precipitous drop in blood pressure.) Estimates suggest that less than 10% of ADRs are of the allergic type.

The intensity of an allergic reaction is determined primarily by the degree of sensitization of the immune system, not

by drug dosage. Put another way, *the intensity of allergic reactions is largely independent of dosage*. As a result, a dose that elicits a very strong reaction in one allergic patient may elicit a very mild reaction in another. Furthermore, since a patient's sensitivity to a drug can change over time, a dose that elicits a mild reaction early in treatment may produce an intense reaction later on.

Very few medications cause severe allergic reactions. In fact, most serious reactions are caused by just one drug family—the *penicillins*. Other drugs noted for causing allergic reactions include the nonsteroidal anti-inflammatory drugs (eg, aspirin) and the sulfonamide group of compounds, which includes certain diuretics, antibiotics, and oral hypoglycemic agents.

Idiosyncratic Effect

An idiosyncratic effect is defined as *an uncommon drug response resulting from a genetic predisposition*. To illustrate this concept, let's consider responses to succinylcholine, a drug used to produce flaccid paralysis of skeletal muscle. In most patients, succinylcholine-induced paralysis is brief, lasting only a few minutes. In contrast, genetically predisposed patients may become paralyzed for hours. Why the difference? Because in all patients the effects of succinylcholine are terminated through enzymatic inactivation of the drug. Since most people have very high levels of the inactivating enzyme, paralysis is short lived. However, in a small percentage of patients, the genes that code for succinylcholine-metabolizing enzymes are abnormal, producing enzymes that inactivate the drug very slowly. As a result, paralysis is greatly prolonged.

Iatrogenic Disease

The word *iatrogenic* is derived from two words: *iatros*, the Greek word for physician, and *-genic*, a combining form meaning *to produce*. Hence, an iatrogenic disease is *a disease produced by a physician*. The term *iatrogenic disease* is also used to denote *a disease produced by drugs*.

Iatrogenic diseases are nearly identical to idiopathic (naturally occurring) diseases. For example, patients taking certain antipsychotic drugs may develop a syndrome whose symptoms closely resemble those of Parkinson's disease. Because this syndrome is (1) drug induced and (2) essentially identical to a naturally occurring pathology, we would call the syndrome an iatrogenic disease.

Physical Dependence

Physical dependence develops during long-term use of certain drugs, such as opioids, alcohol, barbiturates, and amphetamines. We can define physical dependence as a state in which the body has adapted to drug exposure in such a way that an abstinence syndrome will result if drug use is discontinued. The precise nature of the abstinence syndrome is determined by the drug involved.

Although physical dependence is usually associated with "narcotics" (heroin, morphine, and other opioids), these are not the only dependence-inducing drugs. In addition to the opioids, a variety of other centrally acting drugs (eg, ethanol, barbiturates, amphetamines) can promote dependence. Furthermore, some drugs that work outside the central nervous system can cause physical dependence of a sort. Because a variety of drugs can cause physical dependence of one type or another, and because withdrawal reactions have the potential

for harm, *patients should be warned against abrupt discontinuation of any medication without first consulting a health professional*.

Carcinogenic Effect

The term *carcinogenic effect* refers to the ability of certain medications and environmental chemicals to cause cancers. Fortunately, only a few therapeutic agents are carcinogenic. Ironically, several of the drugs used to *treat* cancer are among those with the greatest carcinogenic potential.

Evaluating drugs for the ability to cause cancer is extremely difficult. Evidence of neoplastic disease may not appear until 20 or more years after initial exposure to a cancer-causing compound. Consequently, it is nearly impossible to detect carcinogenic potential during preclinical and clinical trials. Accordingly, when a new drug is released for general marketing, we cannot know with certainty that it will not eventually prove carcinogenic.

Diethylstilbestrol (DES) illustrates the problem posed by the delayed appearance of cancer following exposure to a carcinogenic drug. DES is a synthetic hormone with actions similar to those of estrogen. At one time, DES was used to prevent spontaneous abortion during high-risk pregnancies. It was not until years later, when vaginal and uterine cancers developed in females who had been exposed to this drug *in utero*, that the carcinogenic actions of DES became known.

Teratogenic Effect

A *teratogenic effect* can be defined as a drug-induced birth defect. Medicines and other chemicals capable of causing birth defects are called teratogens. Teratogenesis is discussed at length in Chapter 9.

Organ-Specific Toxicity

Many drugs are toxic to specific organs. Common examples include injury to the kidneys caused by amphotericin B (an antifungal drug), injury to the heart caused by doxorubicin (an anticancer drug), injury to the lungs caused by amiodarone (an antidysrhythmic drug), and injury to the inner ear caused by aminoglycoside antibiotics (eg, gentamicin). Patients using such drugs should be monitored for signs of developing injury. In addition, patients should be educated about these signs and advised to seek medical attention if they appear.

Two types of organ-specific toxicity deserve special comment. These are (1) injury to the liver and (2) altered cardiac function, as evidenced by a prolonged QT interval on the electrocardiogram. Both are discussed below.

Hepatotoxic Drugs

In the United States, drugs are the leading cause of acute liver failure, a rare condition that can rapidly prove fatal. Most cases end with a liver transplant or in death. The ability to cause severe liver damage is the most common reason for withdrawing an approved drug from the market.

Fortunately, liver failure from using known hepatotoxic drugs is rare, with an incidence of less than 1 in 50,000. (Drugs that cause liver failure more often than this are removed from the market—unless they are indicated for a life-threatening illness.) More than 50 drugs are known to be hepatotoxic. Some of these are listed in Table 7-1.

TABLE 7-1 • Some Hepatotoxic Drugs

Statins and Other Lipid-Lowering Drugs

Atorvastatin [Lipitor]
 Fenofibrate [Tricor]
 Fluvastatin [Lescol]
 Gemfibrozil [Lopid]
 Lovastatin [Mevacor]
 Niacin [Niaspan, others]
 Pravastatin [Pravachol]
 Simvastatin [Zocor]

Oral Antidiabetic Drugs

Acarbose [Precose]
 Pioglitazone [Actos]
 Rosiglitazone [Avandia]

Antiseizure Drugs

Carbamazepine [Tegretol]
 Felbamate [Felbatol]
 Valproic acid [Depakene, others]

Antifungal Drugs

Itraconazole [Sporanox]
 Ketoconazole [Nizoral]
 Terbinafine [Lamisil]

Drugs for Tuberculosis

Isoniazid
 Pyrazinamide
 Rifampin [Rifadin]

Immunosuppressants

Azathioprine [Imuran]
 Methotrexate [Rheumatrex]

Antiretroviral Drugs

Nevirapine [Viramune]
 Ritonavir [Norvir]

Other Drugs

Acetaminophen [Tylenol, others], but only when combined with alcohol, or when taken in excessive dosage
 Amiodarone [Cordarone]
 Diclofenac [Voltaren]
 Duloxetine [Cymbalta]
 Halothane [Fluothane]
 Leflunomide [Arava]
 Methyldopa [Aldomet]
 Nefazodone
 Nitrofurantoin [Macrochantin]
 Tacrine [Cognex]
 Tamoxifen [Nolvadex]
 Zileuton [Zyflo]

How do drugs damage the liver? Recall that the liver is the primary site of drug metabolism. As some drugs undergo metabolism, they are converted to toxic products that can injure liver cells.

Combining a hepatotoxic drug with certain other drugs may increase the risk of liver damage. A good example is the combination of acetaminophen [Tylenol] with alcohol. When taken in *therapeutic* doses in the absence of alcohol, acetaminophen cannot harm the liver. However, if the drug is taken with just two or three drinks, severe liver injury can result. Of course, excessive doses of acetaminophen, without any alcohol, can also damage the liver.

Patients taking hepatotoxic drugs should undergo liver function tests (LFTs) at baseline and periodically thereafter. How do we assess liver function? By testing a blood sample for the presence of two liver enzymes: *aspartate aminotransferase* (AST, formerly known as SGOT) and *alanine aminotransferase* (ALT, formerly known as SGPT). Under normal conditions blood levels of AST and ALT are low. However, when liver cells are injured, blood levels of these enzymes rise. LFTs are performed on a regular schedule (eg, every 3 months) in hopes of detecting injury early. Unfortunately, since drug-induced liver injury can develop very quickly, it may progress from undetectable to advanced between scheduled tests. Nonetheless, since death from liver failure can often be avoided with early detection, routine testing of liver function is still indicated.

All patients receiving hepatotoxic drugs should be informed about signs of liver injury—jaundice (yellow skin and eyes), dark urine, light-colored stools, nausea, vomiting, malaise, abdominal discomfort, loss of appetite—and advised to seek medical attention if these develop.

QT Interval Drugs

The term *QT interval drugs*—or simply *QT drugs*—refers to the ability of some medications to prolong the QT interval on the electrocardiogram, thereby creating a risk of serious dysrhythmias. As discussed in Chapter 49 (Antidysrhythmic Drugs), the QT interval is a measure of the time required for the ventricles to repolarize after each contraction. When the QT interval is prolonged, patients can develop a dysrhythmia known as *torsades de pointes*, which can progress to potentially

fatal ventricular fibrillation. How long must the QT interval be to be considered long? More than 470 msec for postpubertal males, or more than 480 msec for postpubertal females.

More than 100 drugs are known to cause QT prolongation, torsades de pointes, or both. As shown in Table 7-2, QT drugs are found in many drug families. Seven QT drugs—including astemizole [Hismanal], terfenadine [Seldane], and fenfluramine [Pondimin]—have been withdrawn because of deaths linked to their use, and use of another QT drug—cisapride [Propulsid]—is now restricted. To reduce the risks from QT drugs, the Food and Drug Administration (FDA) now requires that all new drugs be tested for the ability to cause QT prolongation.

When QT drugs are used, care is needed to minimize the risk of dysrhythmias. These agents should be used with caution in patients predisposed to dysrhythmias. Among these are the elderly and patients with bradycardia, heart failure, congenital QT prolongation, and low levels of potassium or magnesium. Women are also at risk. Why? Because their normal QT interval is longer than the QT interval in men. Concurrent use of two or more QT drugs should be avoided, as should the concurrent use of a QT drug with another drug that can raise its blood level (eg, by inhibiting its metabolism). Obviously, excessive dosing should be avoided. Additional information on QT drugs, including a current list of these agents, is available online at www.QTdrugs.org.

Identifying Adverse Drug Reactions

It can be very difficult to determine whether a specific drug is responsible for an observed adverse event. Why? Because other factors—especially the underlying illness and other drugs being taken—could be the actual cause. To help determine if a particular drug is responsible, the following questions should be asked:

- Did symptoms appear shortly after the drug was first used?
- Did symptoms abate when the drug was discontinued?
- Did symptoms reappear when the drug was reinstated?
- Is the illness itself sufficient to explain the event?
- Are other drugs in the regimen sufficient to explain the event?

TABLE 7-2 • Drugs That Prolong the QT Interval, Induce Torsades de Pointes, or Both

Cardiovascular: Antidysrhythmics

Amiodarone [Cordarone]
 Disopyramide [Norpace]
 Dofetilide [Tikosyn]
 Flecainide [Tambocor]
 Ibutilide [Corvert]
 Mexiletine [Mexitil]
 Procainamide [Procan, Pronestyl]
 Quinidine
 Sotalol [Betapace]

Cardiovascular: ACE Inhibitors/CCBs

Bepidil [Vascor]
 Isradipine [DynaCirc]
 Moexipril
 Nicardipine [Cardene]

Cardiovascular: Others

Dobutamine [Dobutrex]
 Dopamine
 Norepinephrine [Levophed]
 Ranolazine [Ranexa]

Antibiotics

Azithromycin [Zithromax]
 Clarithromycin [Biaxin]
 Erythromycin
 Gatifloxacin [Tequin]
 Gemifloxacin [Factive]
 Levofloxacin [Levaquin]
 Moxifloxacin [Avelox]
 Ofloxacin [Floxin]
 Sparfloxacin [Zagam]
 Telithromycin [Ketek]

Antifungal Drugs

Fluconazole [Diflucan]
 Itraconazole [Sporanox]
 Ketoconazole [Nizoral]
 Voriconazole [Vfend]

Antidepressants

Amitriptyline [Elavil]
 Citalopram [Celexa]
 Desipramine [Norpramin]
 Doxepin [Sinequan]
 Fluoxetine [Prozac]
 Imipramine [Tofranil]
 Protriptyline [Pamelor, Aventyl]
 Sertraline [Zoloft]
 Trimipramine [Surmontil]
 Venlafaxine [Effexor]

Antipsychotics

Chlorpromazine [Thorazine]
 Clozapine [Clozaril]
 Haloperidol [Haldol]
 Mesoridazine [Serenil]
 Pimozide [Orap]
 Quetiapine [Seroquel]
 Risperidone [Risperdal]
 Thioridazine [Mellaril]
 Ziprasidone [Geodon]

Antiemetics/Antinausea Drugs

Dolasetron [Anzemet]
 Domperidone [Motilium]
 Droperidol [Inapsine]
 Granisetron [Kytrel]
 Ondansetron [Zofran]

Bronchodilators

Albuterol [Proventil, Ventolin]
 Ephedrine
 Epinephrine [Bronkaid, Primatene]
 Isoproterenol [Isuprel]
 Levalbuterol [Xopenex]
 Metaproterenol [Alupent]
 Salmeterol [Serevent]
 Terbutaline

Anticancer Drugs

Arsenic trioxide [Trisenox]
 Sunitinib [Sutent]
 Tamoxifen [Nolvadex]

Drugs for ADHD

Amphetamine/dextroamphetamine [Adderall]
 Atomoxetine [Strattera]
 Dexmethylphenidate [Focalin]
 Dextroamphetamine [Dexedrine]
 Methylphenidate [Ritalin, Concerta]

Nasal Decongestants

Phenylephrine [Neo-Synephrine, Sudafed PE]
 Pseudoephedrine [Sudafed]

Other Drugs

Alfuzosin [Uroxatral]
 Amantadine [Symmetrel]
 Chloroquine [Aralen]
 Cisapride [Propulsid]*
 Cocaine
 Felbamate [Felbatol]
 Foscarnet [Foscavir]
 Fosphenytoin [Cerebyx]
 Galantamine [Razadyne]
 Halofantrine [Halfan]
 Indapamide [Lozol]
 Lithium [Lithobid, Eskalith]
 Methadone [Dolophine]
 Midodrine [ProAmatine]
 Octreotide [Sandostatatin]
 Pentamidine [Pentam, Nebupent]
 Phentermine [Fastin]
 Ritodrine [Yutopar]
 Salmeterol [Serevent]
 Solifenacin [Vesicare]
 Tacrolimus [Prograf]
 Tizanidine [Zanaflex]
 Tolterodine [Detrol]
 Vardenafil [Levitra]

ACE = angiotensin-converting enzyme; ADHD = attention-deficit/hyperactivity disorder; CCB = calcium channel blocker.
 *Restricted availability.

If the answers reveal a temporal relationship between the presence of the drug and the adverse event, and if the event cannot be explained by the illness itself or by other drugs in the regimen, then there is a high probability that the drug under suspicion is indeed the culprit. Unfortunately, this process is limited: It can only identify adverse effects that occur while the drug is being used; it cannot identify adverse events that develop years after drug withdrawal. Nor can it identify effects that develop slowly, that is, over the course of prolonged drug use.

Adverse Reactions to New Drugs

As we discussed in Chapter 3, preclinical and clinical trials of new drugs cannot detect all of the ADRs that a drug may be able to cause. In fact, about 50% of all new drugs have serious ADRs that are not revealed during Phase II and Phase III trials.

Because newly released drugs may have as-yet unreported adverse effects, you should be alert for unusual responses when giving new drugs. If the patient develops new symptoms, it is wise to suspect that the drug may be responsible—even if the symptoms are not described in the literature. If the drug is especially new, you may be the first clinician to have observed the effect.

If you suspect a drug of causing a previously unknown adverse effect, you should report the effect to MEDWATCH, the FDA Medical Products Reporting Program. You can file your report online at www.fda.gov/medwatch. The form used for reporting is shown in Figure 7-1. Because voluntary reporting by healthcare professionals is an important mechanism for bringing ADRs to light, you should report all suspected ADRs, even if absolute proof of the drug's complicity has not been established.

In addition to the MEDWATCH program, which applies to all drugs, both new and old, the FDA has launched a new pro-

U.S. Department of Health and Human Services

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page ___ of ___

FDA USE ONLY	
Triage unit sequence #	

A. PATIENT INFORMATION			
1. Patient Identifier <small>In confidence</small>	2. Age at Time of Event, or Date of Birth:	3. Sex <input type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight lb or kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR	
Check all that apply:	
<input type="checkbox"/> Adverse Event <input type="checkbox"/> Product Problem (e.g., defects/malfunctions) <input type="checkbox"/> Product Use Error <input type="checkbox"/> Problem with Different Manufacturer of Same Medicine	
2. Outcomes Attributed to Adverse Event (Check all that apply)	
<input type="checkbox"/> Death: _____ (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)	
3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)

5. Describe Event, Problem or Product Use Error

6. Relevant Tests/Laboratory Data, including Dates

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

C. PRODUCT AVAILABILITY	
Product Available for Evaluation? (Do not send product to FDA)	
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Returned to Manufacturer on: _____ (mm/dd/yyyy)	

D. SUSPECT PRODUCTS(S)	
1. Name, Strength, Manufacturer (from product label)	
#1 Name	Strength
Manufacturer	
#2 Name	Strength
Manufacturer	

2. Dose or Amount			Frequency			Route		
#1								
#2								
3. Dates of Use (If unknown, give duration) from/to (or best estimate)						5. Event Abated After Use Stopped or Dose Reduced?		
#1						#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply		
#2						#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply		
4. Diagnosis or Reason for Use (Indication)						8. Event Reappeared After Reintroduction?		
#1						#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply		
#2						#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply		
6. Lot #			7. Expiration Date			9. NDC # or Unique ID		
#1			#1					
#2			#2					

E. SUSPECT MEDICAL DEVICE				
1. Brand Name				
2. Common Device Name				
3. Manufacturer Name, City and State				
4. Model #		Lot #		5. Operator of Device <input type="checkbox"/> Health Professional <input type="checkbox"/> Lay User/Patient <input type="checkbox"/> Other:
Catalog #		Expiration Date (mm/dd/yyyy)		
Serial #		Other #		
6. If Implanted, Give Date (mm/dd/yyyy)			7. If Explanted, Give Date (mm/dd/yyyy)	
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? <input type="checkbox"/> Yes <input type="checkbox"/> No				
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor				

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS	
Product names and therapy dates (exclude treatment of event)	

G. REPORTER (See confidentiality section on back)			
1. Name and Address			
Name:			
Address:			
City:		State:	ZIP:
Phone #		E-mail	
2. Health Professional? <input type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation	
4. Also Reported to: <input type="checkbox"/> Manufacturer <input type="checkbox"/> User Facility <input type="checkbox"/> Distributor/Importer			
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: <input type="checkbox"/>			

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Figure 7-1 • Form for reporting adverse drug events to the FDA.

gram—*Postmarketing Drug Safety Evaluations*—dedicated to providing safety information on recently approved drugs. Evaluations are conducted 18 months after a drug is approved, or after 10,000 patients have used the drug, whichever comes later. Data for the evaluations are drawn from multiple sources, including MEDWATCH, the Vaccine Adverse Event Reporting System, safety reports from manufacturers, postapproval clinical trials, and the medical literature. Summaries of the safety evaluations are available online at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm.

Ways to Minimize Adverse Drug Reactions

The responsibility for reducing ADRs lies with everyone associated with drug production and use. The pharmaceutical industry must strive to produce the safest medicines possible; the prescriber must select the least harmful medicine for a particular patient; the nurse must evaluate patients for ADRs and educate patients in ways to avoid or minimize harm; and patients and their families must watch for signs that an ADR may be developing, and should seek medical attention if one appears.

Anticipating ADRs can help minimize them. Nurses and patients should know the major ADRs that a drug can produce. This knowledge allows early identification of adverse effects, thereby permitting timely implementation of measures to minimize harm.

As noted, certain drugs are toxic to specific organs. When patients are using these drugs, function of the target organ should be monitored. The liver, kidneys, and bone marrow are important sites of drug toxicity. For drugs that are toxic to the liver, the patient should be monitored for signs and symptoms of liver damage (jaundice, dark urine, light-colored stools, nausea, vomiting, malaise, abdominal discomfort, loss of appetite), and periodic LFTs should be performed. For drugs that are toxic to the kidneys, the patient should undergo routine urinalysis and measurement of serum creatinine. In addition, periodic tests of creatinine clearance should be performed. For drugs that are toxic to bone marrow, periodic blood cell counts are required.

Adverse effects can be reduced by individualizing therapy. When choosing a drug for a particular patient, the prescriber must balance potential risks of that drug versus its probable benefits. Drugs that are likely to harm a specific patient should be avoided. For example, if a patient has a history of penicillin allergy, we can avoid a potentially severe reaction by withholding penicillin and administering a suitable substitute. Similarly, when treating pregnant patients, we must withhold drugs that can injure the fetus (see Chapter 9).

Lastly, we must be aware that patients with chronic disorders are especially vulnerable to ADRs. In this group are patients with hypertension, epilepsy, heart disease, and psychoses. When drugs must be used long term, the patient should be informed about the adverse effects that may develop over time and should be monitored for their appearance.

Medication Guides, Boxed Warnings, and REMS

For drugs with especially serious adverse effects, the FDA now requires one or more of the following: a *Medication Guide* for patients, a *boxed warning* to alert prescribers, and/

or a *Risk Evaluation and Mitigation Strategy (REMS)*, which can involve patients, prescribers, and pharmacists.

Medication Guides

Medication Guides, commonly called MedGuides, are FDA-approved documents created to educate patients about how to minimize harm from potentially dangerous drugs. In addition, a Medication Guide is required when the FDA has determined that (1) patient adherence to directions for drug use is essential for efficacy or (2) patients need to know about potentially serious effects when deciding to use a drug.

All Medication Guides use a standard format that provides information under the following main headings:

- What is the most important information I should know about (*name of drug*)?
- What is (*name of drug*)? Including: a description of the drug and its indications.
- Who should not take (*name of drug*)?
- How should I take (*name of drug*)? Including: importance of adherence to dosing instructions, special instructions about administration, what to do in case of overdose, and what to do if a dose is missed.
- What should I avoid while taking (*name of drug*)? Including: activities (eg, driving, sunbathing), other drugs, foods, pregnancy, breast-feeding.
- What are the possible or reasonably likely side effects of (*name of drug*)?
- General information about the safe and effective use of prescription drugs.

Additional headings may be added by the manufacturer as appropriate, with the approval of the FDA.

The Medication Guide should be provided whenever a prescription is filled, and even when drug samples are handed out. However, under special circumstances, the Guide can be withheld. For example, if the prescriber feels that the information in the Guide might deter a patient from taking a potentially lifesaving drug, the prescriber can ask the pharmacy to withhold the Guide. Nonetheless, if the patient asks for the information, the pharmacist must provide it, regardless of the request to withhold it.

Medication Guides for all drug products that have one are available online at www.fda.gov/Drugs/DrugSafety/UCM085729.

Boxed Warnings

The *boxed warning*, also known as a *black box warning*, is the strongest safety warning a drug can carry and still remain on the market. Text for the warning is presented inside a box with a heavy black border. The FDA requires a boxed warning for drugs it considers especially dangerous. The purpose of the warning is to alert prescribers to (1) potentially severe side effects (eg, life-threatening dysrhythmias, suicidality, major fetal harm) as well as (2) ways to prevent or reduce harm (eg, avoiding a teratogenic drug during pregnancy). The boxed warning should provide a *concise summary* of the adverse effects of concern, not a detailed explanation. A boxed warning must appear prominently on the package insert, on the product label, and even in magazine advertising. Drugs that have a boxed warning must also have a Medication Guide.

Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is simply a plan to minimize drug-induced harm. Many REMS are very simple, but some are complex. The simplest REMS have only one component: a Medication Guide. For the majority of drugs that have a REMS, a Medication Guide is all that is needed. For a few drugs, however, the REMS may have additional components. For example, the REMS for isotretinoin, a drug for severe acne, has provisions that pertain to the patient, prescriber, and pharmacist. This program, known as iPLEDGE, is needed because isotretinoin can cause serious birth defects. The iPLEDGE program was designed to ensure that women who are pregnant, or may become pregnant, will not have access to the drug. Details of the iPLEDGE program are presented in Chapter 105 (Drugs for the Skin). All REMS that have received FDA approval can be accessed online at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

MEDICATION ERRORS

Medication errors are a major cause of morbidity and mortality, as documented in two landmark reports: *To Err is Human*, issued in 1999, and *Preventing Medication Errors*, issued in 2006. Both were produced by special committees of the Institute of Medicine (IOM), a branch of the National Academies. According to the IOM reports, every year medication errors injure at least 1.5 million Americans, and kill an estimated 7000. The financial costs are staggering: Among hospitalized patients alone, treatment of drug-related injuries costs about \$3.5 billion a year. Some authorities argue that the IOM estimates exaggerate the problem; others argue that the estimates are too low. However, all agree that medication errors are a real problem—even if the IOM estimates are in dispute. In response to the IOM reports, healthcare organizations throughout the country intensified efforts to reduce medical errors and thereby improve patient safety.

What's a Medication Error and Who Makes Them?

The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use." Note that, by this definition, medication errors can be made by many people—beginning with workers in the pharmaceutical industry, followed by people in the healthcare delivery system, and ending with patients and their family members.

In the hospital setting, a medication order must be processed by several people before it reaches the patient. All of these people can make a mistake. Fortunately, most are also in a position to catch mistakes made by others. The process typically begins with a physician or nurse practitioner writing

a prescription; then someone transcribes the order; in the pharmacy, someone enters the order into a computer; then a pharmacy technician prepares the order, after which a pharmacist checks it; and finally a nurse checks the order again and then administers the drug. Each of these people is in a position to make an error. Except for the prescriber, each is also in a position to catch errors made by others as the order moves down the line. Because the nurse is the last person in the sequence, the nurse is the patient's last line of defense against mistakes—and also the last person with the opportunity to make one. Note also that the nurse is the only person whose actions are not routinely checked by anyone else. Because the nurse is the last person who can catch mistakes made by others, and because no one is there to catch mistakes the nurse might make, the nurse bears a heavy responsibility for ensuring patient safety. Can you think of a better reason to learn all you can about drugs?

Types of Medication Errors

Medication errors fall into 13 major categories (Table 7-3). Some types of errors cause harm directly, and some cause harm indirectly. For example, giving an excessive dose can cause direct harm (adverse effects or even death) from having too much drug in the body. Conversely, giving too little medication can lead to harm, not through direct effects of the drug, but through failure to adequately treat an illness. According to the 1999 IOM report, among *fatal* medication errors, the most common types are giving an overdose (36.4%), giving the wrong drug (16.2%), and using the wrong route (9.5%).

Causes of Medication Errors

Medication errors can result from many causes (Table 7-4). Among fatal medication errors, the 1999 IOM report identified three categories—human factors, communication mistakes, and name confusion—that account for 90% of all errors. Of the human factors that can cause errors, performance deficits (eg, administering a drug IV instead of IM) are the most common (29.8%), followed by knowledge deficits (14.2%) and miscalculation of dosage (13%).

TABLE 7-3 ■ Types of Medication Errors

Wrong patient
Wrong drug
Wrong route
Wrong time
Wrong dose
Overdose
Underdose
Extra dose
Omitted dose
Wrong dosage form
Wrong diluent
Wrong strength/concentration
Wrong infusion rate
Wrong technique (includes inappropriate crushing of tablets)
Deteriorated drug error (dispensing a drug after its expiration date)
Wrong duration of treatment (continuing too long or stopping too soon)

TABLE 7-4 • Causes of Medication Errors

Cause	Examples
Human Factors	
Performance deficit	Administration by IV infusion when IM injection was intended
Knowledge deficit	Failure to know and follow reasonable practice standards
Miscalculation of dosage	
Drug preparation error	Using the wrong diluent; using the wrong amount of diluent; adding the wrong drug, adding the wrong amount of drug
Computer error	Incorrect selection from a list by computer operator; incorrect programming into the database; inadequate screening for allergies, interactions, etc.
Stocking error	Error in stocking or restocking; error in cart filling
Transcription error	Original to paper/carbon paper; original to computer; original to fax
Stress	High-volume workload, etc.
Fatigue or lack of sleep	
Communication	
Written miscommunication	Illegible handwriting; misreading or failure to read; confusion regarding decimal point placement in dosage
Oral miscommunication	
Name Confusion	
Trade name confusion	Name sounds or looks like another drug name
Generic name confusion	Name sounds or looks like another drug name
Packaging, Formulations, and Delivery Devices	
Inappropriate packaging	Topical product packaged in sterile IV multidose vial
Tablet or capsule confusion	Confusion because the tablet or capsule is similar in color, shape, or size to tablets or capsules that contain a different drug or a different strength of the same drug
Delivery device problems	Malfunction; infusion pump problems; selection of wrong device
Labeling and Reference Materials	
Manufacturer's carton	Carton looks similar to other cartons from the same manufacturer or cartons from a different manufacturer
Manufacturer's container label	Label looks similar to other labels from the same manufacturer or to labels from a different manufacturer
Label of dispensed product	Wrong patient name; wrong drug name; wrong strength; wrong or incomplete directions
Reference materials (package insert and other printed material, electronic material)	Inaccurate, incomplete, misleading, or outdated information

Miscommunication involving oral and written orders underlies 15.8% of fatal errors. Poor handwriting is an infamous cause of mistakes. In one example, an order for 2 mg of warfarin (an anticoagulant) was misread as 5 mg, and resulted in death from hemorrhage. In another case, a woman with arthritis died because her prescription to take 10 mg of methotrexate (an immunosuppressant) once a week was misread as 10 mg once a day. Because of illegible handwriting by prescribers, pharmacists make an estimated 150 million phone calls a year for clarification. When patients are admitted to the hospital, errors can result from poor communication regarding medications they were taking at home. For example, a child who was taking cisapride at home died because his prescription for one-fourth of a 10-mg tablet 4 times a day was incorrectly transcribed to read one 10-mg tablet 4 times a day. Other causes of communication errors include careless use of zeros and decimal points, and confusion between metric and apothecary units.

Confusion over drug names underlies 15% of all reports to the Medication Errors Reporting Program (see below).

Why is there confusion? Because many drugs have names that sound like or look like the names of other drugs. Table 7-5 lists some good examples, such as *Anaspaz/Antispas*, *Nasarel/Nizoral*, and *Renagel/Remegel*. Note that most of the examples in Table 7-5 are trade names, not generic names. The potential for lethal confusion among trade names is a powerful reason for abandoning them in favor of universal use of generic names. (In case you skipped the discussion on trade names in Chapter 3, your author feels very strongly that trade names should be outlawed.) To reduce name-related medication errors, all hospitals are now required to have a "read-back" system, in which verbal orders given to pharmacists or medical staff are transcribed and then read back to the prescriber.

Ways to Reduce Medication Errors

Healthcare organizations throughout the country are working to design and implement measures to reduce medication errors. A central theme in these efforts is to change institutional culture—

TABLE 7-5 ■ Examples of Drugs with Names That Sound Alike or Look Alike*

<i>Amicar</i>	<i>Omicar</i>
<i>Anaspaz</i>	<i>Antispas</i>
<i>Celebrex</i>	<i>Cerebyx</i>
<i>Clinoril</i>	<i>Clozaril</i>
<i>Cycloserine</i>	<i>Cyclosporine</i>
<i>Depo-Estradiol</i>	<i>Depo-Testadiol</i>
<i>Dioval</i>	<i>Diovan</i>
<i>Estratab</i>	<i>Estratest</i>
<i>Etidronate</i>	<i>Etretinate</i>
<i>Flomax</i>	<i>Volmax</i>
<i>Lamisil</i>	<i>Lamictal</i>
<i>Levoxine</i>	<i>Levoxyl</i>
<i>Lithobid</i>	<i>Lithostat</i>
<i>Lodine</i>	<i>Iodine</i>
<i>Naprelan</i>	<i>Naprosyn</i>
<i>Nasarel</i>	<i>Nizoral</i>
<i>Neoral</i>	<i>Neosar</i>
<i>Nephron</i>	<i>Nephrox</i>
<i>Nicoderm</i>	<i>Nitroderm</i>
<i>Preven</i>	<i>Preveon</i>
<i>Renagel</i>	<i>Remegel</i>
<i>Sarafem</i>	<i>Serophene</i>
<i>Serentil</i>	<i>Seroquel</i>
<i>Synagis</i>	<i>Synergis</i>
<i>Tamiflu</i>	<i>Theraflu</i>
<i>Tramadol</i>	<i>Toradol</i>

*Trade names are italicized; generic names are not.

TABLE 7-6 ■ Sixteen Ways to Cut Medication Errors*

Institutional Culture

- Establish an organizational commitment to a culture of safety.
- Provide medication safety education for all new and existing professional employees.
- Maintain ongoing recognition of safety innovation.
- Create a nonpunitive environment that encourages identification of errors and the development of new patient safety systems.

Infrastructure

- Designate a medication safety coordinator/officer and identify physician champions.
- Promote greater use of clinical pharmacists in high-risk areas.
- Establish area-specific guidelines for unit-stocked medications.
- Establish a mechanism to ensure availability of critical medication information to all members of the patient's care team.

Clinical Practice

- Eliminate dangerous abbreviations and dose designations.
- Implement safety checklists for high-alert medications.
- Implement safety checklists for infusion pumps.
- Develop limitations and safeguards regarding verbal orders.
- Perform failure-mode analysis during procurement process.
- Implement triggers and markers to indicate potential adverse medication events.

Technology

- Eliminate the use of infusion pumps that lack free-flow protection.
- Prepare for implementation of computerized prescriber order entry systems.

*These strategies are recommended in the Regional Medication Safety Program for Hospitals (RMSPH), developed by a consortium of hospitals in southeastern Pennsylvania.

from one that focuses on “naming, shaming, and blaming” those who make mistakes to one focused on designing institution-wide processes and systems that can prevent errors from happening. Measures stressed in the 2006 IOM report include (1) helping and encouraging patients and their families to be active, informed members of the healthcare team, and (2) giving healthcare providers the tools and information needed to prescribe, dispense, and administer drugs as safely as possible.

In southeastern Pennsylvania, a consortium of hospitals has developed a unique system for reducing medication errors. This system, known as the Regional Medication Safety Program for Hospitals (RMSPH), can be considered a model for other hospitals to follow. The RMSPH has a total of 16 action goals divided into four major categories: institutional culture, infrastructure, clinical practice, and technology (Table 7-6). Note that creating an institutional culture dedicated to safety tops the list, and that the institutional environment should be nonpunitive so as to encourage both the identification of errors and the development of new safety systems. This is a radical departure from the past, when organizations focused largely on identifying and punishing caregivers who made mistakes. As you read through Table 7-6, the potential benefits of all 16 objectives should be apparent. To help practitioners achieve these 16 goals, the RMSPH contains a “tool kit” with detailed supporting information on how to meet each objective. For example, the kit includes safety checklists to follow when using high-alert drugs, such as anticoagulants, thrombolytics, and neuromuscular blocking agents. (About 20 such drugs cause 80% of medication error-related deaths.)

Some measures to reduce errors have had remarkable success. For example,

- Replacing handwritten medication orders with a computerized order entry system has reduced medication errors by 50%. (The 2006 IOM report recommended that all prescriptions be written electronically by the year 2010.)
- In ICUs, medication errors have been reduced by 66% by having a senior clinical pharmacist accompany physicians on rounds.
- Hospitals in the Department of Veterans Affairs (VA) system have reduced medication errors by up to 70% with a bar-code system. In this system, all nurses and patients wear bar-coded ID strips, and all medications have bar codes too. Before giving a medication, the nurse scans all three codes into a computer, which then either (1) verifies that the patient-drug match is correct and adverse interactions are unlikely or (2) flashes a warning if there is a potential problem. (In 2006, the FDA issued a rule requiring that all hospitals employ a bar-code system like the one used in VA hospitals.)
- As discussed in Box 7-1, *medication reconciliation* can reduce errors that occur when patients undergo a transition in care (eg, hospital admission, transfer from one hospital unit to another, transfer from hospital to home.).

MEDICATION RECONCILIATION

Since 2005, The Joint Commission has required all hospitals to conduct medication reconciliations for all patients. The purpose is to reduce medication errors (eg, omissions, duplications, dosing errors) as well as adverse drug events and interactions.

What Is Medication Reconciliation and When Is It Done?

Medication reconciliation is the process of comparing a list of all medications that a patient is currently taking with a list of new medications that are about to be provided. Reconciliation is conducted whenever a patient undergoes a *transition in care* in which new medications may be ordered, or existing orders may be changed. Transitions in care include hospital admission, hospital discharge, and stepping up or stepping down to a different level of care within a hospital.

How Is Medication Reconciliation Conducted?

There are 5 steps:

- Step 1.** Create a list of current medications. For each drug, include the name, indication, route, dosage size, and dosing interval. For patients entering a hospital, the list would consist of all medications being taken at home, including vitamins, herbal products, and prescription and nonprescription drugs.
- Step 2.** Create a list of all medications to be prescribed in the new setting.
- Step 3.** Compare the medications on both lists.
- Step 4.** Adjust medications based on the comparison. For example, the prescriber would discontinue drugs that are duplicates or inappropriate, and would avoid drugs that can interact adversely.

As noted above, many medication errors result from errors in communication. To help reduce such errors, the Institute for Safe Medication Practices (ISMP) has compiled a list of error-prone abbreviations, symbols, and dose designations (Table 7-7), and has recommended against their use. This list includes eight entries (at the top of Table 7-7) that have been *banned* by The Joint Commission (TJC), formerly known as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). These banned abbreviations can no longer be used by hospitals and other organizations that require TJC accreditation.

There is a wealth of information available on reducing medication errors. If you would like more, a good place to start is the 2006 IOM report: *Reducing Medication Errors*. You can purchase the full report or download free summaries from the National Academies Press at www.nap.edu/catalog.php?record_id=11623. Comprehensive information can also be found at www.nccmerp.org, the web site of the National Coordinating Council for Medication Error Reporting and Prevention. The NCC MERP was established to facilitate the reporting, understanding, and prevention of medication errors. Member organizations include the American Nurses Association, American Medical Association, American Hospital Association, FDA, and U.S. Pharmacopeia (USP). The NCC MERP web site has exten-

Step 5. When the next transition in care occurs, provide the updated, reconciled list to the patient and the new provider. By consulting the list, the new provider will be less likely to omit a prescribed medication or commit a dosing error, and less likely to prescribe a new medication that might duplicate or negate the effects of a current medication, or interact with a current medication to cause a serious adverse event.

Every time a new transition in care occurs, reconciliation should be conducted again.

Does Medication Reconciliation Reduce Medication Errors?

Definitely. Roughly 60% of medication errors occur when patients undergo a transition in care. Medication reconciliation can eliminate most of these errors.

Should Medication Reconciliation Be Conducted at Discharge?

Definitely. When patients leave a facility, they should receive a single, clear, comprehensive list of *all* medications they will be taking after discharge. The list should include any medications ordered at the time of discharge, as well as any other medications the patient will be taking, including over-the-counter drugs, vitamins, and herbal products and other nutritional supplements. In addition, the list should include all prescription medications that the patient had been taking at home but had been temporarily discontinued during the episode of care. The discharge list should *not* include drugs that had been used during the episode of care but are no longer needed. Who should receive the discharge list? The patient, and, with the patient's permission, the next provider of care, so that the new provider will be able to continue the reconciliation process.

sive recommendations for reducing medication errors related to drug administration, drug dispensing, and verbal medication orders and prescriptions. In addition, the site presents recommendations for promoting and standardizing bar coding on medication packaging. Even more information is available from the ISMP (at <http://www.ismp.org/MSAarticles/AHA-ISMP.html>) and the FDA (at <http://www.fda.gov/Drugs/DrugSafety/MedicationErrors/default.htm>).

How to Report a Medication Error

You can report a medication error via the *Medication Error Reporting (MER) Program*, a nationwide system run by the ISMP. All reporting is confidential and can be done by phone or fax, or through the Internet. Details on submitting a report are available online at <https://www.ismp.org/orderForms/reporterrortoISMP.asp>. The MER Program encourages participation by all healthcare providers, including pharmacists, nurses, physicians, and students. The objective is not to establish blame, but to improve patient safety by increasing our knowledge of medication errors. All information gathered by the MER Program is forwarded to the FDA, the ISMP, and the product manufacturer.

TABLE 7-7 ■ Abbreviations, Symbols, and Dose Designations That Can Promote Medication Errors

Abbreviations, Symbols, or Dose Designations	Intended Meaning	Potential Misinterpretation	Preferred Alternative
Abbreviations and Notations for Which the Alternative MUST be Used (TJC Mandated)			
U or u	Unit	Misread as 0 or 4 (eg, 4U seen as 40; 4u seen as 44); mistaken to mean "cc" so dose given in volume instead of units (eg, 4u mistaken to mean 4cc)	Write "unit"
IU	International unit	Misread as IV (intravenous) or "10"	Write "international unit"
q.d./Q.D.	Every day	Misread as q.i.d. (four times a day)	Write "daily"
q.o.d./Q.O.D.	Every other day	Misread as q.d. (daily) or q.i.d. (four times a day)	Write "every other day"
MS or MSO ₄	Morphine sulfate	Mistaken as magnesium sulfate	Write "morphine sulfate"
MgSO ₄	Magnesium sulfate	Mistaken as morphine sulfate	Write "magnesium sulfate"
Trailing zero after final decimal point (eg, 1.0 mg)	1 mg	Mistaken as 10 mg if the decimal point is missed	Never write a zero by itself after a decimal point
Leading decimal point not preceded by a zero (eg, .5 mg)	0.5 mg	Mistaken as 5 mg if the decimal point is missed	Write "0" before a leading decimal point
Some Abbreviations and Notations for Which the Alternative is RECOMMENDED (but not yet TJC mandated)			
µg	Microgram	Mistaken as "mg"	Write "mcg"
cc	Cubic centimeters	Mistaken as "u" (units)	Write "mL"
IN	Intranasal	Mistaken as "IM" or "IV"	Write "intranasal" or "NAS"
H.S., hs	Half-strength; at bedtime	Mistaken as opposite of what was intended	Write "half-strength" or "at bedtime"
qhs	At bedtime	Mistaken as qhr (every hour)	Write "at bedtime"
qId	Daily	Mistaken as q.i.d. (four times daily)	Write "daily"
q6PM, etc.	Nightly at 6 PM	Mistaken as every 6 hours	Write "nightly at 6 PM"
T.I.W.	Three times a week	Mistaken as three times a day or twice weekly	Write "three times weekly"
SC, SQ, sub q	Subcutaneous	SC mistaken as "SL" (sublingual); SQ mistaken as "5 every"; the "q" in "sub q" mistaken as "every" (eg, a heparin dose ordered "sub q 2 hours before surgery" mistaken as "every 2 hours before surgery")	Write "subQ," "sub-Q," "subcut," or "subcutaneously"; write "every"
D/C	Discharge or discontinue	Premature discontinuation of medications if D/C (intended to mean "discharge") has been interpreted as "discontinued" when followed by a list of discharge medications	Write "discharge" or "discontinue"
AD, AS, AU	Right ear, left ear, each ear	Mistaken as OD, OS, OU (right eye, left eye, each eye)	Write "right ear," "left ear," or "each ear"
OD, OS, OU	Right eye, left eye, each eye	Mistaken as AD, AS, AU (right ear, left ear, each ear)	Write "right eye," "left eye," or "each eye"
Per os	By mouth, orally	The "os" can be mistaken as "left eye" (OS = oculus sinister)	Write "PO," "by mouth," or "orally"
> or <	Greater than or less than	Mistaken for the opposite	Write "greater than" or "less than"
AZT	Zidovudine [Retrovir]	Mistaken as azathioprine or aztreonam	Write complete drug name
CPZ	Prochlorperazine [Compazine]	Mistaken as chlorpromazine	Write complete drug name
ARA A	Vidarabine	Mistaken as cytarabine (ARA C)	Write complete drug name
HCT	Hydrocortisone	Mistaken as hydrochlorothiazide	Write complete drug name
HCTZ	Hydrochlorothiazide	Mistaken as hydrocortisone	Write complete drug name

TJC = The Joint Commission, formerly known as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Adapted from a list compiled by the Institute for Safe Medication Practices, as modified in 2005. The complete list is available online at www.ismp.org/PDF/ErrorProne.pdf.

KEY POINTS

- An adverse drug reaction can be defined as any noxious, unintended, and undesired effect that occurs at normal drug doses.
- Patients at increased risk of adverse drug events include the very young, the elderly, the very ill, and those taking multiple drugs.
- An iatrogenic disease is a drug- or physician-induced disease.
- An idiosyncratic effect is an adverse drug reaction based on a genetic predisposition.
- A carcinogenic effect is a drug-induced cancer.
- A teratogenic effect is a drug-induced birth defect.
- The intensity of an allergic drug reaction is based on the degree of immune system sensitization—not on drug dosage.
- Drugs are the most common cause of acute liver failure, and hepatotoxicity is the most common reason for removing drugs from the market.
- Drugs that prolong the QT interval pose a risk of torsades de pointes, a dysrhythmia that can progress to fatal ventricular fibrillation.
- At the time a new drug is released, it may well be able to cause adverse effects that are as yet unreported.
- Measures to minimize adverse drug events include avoiding drugs that are likely to harm a particular patient, monitoring the patient for signs and symptoms of likely adverse effects, educating the patient about possible adverse effects, and monitoring organs that are vulnerable to a particular drug.
- To reduce the risk of serious reactions to certain drugs, the FDA may require the manufacturer to create a Medication Guide for patients, a boxed warning to alert prescribers, and/or a Risk Evaluation and Mitigation Strategy, which may involve patients, prescribers, and pharmacists.
- Medication errors are a major cause of morbidity and mortality.
- Medication errors can be made by many people, including pharmaceutical workers, pharmacists, prescribers, transcriptionists, nurses, and patients and their families.
- In a hospital, a medication order is processed by several people. Each is in a position to introduce errors, and, except for the prescriber, each is in a position to catch errors made by others.
- The nurse is the patient's last line of defense against medication errors made by others—and the last person with the opportunity to introduce an error.
- Because the nurse is the last person who can catch mistakes made by others, and because no one is there to catch mistakes the nurse might make, the nurse bears a unique responsibility for ensuring patient safety.
- The three most common *types* of fatal medication errors are giving an overdose, giving the wrong drug, and using the wrong route.
- The three most common *causes* of fatal medication errors are human factors (eg, performance or knowledge deficits), miscommunication (eg, because of illegible prescriber handwriting), and confusion caused by similarities in drug names.
- At the heart of efforts to reduce medication errors is a change in institutional culture—from a punitive system focused on “naming, blaming, and shaming” to a nonpunitive system in which medication errors can be discussed openly, thereby facilitating the identification of errors and the development of new safety procedures.
- Effective measures for reducing medication errors include (1) using a safety checklist for high-alert drugs; (2) replacing handwritten medication orders with a computerized order entry system; (3) having a clinical pharmacist accompany ICU physicians on rounds; (4) avoiding error-prone abbreviations; (5) helping and encouraging patients and their families to be active, informed participants in the healthcare team; (6) conducting a medication reconciliation whenever a patient undergoes a transition in care; and (7) using a computerized bar-code system that (a) identifies the administering nurse and (b) ensures that the drug is going to the right patient and that adverse interactions are unlikely.

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Individual Variation in Drug Responses

Body Weight and Composition

Age

Pathophysiology

Kidney Disease

Liver Disease

Acid-Base Imbalance

Altered Electrolyte Status

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Genetic Variants That Alter Drug Targets

Genetic Variants That Alter Immune Responses to Drugs

Gender

Race

Drug Interactions

Diet

Failure to Take Medicine as Prescribed

Box 8-1. Has the Placebo Lost Its Effect?

Individual variation in drug responses has been a recurrent theme throughout the early chapters of this text. We noted that, because of individual variation, we must tailor drug therapy to each patient. In this chapter, we discuss the major factors that can cause one patient to respond to drugs differently than another. With this information, you will be better prepared to reduce individual variation in drug responses, thereby maximizing the benefits of treatment and reducing the potential for harm. Much of this chapter is a review of information presented in previous chapters.

BODY WEIGHT AND COMPOSITION

If we do not adjust dosage, body size can be a significant determinant of drug effects. Recall that the intensity of the response to a drug is determined in large part by the concentra-

tion of the drug at its sites of action—the higher the concentration, the more intense the response. Common sense tells us that, if we give the same dose to a small person and a large person, the drug will achieve a higher concentration in the small person, and therefore will produce more intense effects. To compensate for this potential source of individual variation, dosages must be adapted to the size of the patient.

When adjusting dosage to account for body weight, the prescriber may base the adjustment on body surface area rather than on weight per se. Why? Because surface area determinations account not only for the patient's weight but also for how fat or lean he or she may be. Since percentage body fat can change drug distribution, and since altered distribution can change the concentration of a drug at its sites of action, dosage adjustments based on body surface area provide a more precise means of controlling drug responses than do adjustments based on weight alone.

AGE

Drug sensitivity varies with age. Infants are especially sensitive to drugs, as are the elderly. In the very young, heightened drug sensitivity is the result of organ immaturity. In the elderly, heightened sensitivity results largely from organ degeneration. Other factors that affect sensitivity in the elderly are increased severity of illness, the presence of multiple pathologies, and treatment with multiple drugs. The clinical challenge created by heightened drug sensitivity in the very young and in the elderly is the subject of Chapters 10 and 11, respectively.

PATHOPHYSIOLOGY

Abnormal physiology can alter drug responses. In this section we examine the impact of four pathologic conditions: (1) kidney disease, (2) liver disease, (3) acid-base imbalance, and (4) altered electrolyte status.

Kidney Disease

Kidney disease can reduce drug excretion, causing drugs to accumulate in the body. If dosage is not lowered, drugs may accumulate to toxic levels. Accordingly, if a patient is taking a drug that is eliminated by the kidneys, and if renal function declines, dosage must be decreased.

The impact of kidney disease is illustrated in Figure 8-1, which shows the decline in plasma levels of kanamycin (an antibiotic) following injection into two patients, one with healthy kidneys and one with renal failure. (Elimination of

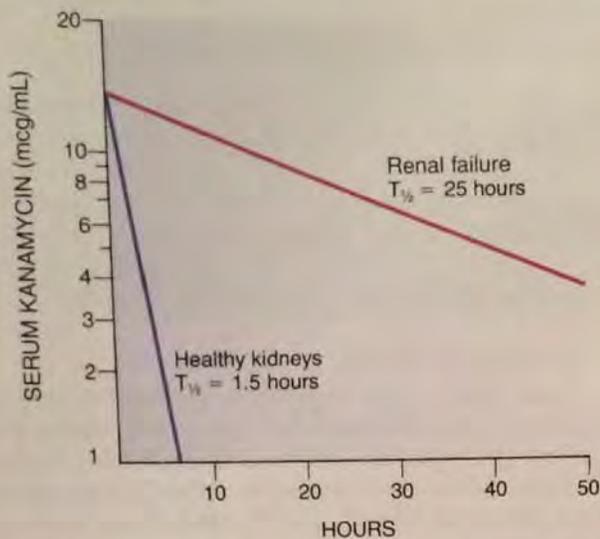


Figure 8-1 • Effect of renal failure on kanamycin half-life. Kanamycin was administered at time "0" to two patients, one with healthy kidneys and one with renal failure. Note that drug levels declined very rapidly in the patient with healthy kidneys and extremely slowly in the patient with renal failure, indicating that renal failure greatly reduced the capacity to remove this drug from the body. ($T_{1/2}$ = half-life.)

kanamycin is exclusively renal.) As indicated, kanamycin levels fall off rapidly in the patient with good kidney function. In this patient, the drug's half-life is brief—only 1.5 hours. In contrast, drug levels decline very slowly in the patient with renal failure. Because of kidney disease, the half-life of kanamycin has increased by nearly 17-fold—from 1.5 hours to 25 hours. Under these conditions, if dosage is not reduced, kanamycin will quickly accumulate to dangerous levels.

Liver Disease

Like kidney disease, liver disease can cause drugs to accumulate. Recall that the liver is the major site of drug metabolism. Hence, if liver function declines, rates of metabolism will decline too, and drug levels will climb. Accordingly, to prevent accumulation to toxic levels, dosage must be reduced if liver disease develops. Of course, this guideline applies only to those drugs that are eliminated primarily by the liver, not to drugs that are eliminated by the kidneys and other nonhepatic routes.

Acid-Base Imbalance

By altering pH partitioning (see Chapter 4), changes in acid-base status can alter the absorption, distribution, metabolism, and excretion of drugs.

Figure 8-2 illustrates the impact of altered acid-base status on drug distribution. Specifically, it shows the results of altered acid-base status on the distribution of phenobarbital (a weak acid) in a dog. The upper curve shows plasma levels of phenobarbital. The lower curve shows plasma pH. Acid-base status was altered by having the dog inhale a mixture of gas rich in carbon dioxide (CO_2), thereby causing respiratory acidosis. In the figure, acidosis is indicated by the drop in plasma pH. Note that the decline in pH is associated with a parallel drop in levels of phenobarbital. Upon discontinuation of CO_2 , plasma pH returned to normal and phenobarbital levels moved upward.

Why did acidosis alter plasma levels of phenobarbital? Recall that, because of pH partitioning, if there is a difference in pH on two sides of a membrane, a drug will accumulate on the side where the pH most favors its ionization. Hence, because acidic drugs ionize in alkaline media, acidic drugs will accumulate on the alkaline side of the membrane. Conversely, basic drugs will accumulate on the acidic side. Since phenobarbital is a weak acid,

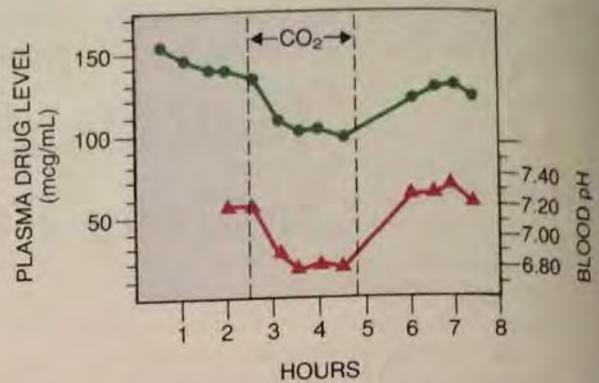


Figure 8-2 • Altered drug distribution in response to altered plasma pH.

Lower curve, Plasma (extracellular) pH. Note the decline in pH in response to inhalation of CO_2 . Upper curve, Plasma levels of phenobarbital. Note the decline in plasma drug levels during the period of extracellular acidosis. This decline results from the redistribution of phenobarbital into cells. (See text for details.) (Redrawn from Waddell WJ, Butler TC: The distribution and excretion of phenobarbital. *J Clin Invest* 36:1217, 1957.)

it tends to accumulate in alkaline environments. Accordingly, when the dog inhaled CO_2 , causing extracellular pH to decline, phenobarbital left the plasma and entered cells, where the environment was less acidic (more alkaline) than in plasma. When CO_2 administration ceased and plasma pH returned to normal, the pH partitioning effect caused phenobarbital to leave cells and re-enter the blood, causing blood levels to rise.

Altered Electrolyte Status

Electrolytes (eg, potassium, sodium, calcium, magnesium) have important roles in cell physiology. Consequently, when electrolyte levels become disturbed, multiple cellular processes can be disrupted. Excitable tissues (nerves and muscles) are especially sensitive to alterations in electrolyte status. Given that disturbances in electrolyte balance can have widespread effects on cell physiology, we might expect that electrolyte imbalances would cause profound and widespread effects on responses to drugs. However, this does not seem to be the case; examples in which electrolyte changes have a significant impact on drug responses are rare.

Perhaps the most important example of an altered drug effect occurring in response to electrolyte imbalance involves digoxin, a drug for heart disease. The most serious toxicity of digoxin is production of potentially fatal dysrhythmias. The tendency of digoxin to disturb cardiac rhythm is related to levels of potassium: When potassium levels are depressed, the ability of digoxin to induce dysrhythmias is greatly increased. Accordingly, all patients receiving digoxin must undergo regular measurement of serum potassium to ensure that levels remain within a safe range. Digoxin toxicity and its relationship to potassium levels are discussed at length in Chapter 48.

TOLERANCE

Tolerance can be defined as *decreased responsiveness to a drug as a result of repeated drug administration*. Patients who are tolerant to a drug require higher doses to produce effects equivalent to those that could be achieved with lower doses before tolerance developed. There are three categories of drug tolerance: (1) pharmacodynamic tolerance, (2) metabolic tolerance, and (3) tachyphylaxis.

Pharmacodynamic Tolerance

The term *pharmacodynamic tolerance* refers to the familiar type of tolerance associated with long-term administration of drugs such as morphine and heroin. The person who is phar

macodynamically tolerant requires increased drug levels to produce effects that could formerly be elicited at lower drug levels. Put another way, in the presence of pharmacodynamic tolerance, the minimum effective concentration (MEC) of a drug is abnormally high. Pharmacodynamic tolerance is the result of adaptive processes that occur in response to chronic receptor occupation.

Metabolic Tolerance

Metabolic tolerance is defined as tolerance resulting from accelerated drug metabolism. This form of tolerance is brought about by the ability of certain drugs (eg, barbiturates) to induce synthesis of hepatic drug-metabolizing enzymes, thereby causing rates of drug metabolism to increase. Because of increased metabolism, dosage must be increased to maintain therapeutic drug levels. Unlike pharmacodynamic tolerance, which causes the MEC to increase, metabolic tolerance does not affect the MEC.

The experiment summarized in Table 8-1 demonstrates the development of metabolic tolerance in response to repeated administration of pentobarbital, a central nervous system depressant. The study employed two groups of rabbits, a control group and an experimental group. Rabbits in the experimental group were pretreated with pentobarbital for 3 days (60 mg/kg/day subQ) and then given an IV challenging dose (30 mg/kg) of the same drug. Drug effect (sleeping time) and plasma drug levels were then measured. The control rabbits received the challenging dose of pentobarbital but did not receive any pretreatment. As indicated in Table 8-1, the challenging dose of pentobarbital had less effect on the pretreated rabbits than on the control animals. Specifically, whereas the control rabbits slept an average of 67 minutes, the pretreated rabbits slept only 30 minutes—less than half the sleeping time seen in controls.

Why was pentobarbital less effective in the pretreated animals? The data on half-life suggest an answer. As shown in the table, the half-life of pentobarbital was much shorter in the experimental group than in the control group. Since pentobarbital is eliminated primarily by hepatic metabolism, the reduced half-life indicates accelerated metabolism. This increase in metabolism, which was brought on by pentobarbital pretreatment, explains why the experimental rabbits were more tolerant than the controls.

You might ask, "How do we know that the experimental rabbits had not developed pharmacodynamic tolerance?" The answer lies in the plasma drug levels when the rabbits awoke. In the pretreated rabbits, the waking drug levels were slightly below the waking drug levels in the control group. Had the experimental animals developed pharmacodynamic tolerance, they would have required an increase in drug concentration to maintain sleep. Hence, if pharmacodynamic tolerance were present, drug levels would have been abnormally high at the time of awakening, rather than reduced.

TABLE 8-1 • Development of Metabolic Tolerance as a Result of Repeated Pentobarbital Administration

Results	Type of Pretreatment	
	None	Pentobarbital
Sleeping time (minutes)	67 ± 4	30 ± 7
Pentobarbital half-life in plasma (minutes)	79 ± 3	26 ± 2
Plasma level of pentobarbital upon awakening (mcg/mL)	9.9 ± 1.4	7.9 ± 0.6

Data from Remmer H: Drugs as activators of drug enzymes. In Brodie BB, Erdos EG (eds): *Metabolic Factors Controlling Duration of Drug Action* (Proceedings of First International Pharmacological Meeting, Vol 6). New York: Macmillan, 1962:235. (See text for details.)

Tachyphylaxis

Tachyphylaxis is a form of tolerance that can be defined as a reduction in drug responsiveness brought on by repeated dosing over a short time. Hence, unlike pharmacodynamic and metabolic tolerance, which take days to develop, tachyphylaxis occurs quickly. Tachyphylaxis is not a common mechanism of drug tolerance.

Transdermal nitroglycerin provides a good example of tachyphylaxis. When nitroglycerin is administered using a transdermal patch, effects are lost in less than 24 hours (if the patch is left in place around the clock). As discussed in Chapter 51, the loss of effect results from depletion of a cofactor required for nitroglycerin to act. When nitroglycerin is administered on an intermittent schedule, rather than continuously, the cofactor can be replenished between doses and no loss of effect occurs.

PLACEBO EFFECT

A *placebo* is a preparation that is devoid of intrinsic pharmacologic activity. Hence, any response that a patient may have to a placebo is based solely on his or her psychologic reaction to the idea of taking a medication and not to any direct physiologic or biochemical action of the placebo itself. The primary use of the placebo is as a control preparation during clinical trials.

In pharmacology, the *placebo effect* is defined as that component of a drug response that is caused by psychologic factors and not by the biochemical or physiologic properties of the drug. Although it is impossible to assess with precision the contribution that psychologic factors make to the overall response to any particular drug, it is widely believed that, with practically all medications, some fraction of the total response results from a placebo effect. Although placebo effects are determined by psychologic factors and not physiologic ones, the presence of a placebo response does not imply that a patient's original pathology was "all in the head."

Not all placebo responses are beneficial; placebo responses can also be negative. If a patient believes that a medication is going to be effective, then placebo responses are likely to help promote recovery. Conversely, if a patient is convinced that a particular medication is ineffective or perhaps even harmful, then placebo effects are likely to detract from his or her progress.

Because the placebo effect depends on the patient's attitude toward medicine, fostering a positive attitude may help promote beneficial effects. In this regard, it is desirable that all members of the healthcare team present the patient with an optimistic (but realistic) assessment of the effects that therapy is likely to produce. It is also important that members of the team be consistent with one another; the beneficial placebo responses may well be decreased if, for example, nurses on the day shift repeatedly reassure a patient about the likely benefits of his or her regimen, while nurses on the night shift express pessimism about those same drugs.

Until recently, the power of the placebo effect was unquestioned by most clinicians and researchers. However, evidence now suggests that responses to placebos may be much smaller than previously believed (Box 8-1).

VARIABILITY IN ABSORPTION

Both the rate and extent of drug absorption can vary among patients. As a result, both the timing and intensity of responses can be changed. Differences in manufacturing are a

HAS THE PLACEBO LOST ITS EFFECT?

In 1955, H. K. Beecher wrote his famous paper—"The Powerful Placebo"¹—which was heralded as solid proof for the long-held (but largely unsubstantiated) belief that placebos can effectively relieve symptoms in many patients. This widely cited paper had gone unchallenged until 2001, when two Danish scientists—Hróbjartsson and Gotzsche—wrote their own paper on the subject, titled "Is the Placebo Powerless?"² From their research, the Danes concluded that, at least in the context of clinical trials, placebo treatment has little or no measurable effect. Who's right? Let's consider both papers and see if we can decide.

Beecher analyzed the data from 15 placebo-controlled clinical trials. In all of these trials, patients in the placebo groups were evaluated at baseline, treated with placebo for a prescribed time, and then re-evaluated. Beecher then looked to see if improvement took place between baseline and the end of the treatment period. Based on his analysis, he concluded "It is evident that placebos have a high degree of effectiveness, decided improvement . . . being produced in 35.2% of cases." Pretty impressive. Unfortunately, there's a flaw: How do we know the placebos produced the benefits? Perhaps 35.2% of the patients would have improved with no treatment, owing simply to the natural course of their disease or to other factors. After all, many people *do* get better on their own—without doctors, drugs, placebos, or anything else. Furthermore, although Beecher claims to have selected the 15 papers at random, this seems improbable in that seven of them were his own.

To address questions left open by Beecher, Hróbjartsson and Gotzsche took a different approach. First, they analyzed data from 114 published trials—not just 15. More than 8500 patients were involved. More importantly, in all of these trials, placebo treatment was compared with *no treatment*. That is, in each trial, some subjects received placebo treatment and some received no treatment. (Of course, in most [112] of the trials, there was a third group of subjects who received an active treatment.) The trials involved 40 clinical conditions, including anemia, asthma, hypertension, hyperglycemia, epilepsy, Parkinson's disease, schizophrenia, depression, smoking, and pain. In 38 of the trials, the measured outcomes were *objective* (eg, reduction in blood pressure, increase in red blood cell count), and in 76 the outcomes were *subjective* (eg, improvement in mood, reduction of pain). Of the 114 trials, 45 evaluated pharmacologic interventions, 26 evaluated physical interventions, and 43 evaluated psychologic interventions. The type of placebo employed was matched to the active treatment: For the pharmacologic studies, typical placebo treatment consisted of giving a lactose pill; for the physical studies (eg, evaluating the effect of transcutaneous electrical nerve stimulation on pain), typical placebo treatment consisted of performing the procedure but with the equipment turned off; and for the psychologic studies (eg, evaluating the effect of psychotherapy on depression), typical placebo treatment consisted of nondirectional, neutral discussion between the patient and the treatment provider.

What did the analysis reveal? In trials with *objective* outcomes, placebo treatment had *virtually no measurable effects*: outcomes in patients receiving placebo treatment were identical to those in patients receiving no treatment at all. However, in some trials with *subjective* outcomes, placebo treatment *did* have a convincing effect—but it was small, and limited primarily to studies of *pain*. In their conclusion, the authors stated, "We found little evidence that placebos in general have powerful clinical effects," although they go on to say they did find "significant effects of placebo . . . for the treatment of pain." In addition, they concede that their analysis does "leave open the question of whether placebo effects in clinical practice might differ from placebo effects among research subjects."

Is this the end of the story? Is the placebo effect really just a myth? Well, we really can't say. Yes, the Danish study, which was far superior to Beecher's, failed to reveal a powerful effect of placebo treatment. However, this does not prove there is no placebo effect. Rather, it may simply indicate that we can't readily measure a placebo effect in clinical trials. There are some good arguments supporting this possibility:

- If the placebo response is based primarily on the clinician-patient relationship, then, even if there is a placebo response, it would be invisible in clinical trials. Why? Because subjects who receive placebo treatment and those who receive no treatment all share the same relationship with the clinician.
- Placebo responses (assuming they exist) are based on the patient's strong belief that he or she is getting an effective treatment. However, in clinical trials, there is always *doubt*—because all participants are aware that they may be getting a placebo, rather than the real deal. In the presence of significant doubt, the placebo effect may be greatly diminished. If this is true, then placebo effects would not be expected in clinical trials.
- If placebo effects exist only in real practice—and not in clinical trials—then proving their existence may well be impossible. Why? Because we'd have to do a clinical trial to prove they exist—and we already know we can't see them in clinical trials.

What's the bottom line? First, owing to a major weakness in design, Beecher's study does not constitute proof that placebos have beneficial effects. Second, by using a more appropriate design, Hróbjartsson and Gotzsche have shown clearly that, in the context of clinical trials, placebo interventions are largely devoid of measurable effects—with the exception of producing modest reductions in pain. Third, although Hróbjartsson and Gotzsche failed to see a placebo effect, their study does not rule out the possibility that, in the real world, placebo treatments can indeed be beneficial. However, this is yet to be proved—and possibly never will be.

¹Beecher HK: The powerful placebo. JAMA 159:1602-1606, 1955.

²Hróbjartsson A, Gotzsche PC: Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 344:1594-1602, 2001.

major cause of variability in drug absorption. Other causes include the presence or absence of food, diarrhea or constipation, and differences in gastric emptying time. Several causes of variable absorption are discussed in previous chapters, primarily Chapter 4 (Pharmacokinetics) and Chapter 6 (Drug Interactions), and hence their discussion here is brief.

Bioavailability

The term *bioavailability* refers to the ability of a drug to reach the systemic circulation from its site of administration. Different formulations of the same drug can vary in bioavailability. As discussed in Chapter 4, such factors as tablet disintegration time, enteric coatings, and sustained-release formulations can alter bioavailability, and can thereby make drug responses variable.

Differences in bioavailability occur primarily with oral preparations rather than parenteral preparations. Fortunately, even with oral agents, when differences in bioavailability do exist between preparations, those differences are usually so small as to lack clinical significance.

Differences in bioavailability are of greatest concern for drugs with a narrow therapeutic range. Why? Because with these agents, a relatively small change in drug level can produce a significant change in response: A small decline in drug level may cause therapeutic failure, whereas a small increase in drug level may cause toxicity. Under these conditions, differences in bioavailability could have a significant impact.

Other Causes of Variable Absorption

Several factors in addition to bioavailability can alter drug absorption, and thereby lead to variations in drug responses. Alterations in gastric pH can affect absorption through the pH partitioning effect. For drugs that undergo absorption in the intestine, absorption will be delayed when gastric emptying time is prolonged. Diarrhea can reduce absorption by accelerating transport of drugs through the intestine. Conversely, constipation can enhance absorption by prolonging the time available for absorption. The presence of food in the stomach tends to *slow* the absorption of most drugs, without reducing the total amount absorbed. However, in some cases, food can decrease the *extent* of absorption as well. For example, absorption of tetracycline is reduced substantially by milk or any other dairy product that contains calcium. Lastly, there are multiple mechanisms by which drug interactions can decrease or increase absorption (see Chapter 6).

GENETICS AND PHARMACOGENOMICS

A patient's unique genetic makeup can lead to drug responses that are qualitatively and quantitatively different from those of the population at large. Adverse effects and therapeutic effects may be increased or reduced. The major underlying causes of these unique responses are alterations in genes that code for drug-metabolizing enzymes and drug targets.

Pharmacogenomics is the study of how genetic variations can affect individual responses to drugs. Although pharmacogenomics is a relatively young science, it has already produced clinically relevant information—information that can be used to enhance therapeutic effects and reduce harm. As a re-

sult, genetic testing is now done routinely for some drugs. In fact, for a few drugs, such as maraviroc [Selzentry] and trastuzumab [Herceptin], the Food and Drug Administration (FDA) now *requires* genetic testing before use, and for a few other drugs, including warfarin [Coumadin] and carbamazepine [Tegretol], genetic testing is recommended but not required. In the distant future, pharmacogenetic analysis of each patient may allow us to pick a drug and dosage that best fits his or her genotype, thereby reducing the risk of adverse reactions, increasing the likelihood of a strong therapeutic response, and decreasing the cost, inconvenience, and risks associated with prescribing a drug to which the patient is unlikely to respond.

In the discussion below, we look at ways in which genetic variations can influence an individual's responses to drugs, and then indicate how pharmacogenomic tests may be used to guide treatment. Table 8-2 summarizes much of the information from the discussion below.

Genetic Variants That Alter Drug Metabolism

The most common mechanism by which genetic variants modify drug responses is by altering drug metabolism. These gene-based changes can either accelerate or slow the metabolism of many drugs. The usual consequence is either a reduction in benefits or an increase in toxicity.

For drugs that have a high therapeutic index (TI), altered rates of metabolism may have little effect on the clinical outcome. However, if the TI is low, then relatively small increases in drug levels can lead to toxicity, and relatively small decreases in drug levels can lead to therapeutic failure. In these cases, altered rates of metabolism can be significant.

The following examples show how a genetically determined variation in drug metabolism can *reduce the benefits* of therapy:

- Variants in the gene that codes for cytochrome P450-2D6 (CYP2D6) can greatly reduce the benefits of tamoxifen [Nolvadex, Tamofen ♦], a drug used to prevent breast cancer recurrence. Here's how. In order to work, tamoxifen must first be converted to its active form—endoxifen—by CYP2D6. Women with an inherited deficiency in the CYP2D6 gene cannot activate the drug well, and hence get minimal benefit from treatment. In one study, the cancer recurrence rate in these poor metabolizers was 9.5 times higher than in good metabolizers. Who are the poor metabolizers? Between 8% and 10% of Caucasian women have gene variants that prevent them from metabolizing tamoxifen to endoxifen. At this time, the FDA neither requires nor recommends testing for variants in the CYP2D6 gene. However, a test kit is available.
- Variants of the gene that codes for CYP2C19 can greatly reduce the benefits of clopidogrel [Plavix], a drug that prevents platelet aggregation. Like tamoxifen, clopidogrel is a prodrug that must undergo conversion to an active form. With clopidogrel, the conversion is catalyzed by CYP2C19. Unfortunately, about 25% of patients produce a variant form of the enzyme—CYP2C19*2—that doesn't work very well. As a result, these people experience a weak antiplatelet response, and hence are at increased risk of stroke, myocardial infarction, and other events. People with this genetic variation should use a different antiplatelet drug.

TABLE 8-2 • Examples of How Genetic Variations Can Affect Drugs Responses

Genetic Variation	Drug Affected	Impact of the Genetic Variation	Explanation	FDA Stand on Genetic Testing
Variants That Alter Drug Metabolism				
CYP2D6 variants	Tamoxifen [Nolvadex]	Reduced therapeutic effect	Women with inadequate CYP2D6 activity cannot convert tamoxifen to its active form, and hence the drug cannot protect them from breast cancer.	No recommendation
CYP2C19 variants	Clopidogrel [Plavix]	Reduced therapeutic effect	Patients with inadequate CYP2C19 activity cannot convert clopidogrel to its active form, and hence the drug cannot protect them against cardiovascular events.	No recommendation
CYP2C9 variants	Warfarin [Coumadin]	Increased toxicity	In patients with abnormal CYP2C9, warfarin may accumulate to a level that causes bleeding.	Recommended
TMPT variants	Thiopurines (eg, thioguanine, mercaptopurine)	Increased toxicity	In patients with reduced TPMT activity, thiopurines can accumulate to levels that cause severe bone marrow toxicity.	Recommended
Variants That Alter Drug Targets on Normal Cells				
ADRB1 variants	Metoprolol and other beta blockers	Increased therapeutic effect	Beta ₁ receptors produced by ADRB1 variant genes respond more intensely to beta agonists, and hence the effects of blockade by beta antagonists will also be enhanced.	No recommendation
VKORC1 variants	Warfarin [Coumadin]	Increased drug sensitivity	Variant VKORC1 is readily inhibited by warfarin, allowing anticoagulation with a reduced warfarin dosage.	Recommended
Variants That Alter Drug Targets on Cancer Cells or Viruses				
HER2 overexpression	Trastuzumab [Herceptin]	Increased therapeutic effect	Trastuzumab only acts against breast cancers that overexpress HER2.	Required
EGFR expression	Cetuximab [Erbix]	Increased therapeutic effect	Cetuximab only works against colorectal cancers that express EGFR.	Required
CCR5 tropism	Maraviroc [Selzentry, Celsentri♦]	Increased therapeutic effect	Maraviroc only acts against HIV strains that express CCR5.	Required
Variants That Alter Immune Responses to Drugs				
HLA-B*1502	Carbamazepine [Tegretol, Carbatrol]	Increased toxicity	The HLA-B*1502 variant increases the risk of life-threatening skin reactions in patients taking carbamazepine.	Recommended
HLA-B*5701	Abacavir [Ziagen]	Increased toxicity	The HLA-B*5701 variant increases the risk of fatal hypersensitivity reactions in patients taking abacavir.	Recommended

ADRB1 = gene for beta₁ adrenergic receptor, CCR5 = chemokine receptor 5, CYP2C9 = 2C9 isozyme of cytochrome P450 (CYP), CYP2C19 = 2C19 isozyme of CYP, CYP2D6 = 2D6 isozyme of CYP, EGFR = epidermal growth factor receptor, HER2 = human epidermal growth factor receptor type 2, HLA-B*1502 = human leukocyte antigen B*1502, HLA-B*5701 = human leukocyte antigen B*5701, TPMT = thiopurine methyltransferase, VKORC1 = vitamin K epoxide reductase complex 1.

• Among white Americans, about 52% metabolize isoniazid (a drug for tuberculosis) slowly and 48% metabolize it rapidly. Why? Because, owing to genetic differences, these people produce two different forms of *N*-acetyltransferase-2, the enzyme that metabolizes isoniazid. If dosage is not adjusted for these differences, the rapid metabolizers

may experience treatment failure and the slow metabolizers may experience toxicity.

• About 1 in 14 Caucasians has a form of CYP2D6 that is unable to convert codeine into morphine, the active form of codeine. As a result, codeine cannot relieve pain in these people.

The following examples show how a genetically determined variation in drug metabolism can *increase drug toxicity*:

- Variants in the gene that codes for CYP2C9 can increase the risk of toxicity (bleeding) from *warfarin* [Coumadin], an anticoagulant with a low TI. Bleeding occurs because (1) warfarin is inactivated by CYP2D9 and (2) patients with altered CYP2D9 genes produce a form of the enzyme that metabolizes warfarin slowly, allowing it to accumulate to dangerous levels. To reduce bleeding risk, the FDA now recommends that patients be tested for variants of the CYP2C9 gene. It should be noted, however, that in this case, outcomes using expensive genetic tests are no better than outcomes using cheaper traditional tests, which directly measure the impact of warfarin on coagulation.
- Variants in the gene that codes for *thiopurine methyltransferase* (TPMT) can reduce TPMT activity, and can thereby delay the metabolic inactivation of two thiopurine anticancer drugs: *thioguanine* [Tabloid, Lanvis ♣] and *mercaptopurine* [Purinethol]. As a result, in patients with inherited TPMT deficiency, standard doses of thiopurine or mercaptopurine can accumulate to high levels, posing a risk of potentially fatal bone marrow damage. To reduce risk, the FDA recommends testing for TPMT variants before using either drug. Patients who are found to be TPMT deficient—about 10% of African Americans and Caucasians—should be given these drugs in reduced dosage.
- In the United States, about 1% of the population produces a form of *dihydropyrimidine dehydrogenase* that does a poor job of metabolizing *fluorouracil*, a drug used to treat cancer. Several people with this inherited difference, while receiving standard doses of fluorouracil, have died from central nervous system injury owing to accumulation of the drug to toxic levels.

Genetic Variants That Alter Drug Targets

Genetic variations can alter the structure of drug receptors and other target molecules, and can thereby influence drug responses. These variants have been documented in normal cells, and in cancer cells and viruses.

Genetic variants that affect drug targets on *normal cells* are illustrated by these two examples:

- Variants in the genes that code for the *beta₁-adrenergic receptor* (ADRB1) produce receptors that are hyper-responsive to activation, which can be a mixed blessing. The bad news is that, in people with hypertension, activation of these receptors may produce an exaggerated *increase* in blood pressure. The good news is that, in people with hypertension, blockade of these receptors will therefore produce an exaggerated *decrease* in blood pressure. Population studies indicate that variant ADRB1 receptors occur more often in Caucasians than in African Americans, which may explain why *beta blockers* work better against hypertension in Caucasians than in African Americans.
- The anticoagulant *warfarin* (discussed above) works by inhibiting *vitamin K epoxide reductase complex 1* (VKORC1). Variant genes that code for VKORC1 produce a form of the enzyme that can be easily inhibited, and hence anticoagulation can be achieved with low warfarin doses. If normal

doses are given, anticoagulation will be excessive, and bleeding could result. To reduce risk, the FDA recommends testing for variants in the VKORC1 gene before warfarin is used.

Genetic variants that affect drug targets on *cancer cells* and *viruses* are illustrated by these three examples:

- *Trastuzumab* [Herceptin], used for breast cancer, only works against tumors that overexpress *human epidermal growth factor receptor type 2* (HER2). The HER2 protein, which serves as a receptor for hormones that stimulate tumor growth, is overexpressed in about 25% of breast cancer patients. Overexpression of HER2 is associated with a poor prognosis, but also predicts a better response to trastuzumab. Accordingly, the FDA requires a positive test result for HER2 overexpression before trastuzumab is used.
- *Cetuximab* [Erbix], used mainly for metastatic colorectal cancer, only works against tumors that express the *epidermal growth factor receptor* (EGFR). All other tumors are unresponsive. Accordingly, the FDA requires evidence of EGFR expression if the drug is to be used.
- *Maraviroc* [Selzentry, Celsentri ♣], a drug for HIV infection, works by binding with a viral surface protein known as *chemokine receptor 5* (CCR5), which certain strains of HIV require for entry into immune cells. HIV strains that use CCR5 are known as being *CCR5 tropic*. Clearly, if maraviroc is to be of benefit, patients must be infected with one of these strains. Accordingly, before maraviroc is used, the FDA requires that testing be done to confirm that the infecting strain is indeed CCR5 tropic.

Genetic Variants That Alter Immune Responses to Drugs

Genetic variants that affect the immune system can increase the risk of severe hypersensitivity reactions to certain drugs. Two examples follow.

- *Carbamazepine* [Tegretol, Carbatrol], used for epilepsy and bipolar disorder, can cause life-threatening skin reactions in some patients—specifically, patients of Asian ancestry who carry genes that code for an unusual *human leukocyte antigen* (HLA) known as *HLA-B*1502*. (HLA molecules are essential elements of the immune system.) Although the mechanism underlying toxicity is unclear, a good guess is that interaction between HLA-B*1502 molecules and carbamazepine (or a metabolite) may trigger a cellular immune response. To reduce risk, the FDA recommends that patients of Asian descent be screened for the HLA-B*1502 gene before carbamazepine is used. If the test is positive, carbamazepine should be avoided.
- *Abacavir* [Ziagen], used for HIV infection, can cause potentially fatal hypersensitivity reactions in patients who have a variant gene that codes for HLA-B*5701. Accordingly, the FDA recommends screening for the variant gene before using this drug. If the test is positive, abacavir should be avoided.

GENDER

Men and women can respond differently to the same drug. A drug may be more effective in men than in women, or vice versa. Likewise, adverse effects may be more intense in men

than in women, or vice versa. Unfortunately, for most drugs, we don't know much about gender-related differences. Why? Because, until recently, essentially all drug research was done in men. Nonetheless, enough research *has* been done to indicate that significant gender-related differences really do exist. Here are four examples:

- When used to treat heart failure, digoxin may *increase* mortality in women while having no effect on mortality in men (see Chapter 48, Box 48-1).
- Alcohol is metabolized more slowly by women than by men. As a result, a woman who drinks the same amount as a man (on a weight-adjusted basis) will become more intoxicated.
- Certain opioid analgesics (eg, pentazocine, nalbuphine) are much more effective in women than in men. As a result, pain relief can be achieved at lower doses in women.
- Quinidine causes greater QT interval prolongation in women than in men. As a result, women given the drug are more likely to develop torsades de pointes, a potentially fatal cardiac dysrhythmia.

In 1997, the FDA put pressure on drug companies to include women in trials of new drugs, especially drugs directed at serious or life-threatening illnesses. The information generated by these trials will permit drug therapy in women to be more rational than is possible today. In the meantime, clinicians must keep in mind that the information currently available may fail to accurately predict responses in female patients. Accordingly, clinicians should remain alert for treatment failures and unexpected adverse effects.

It is important to appreciate that gender- and race-related differences in drug responses are, ultimately, genetically based. Hence, the preceding can be considered an extension of our discussion on pharmacogenomics.

RACE

Race-related drug responses have two primary determinants: *genetic variations* and *psychosocial factors*. Hence, to a large extent, discussion here is an extension of our discussion on pharmacogenomics. However, keep in mind that, in addition to genetics, psychosocial factors can be important determinants of how individuals in a particular ethnic group respond to drugs.

In general, "race" is not very helpful as a basis for predicting individual variation in drug responses. Why? To start with, race is nearly impossible to define. Do we define it by skin color and other superficial characteristics? Or do we define it by group genetics? If we define race by skin color, how dark must skin be, for example, to define a patient as "black?" On the other hand, if we define race by group genetics, how many black ancestors must an African American have to be considered genetically "black?" And what about most people, whose ancestry is ethnically heterogeneous? Latinos, for example, represent a mix of multiple ethnic backgrounds from three continents. I think you get the picture. So, if a prescriber can't even decide what "race" a patient belongs to, it would seem very difficult indeed to use race as a basis for making therapeutic decisions.

Of course, what we really care about is not race per se, but rather the specific genetic and psychosocial factors—shared by many members of an ethnic group—that influence drug responses. Armed with this knowledge, we can identify group members who share those genetic and/or psychosocial factors

and tailor drug therapy accordingly. Perhaps more importantly, application of this knowledge is not limited to members of the ethnic group from which the knowledge arose: We can use it in the management of *all* patients, regardless of ethnic background. How can this be? Owing to ethnic heterogeneity, these factors are not limited to members of any one race. Hence, once we know about a factor (eg, a specific genetic variation), we can screen all patients for it, and, if present, adjust drug therapy as indicated.

This discussion of race-based therapy would be incomplete without mentioning BiDil, a fixed-dose combination of two vasodilators: isosorbide dinitrate (ISDN) and hydralazine, both of which have been available separately for years. In 2005, BiDil became the first drug product approved by the FDA for treating members of just one race, specifically, African Americans. Approval was based on results of the African American Heart Failure Trial (A-HeFT), which showed that in self-described black patients, adding ISDN plus hydralazine to standard therapy of heart failure reduced 1-year mortality by 43%—a very impressive and welcome result. Does BiDil benefit African Americans more than white Americans? We don't know: No white patients were enrolled in A-HeFT, so the comparison can't be made. The bottom line? Even though BiDil is approved for treating a specific racial group, there's no proof that it wouldn't work just as well (or even better) in some other group. Why then, you might ask, was A-HeFT conducted? Partly because of older data suggesting a possible increased benefit in black patients. However, the principal reason seems to be a combination of regulatory and market incentives, which made it worthwhile for NitroMed, the manufacturer of BiDil, to limit research to blacks. Here's the story. NitroMed holds two patents on BiDil, one for the fixed-dose combination itself, and one for using the combination in black patients. By getting FDA approval for black patients only, NitroMed acquired patent protection through the year 2020—13 years longer than it would have gotten in the absence of the race-specific indication. Of course, now that BiDil is approved, physicians are free to prescribe it for anyone. So the ploy of getting race-specific approval did not actually limit the number of patients NitroMed could profit from. Is this a great country, or what?

DRUG INTERACTIONS

A drug interaction is a process in which one drug alters the effects of another. Drug interactions can be an important source of variability. The mechanisms by which one drug can alter the effects of another and the clinical consequences of drug interactions are discussed at length in Chapter 6.

DIET

Diet can affect responses to drugs, primarily by affecting the patient's general health status. A diet that promotes good health can enable drugs to elicit therapeutic responses and increase the patient's capacity to tolerate adverse effects. Poor nutrition can have the opposite effect.

Starvation can reduce protein binding of drugs (by decreasing the level of plasma albumin). Because of reduced binding, levels of free drug rise, thereby making drug re-

sponses more intense. For certain drugs (eg, warfarin), the resultant increase in effects could be disastrous.

Although nutrition can affect drug responses by the general mechanisms noted, there are but few examples of a specific nutrient affecting the response to a specific drug. Perhaps the best example involves the monoamine oxidase (MAO) inhibitors, drugs used to treat depression. The most serious adverse effect of these drugs is malignant hypertension, which can be triggered by foods that contain tyramine, a breakdown product of the amino acid tyrosine. Accordingly, patients taking MAO inhibitors must rigidly avoid all tyramine-rich foods (eg, beef liver, ripe cheeses, yeast products, Chianti wine). The interaction of tyramine-containing foods with MAO inhibitors is discussed at length in Chapter 32.

FAILURE TO TAKE MEDICINE AS PRESCRIBED

Medications are not always administered as prescribed: Dosage size and timing may be altered, doses may be omitted, and extra doses may be taken. Failure to administer medication as

prescribed is a common explanation for variability in the response to a prescribed dose. As a rule, such failure results either from poor patient adherence (compliance) or from medication errors made by hospital staff.

Adherence can be hard to achieve. Factors that can influence adherence include manual dexterity, visual acuity, intellectual capacity, psychologic state, attitude toward drugs, and the ability to pay for medication. As noted in Chapter 3, patient education that is both clear and convincing may help improve adherence, and may thereby help reduce variability.

Medication errors are an obvious source of individual variation. Medication errors can originate with physicians, nurses, technicians, and pharmacists. However, since the nurse is usually the last member of the healthcare team to check medications prior to administration, it is ultimately the nurse's responsibility to ensure that medication errors are avoided. Medication errors are discussed at length in Chapter 7.

KEY POINTS

- In order to maximize beneficial drug responses and minimize harm, we must adjust therapy to account for sources of individual variation.
- As a rule, small patients need smaller doses than large patients.
- Dosage adjustments made to account for size are often based on body surface area, rather than simply on body weight.
- Infants and the elderly are more sensitive to drugs than are older children and younger adults.
- Kidney disease can decrease drug excretion, thereby causing drug levels to rise. To prevent toxicity, drugs that are eliminated by the kidneys should be given in reduced dosage.
- Liver disease can decrease drug metabolism, thereby causing levels to rise. To prevent toxicity, drugs that are eliminated by the liver should be given in reduced dosage.
- When a patient becomes tolerant to a drug, the dosage must be increased to maintain beneficial effects.
- Pharmacodynamic tolerance results from adaptive changes that occur in response to prolonged drug exposure. Pharmacodynamic tolerance increases the MEC of a drug.
- Pharmacokinetic tolerance results from accelerated drug metabolism. Pharmacokinetic tolerance does not increase the MEC.
- A placebo effect is defined as the component of a drug response that can be attributed to psychologic factors, rather than to direct physiologic or biochemical actions of the drug. Solid proof that most placebo effects are real is lacking.
- Bioavailability refers to the ability of a drug to reach the systemic circulation from its site of administration.
- Differences in bioavailability matter most for drugs that have a narrow therapeutic range.
- Alterations in the genes that code for drug-metabolizing enzymes can result in increased or decreased metabolism of many drugs.
- Genetic variations can alter the structure of drug receptors and other target molecules, and can thereby influence drug responses.
- Genetic variations that alter immune reactions to drugs can result in severe injury, and even death.
- Therapeutic and adverse effects of drugs may differ between males and females. Unfortunately, for most drugs, data are insufficient to predict what the differences might be.
- Race is a poor predictor of drug responses. What really matters is not race, but rather the specific genetic variations and psychosocial factors, shared by some group members, that can influence drug responses.
- Poor patient adherence and medication errors are major sources of individual variation.

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9

Drug Therapy During Pregnancy and Breast-Feeding

Drug Therapy During Pregnancy: Basic Considerations

Physiologic Changes During Pregnancy and Their Impact on Drug Disposition and Dosing

Placental Drug Transfer

Adverse Reactions During Pregnancy

Drug Therapy During Pregnancy: Teratogenesis

Incidence and Causes of Congenital Anomalies

Teratogenesis and Stage of Development

Identification of Teratogens

FDA Pregnancy Risk Categories

Minimizing the Risk of Drug-Induced Teratogenesis

Responding to Teratogen Exposure

Drug Therapy During Breast-Feeding

Our topic for this chapter is drug therapy in women who are pregnant or breast-feeding. The clinical challenge is to provide effective treatment for the mother while avoiding harm to the fetus or nursing infant. Unfortunately, meeting this challenge is confounded by a shortage of reliable data on drug toxicity during pregnancy or breast-feeding.

DRUG THERAPY DURING PREGNANCY: BASIC CONSIDERATIONS

Drug use during pregnancy is common: About two-thirds of pregnant women take at least one medication, and the majority take more. Some drugs are used to treat pregnancy-related conditions, such as nausea, constipation, and preeclampsia. Some are used to treat chronic disorders, such as hypertension, diabetes, and epilepsy. And some are used for infectious diseases or cancer. In addition to taking these therapeutic agents, pregnant women may take drugs of abuse, such as alcohol, cocaine, and heroin.

Drug therapy in pregnancy presents a vexing dilemma. In pregnant patients, as in all other patients, the benefits of treatment must balance the risks. Of course, when drugs are used during pregnancy, risks apply to the fetus as well as the mother. Unfortunately, most drugs have not been tested during pregnancy. As a result, the risks for most drugs are unknown—hence the dilemma: The prescriber is obliged to balance risks versus benefits, without knowing what the risks really are.

Despite the imposing challenge of balancing risks versus benefits, drug therapy during pregnancy cannot and should

not be avoided. The health of the fetus depends on the health of the mother. Hence, conditions that threaten the mother's health must be addressed—for the sake of the baby as well as the mother. Chronic asthma is a good example. Uncontrolled maternal asthma is far more dangerous to the fetus than the drugs used to treat it. Among asthmatic women who fail to take medication, the incidence of stillbirth is doubled. If all women with asthma took medication, an estimated 2000 babies would be saved each year.

In late 2009, the Food and Drug Administration (FDA) launched a new program to increase our knowledge of drug risks during pregnancy. This program—the *Medication Exposure in Pregnancy Risk Evaluation Program*—is a collaborative effort between the FDA, Kaiser Permanente, Vanderbilt University, and a consortium of health maintenance organizations (HMOs) called the HMO Research Network Center for Education and Research in Therapeutics. Participants will analyze medical records that relate to about 1 million births that took place between 2001 and 2007. The goal is to see if specific drugs are associated with adverse birth outcomes. These data will go a long way toward taking the guesswork out of selecting drugs for pregnant women.

Physiologic Changes During Pregnancy and Their Impact on Drug Disposition and Dosing

Pregnancy brings on physiologic changes that can alter drug disposition. Changes in the kidney, liver, and GI tract are of particular interest. Because of these changes, a compensatory change in dosage may be needed.

By the third trimester, renal blood flow is doubled, causing a large increase in glomerular filtration rate. As a result, there is accelerated clearance of drugs that are eliminated by glomerular filtration. Elimination of lithium, for example, is increased by 100%. To compensate for accelerated excretion, dosage must be increased.

For some drugs, hepatic metabolism increases during pregnancy. Three antiseizure drugs—phenytoin, carbamazepine, and valproic acid—provide examples.

Tone and motility of the bowel decrease in pregnancy, causing intestinal transit time to increase. Because of prolonged transit, there is more time for drugs to be absorbed. In theory, this could increase levels of drugs whose absorption is normally poor. Similarly, there is more time for reabsorption of drugs that undergo enterohepatic recirculation, and hence effects of these drugs could be prolonged. In both cases, a reduction in dosage might be needed.

Placental Drug Transfer

Essentially all drugs can cross the placenta, although some cross more readily than others. The factors that determine drug passage across the membranes of the placenta are the same factors that determine drug passage across all other membranes. Accordingly, drugs that are lipid soluble cross the placenta easily, whereas drugs that are ionized, highly polar, or protein bound cross with difficulty. Nonetheless, for practical purposes, the clinician should assume that *any drug taken during pregnancy will reach the fetus*.

Adverse Reactions During Pregnancy

Drugs taken during pregnancy can adversely affect both the mother and fetus. The effect of greatest concern is teratogenesis (production of birth defects). This issue is discussed separately below. Not only are pregnant women subject to the same adverse effects as everyone else, they may also suffer effects unique to pregnancy. For example, when heparin (an anticoagulant) is taken by pregnant women, it can cause osteoporosis, which in turn can cause compression fractures of the spine. Use of prostaglandins (eg, misoprostol), which stimulate uterine contraction, can cause abortion. Conversely, use of aspirin near term can suppress contractions in labor. In addition, aspirin increases the risk of serious bleeding.

Regular use of dependence-producing drugs (eg, heroin, barbiturates, alcohol) during pregnancy can result in the birth of a drug-dependent infant. If the infant is not supplied with a drug that can support its dependence, a withdrawal syndrome will ensue. Symptoms include shrill crying, vomiting, and extreme irritability. The neonate should be weaned from dependence by giving progressively smaller doses of the drug on which he or she is dependent.

Certain pain relievers used during delivery can depress respiration in the neonate. The infant should be closely monitored until respiration is normal.

DRUG THERAPY DURING PREGNANCY: TERATOGENESIS

The term *teratogenesis* is derived from *teras*, the Greek word for monster. Translated literally, teratogenesis means *to produce a monster*. Consistent with this derivation, we usually think of birth defects in terms of gross malformations, such as cleft palate, clubfoot, and hydrocephalus. However, birth defects are not limited to distortions of gross anatomy; they also include neurobehavioral and metabolic anomalies.

Incidence and Causes of Congenital Anomalies

The incidence of *major* structural abnormalities (eg, abnormalities that are life threatening or require surgical correction) is between 1% and 3%. Half of these are obvious and are reported at birth. The other half involve internal organs (eg, heart, liver, GI tract) and are not discovered until later in life or at autopsy. The incidence of minor structural abnormalities is unknown, as is the incidence of functional abnormalities (eg, growth retardation, mental retardation).

Congenital anomalies have multiple causes, including genetic predisposition, environmental chemicals, and drugs. Genetic factors account for about 25% of all birth defects. Of the genetically based anomalies, Down's syndrome is the most common. Less than 1% of all birth defects are caused by drugs. For the majority of congenital anomalies, the cause is unknown.

Teratogenesis and Stage of Development

Fetal sensitivity to teratogens changes during development, and hence the effect of a teratogen is highly dependent upon when the drug is given. As shown in Figure 9-1, development occurs in three major stages: the *preimplantation/presomite period* (conception through week 2), the *embryonic period* (weeks 3 through 8), and the *fetal period* (week 9 through term). During the preimplantation/presomite period, teratogens act in an "all-or-nothing" fashion. That is, if the dose is sufficiently high, the result is death of the conceptus. Conversely, if the dose is sublethal, the conceptus is likely to recover fully.

Gross malformations are produced by exposure to teratogens during the *embryonic period* (roughly the first trimester). This is the time when the basic shape of internal organs and other structures is being established. Hence, it is not surprising that interference at this stage results in conspicuous anatomic distortions. Because the fetus is especially vulnerable during the embryonic period, expectant mothers must take special care to avoid teratogen exposure during this time.

Teratogen exposure during the *fetal period* (ie, the second and third trimesters) usually disrupts *function* rather than gross anatomy. Of the developmental processes that occur in the fetal period, growth and development of the brain are especially important. Disruption of brain development can result in learning deficits and behavioral abnormalities.

Identification of Teratogens

For the following reasons, human teratogens are extremely difficult to identify:

- The incidence of congenital anomalies is generally low.
- Animal tests may not be applicable.
- Prolonged exposure may be required.
- Teratogenic effects may be delayed.
- Behavioral effects are difficult to document.
- Controlled experiments can't be done in humans.

As a result, only a few drugs are considered *proven* teratogens. Drugs whose teratogenicity has been documented (or at least is highly suspected) are listed in Table 9-1. It is important to note, however, that *lack of proof of teratogenicity does not mean that a drug is safe*; it only means that the available data are insufficient to make a definitive judgment. Conversely, *proof of teratogenicity does not mean that every exposure will result in a birth defect*. In fact, with most teratogens, the risk of malformation following exposure is only about 10%.

To prove that a drug is a teratogen, three criteria must be met:

- The drug must cause a characteristic set of malformations.
- It must act only during a specific window of vulnerability (eg, weeks 4 through 7 of gestation).
- The incidence of malformations should increase with increasing dosage and duration of exposure.

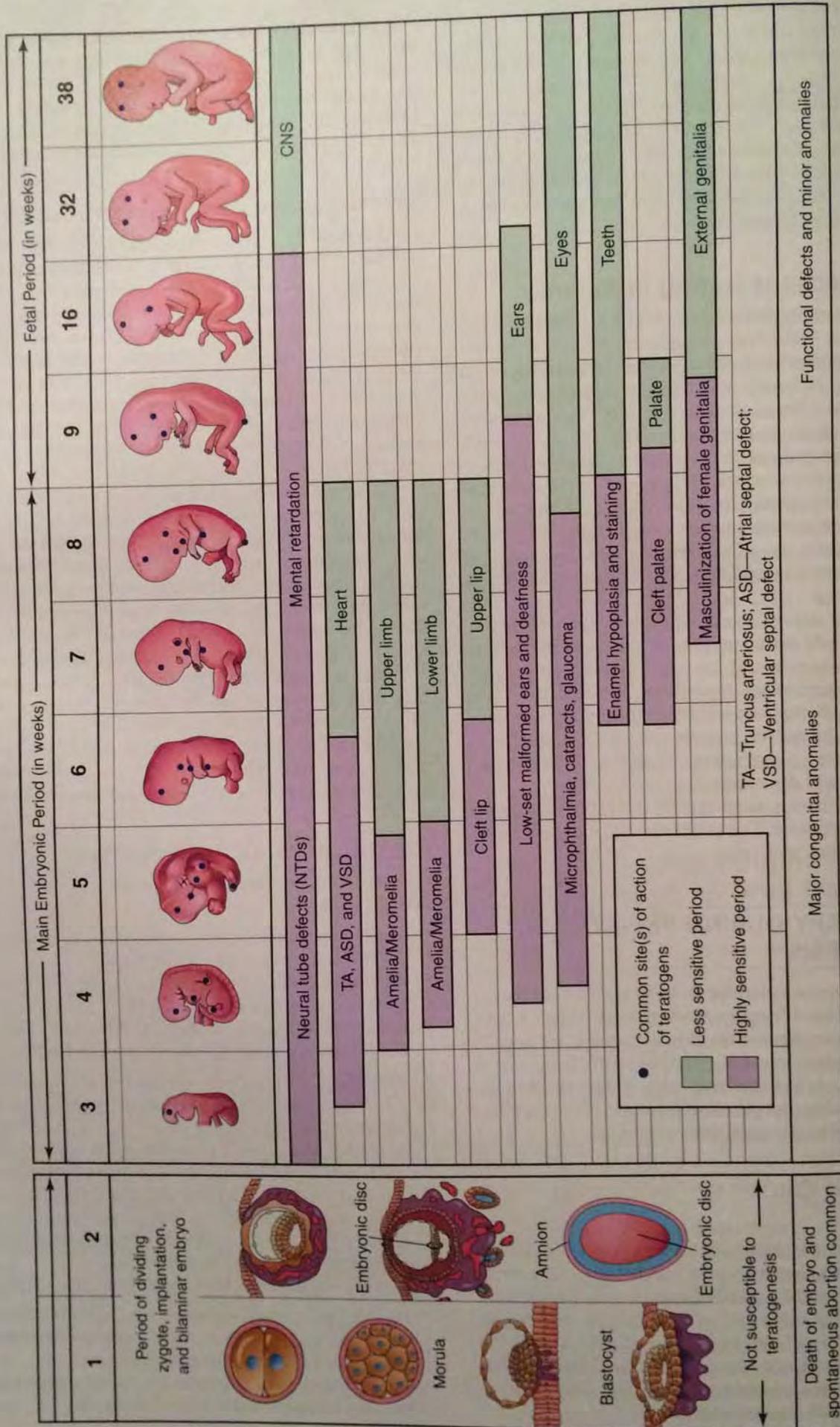


Figure 9-1 = Effects of teratogens at various stages of development of the fetus. (From Moore KL: The Developing Human: Clinically Oriented Embryology, 5th ed. Philadelphia: WB Saunders Company, 1993, with permission.)

TABLE 9-1 ■ Drugs That Should Be Avoided During Pregnancy Because of Proven or Strongly Suspected Teratogenicity*

Drug	Teratogenic Effect
Anticancer/Immunosuppressant Drugs	
Cyclophosphamide	CNS malformation, secondary cancer
Methotrexate	CNS and limb malformations
Antiseizure Drugs	
Carbamazepine	Neural tube defects
Valproic acid	Neural tube defects
Phenytoin	Growth retardation, CNS defects
Sex Hormones	
Androgens (eg, danazol)	Masculinization of the female fetus
Diethylstilbestrol	Vaginal carcinoma in female offspring
Antimicrobials	
Nitrofurantoin	Abnormally small or absent eyes, heart defects, cleft lip with cleft palate
Sulfonamides	Anencephaly, heart defects, transverse limb deficiency, diaphragmatic hernia
Tetracycline	Tooth and bone anomalies
Other Drugs	
Alcohol	Fetal alcohol syndrome, stillbirth, spontaneous abortion, low birth weight, mental retardation
Angiotensin-converting enzyme inhibitors	Renal failure, renal tubular dysgenesis, skull hypoplasia (from exposure during the second and third trimesters)
Antithyroid drugs (propylthiouracil, methimazole)	Goiter and hypothyroidism
Nonsteroidal anti-inflammatory drugs	Premature closure of the ductus arteriosus
Lithium	Ebstein's anomaly (cardiac defects)
Oral hypoglycemic drugs (eg, tolbutamide)	Neonatal hypoglycemia
Isotretinoin and other vitamin A derivatives (etretinate, megadoses of vitamin A)	Multiple defects (CNS, craniofacial, cardiovascular, others)
Thalidomide	Shortened limbs, internal organ defects
Warfarin	Skeletal and CNS defects

CNS = central nervous system.

*The absence of a drug from this table does not mean that the drug is not a teratogen; it only means that teratogenicity has not been proved. For most proven teratogens, the risk of a congenital anomaly is only 10%.

Obviously, we can't do experiments in humans to see if a drug meets these criteria. The best we can do is systematically collect and analyze data on drugs taken during pregnancy in the hope that useful information on teratogenicity will be revealed.

Studies in animals may be of limited value, in part because teratogenicity may depend on species. That is, drugs that are teratogens in laboratory animals may nonetheless be safe in humans. Conversely, and more importantly, drugs that fail to cause anomalies in animals may later prove teratogenic in humans. The most notorious example is thalidomide. In studies with pregnant animals, thalidomide was harmless. However, when thalidomide was taken by pregnant women, about 30% had babies with severe malformations. The take-home message is this: *Lack of teratogenicity in animals is not proof of safety in humans.* Accordingly, we cannot assume that a new drug is safe for use in human pregnancy just because it has met FDA requirements, which are based on tests done in pregnant animals.

Some teratogens act quickly, whereas others require prolonged exposure. Thalidomide represents a fast-acting teratogen: a single dose can cause malformation. In contrast, alcohol (ethanol) must be taken repeatedly in high doses if gross malformation is to result. (Lower doses of alcohol may produce subtle anomalies.) Because a single exposure to a rapid-acting teratogen can produce obvious malformation, rapid-acting teratogens are easier to identify than slow-acting teratogens.

Teratogens that produce delayed effects are among the hardest to identify. The best example is diethylstilbestrol, an estrogenic substance that causes vaginal cancer in female offspring 18 or so years after they were born.

Teratogens that affect behavior may be nearly impossible to identify. Behavioral changes are often delayed, and therefore may not become apparent until the child goes to school. By this time, it may be difficult to establish a correlation between drug use during pregnancy and the behavioral deficit. Furthermore, if the deficit is subtle, it may not even be recognized.

FDA Pregnancy Risk Categories

In 1983, the FDA established a system for classifying drugs according to their probable risks to the fetus. According to this system, *drugs can be put into one of five risk categories: A, B, C, D, and X* (Table 9–2). Drugs in Risk Category A are the least dangerous; controlled studies have been done in pregnant women and have failed to demonstrate a risk of fetal harm. In contrast, drugs in Category X are the most dangerous; these drugs are known to cause human fetal harm, and their risk to the fetus outweighs any possible therapeutic benefit. Drugs in Categories B, C, and D are progressively more dangerous than drugs in Category A and less dangerous than drugs in Category X. The law does not require classification of drugs that were in use before 1983; hence many drugs are not classified.

Although the current rating system is helpful, it is far from ideal, and hence the FDA has proposed major revisions. Specifically, the FDA plans to phase out the use of letter categories, and replace them with detailed information about the effects of drugs during pregnancy. The format employed will have three sections:

- **Fetal Risk Summary**—This section will describe what we know about drug effects on the fetus, and will offer a conclusion, such as, “Human data indicate this drug increases the risk of cardiac abnormalities.”

TABLE 9–2 ■ FDA Pregnancy Risk Categories

Category	Category Description
A	<i>Remote Risk of Fetal Harm:</i> Controlled studies in women have been done and have failed to demonstrate a risk of fetal harm during the first trimester, and there is no evidence of risk in later trimesters.
B	<i>Slightly More Risk Than A:</i> Animal studies show no fetal risk, but controlled studies have not been done in women. <i>or</i> Animal studies do show a risk of fetal harm, but controlled studies in women have failed to demonstrate a risk during the first trimester, and there is no evidence of risk in later trimesters.
C	<i>Greater Risk Than B:</i> Animal studies show a risk of fetal harm, but no controlled studies have been done in women. <i>or</i> No studies have been done in women or animals.
D	<i>Proven Risk of Fetal Harm:</i> Studies in women show proof of fetal damage, but the potential benefits of use during pregnancy may be acceptable despite the risks (eg, treatment of life-threatening disease for which safer drugs are ineffective). A statement on risk will appear in the “WARNINGS” section of drug labeling.
X	<i>Proven Risk of Fetal Harm:</i> Studies in women or animals show definite risk of fetal abnormality. <i>or</i> Adverse reaction reports indicate evidence of fetal risk. The risks clearly outweigh any possible benefit. A statement on risk will appear in the “CONTRAINDICATIONS” section of drug labeling.

- **Clinical Considerations**—This section will describe the likely effects if a drug is taken before a woman knows she is pregnant. The section will also discuss the risks to the mother and fetus of the disease being treated, along with dosing information, and ways to deal with complications.
- **Data**—This section will give detailed evidence from human and animal studies regarding the information presented in the Fetal Risk Summary.

Minimizing the Risk of Drug-Induced Teratogenesis

Common sense tells us that the best way to minimize teratogenesis is to minimize use of drugs. If possible, pregnant women should avoid drugs entirely. At the least, all *unnecessary* drug use should be eliminated. Alcohol and cocaine, for example, which are known to harm the developing fetus, have no valid indications, and their use cannot be justified. Nurses and other health professionals should warn pregnant women against use of all nonessential drugs.

As noted, some disease states (eg, epilepsy, asthma, diabetes) pose a greater risk to fetal health than do the drugs used for treatment. However, even with these disorders, in which drug therapy reduces the risk of disease-induced fetal harm, we must still take steps to minimize harm from drugs. Accordingly, drugs that pose a high risk of teratogenesis should be discontinued and safer alternatives substituted.

Rarely, a pregnant woman has a disease that requires use of drugs that have a high probability of causing teratogenesis. Some anticancer drugs, for example, are highly toxic to the developing fetus, yet cannot be ethically withheld from the pregnant patient. If a woman elects to use such drugs, termination of pregnancy should be considered.

Reducing the risk of teratogenesis also applies to female patients who are *not* pregnant. Why? Because about 50% of pregnancies are unintended. Accordingly, if a woman of reproductive age is taking a teratogenic medication, she should be educated about the teratogenic risk as well as the necessity of using at least one reliable form of birth control.

Responding to Teratogen Exposure

When a pregnant woman has been exposed to a known teratogen, the first step is to determine exactly when the drug was taken, and exactly when the pregnancy began. If drug exposure was not during the period of organogenesis (ie, weeks 3 through 8), the patient should be reassured that the risk of drug-induced malformation is minimal. In addition, she should be reminded that 3% of all babies have some kind of conspicuous malformation, independent of teratogen exposure. This is important because otherwise the drug is sure to be blamed if the baby is abnormal.

What should be done if the exposure *did* occur during organogenesis? First, a reference (eg, Briggs GG, Freeman RK, Yaffe SJ: *Drugs in Pregnancy and Lactation, 9th Edition*. Philadelphia: JB Lippincott, 2011) should be consulted to determine the type of malformation expected. Next, at least two ultrasound scans should be done to assess the extent of injury. If the malformation is severe, termination of pregnancy should be considered. If the malformation is minor (eg, cleft palate), it may be correctable by surgery, either shortly after birth or later in childhood.

DRUG THERAPY DURING BREAST-FEEDING

Drugs taken by lactating women can be excreted in breast milk. If drug concentrations in milk are high enough, a pharmacologic effect can occur in the infant, raising the possibility of harm. Unfortunately, very little systematic research has been done on this issue. As a result, although a few drugs are known to be hazardous (Table 9-3), the possible danger posed by many others remains undetermined.

TABLE 9-3 ■ Drugs That Are Contraindicated During Breast-Feeding

Controlled Substances

Amphetamine
Cocaine
Heroin
Marijuana
Phencyclidine

Anticancer Agents/Immunosuppressants

Cyclophosphamide
Cyclosporine
Doxorubicin
Methotrexate

Others

Bromocriptine
Ergotamine
Lithium
Nicotine

Although nearly all drugs can enter breast milk, the extent of entry varies greatly. The factors that determine entry into breast milk are the same factors that determine passage of drugs across membranes. Accordingly, drugs that are lipid soluble enter breast milk readily, whereas drugs that are ionized, highly polar, or protein bound tend to be excluded.

Most drugs can be detected in milk, but concentrations are generally too low to cause harm. Hence, breast-feeding is usually safe, even though drugs are being taken. Nonetheless, prudence is always in order: If the nursing mother can avoid drugs, she certainly should. Moreover, when drugs *must* be used, steps should be taken to minimize risk. These include:

- Dosing immediately *after* breast-feeding (to minimize drug concentrations in milk at the next feeding)
- Avoiding drugs that have a long half-life
- Avoiding sustained-release formulations
- Choosing drugs that tend to be excluded from milk
- Choosing drugs that are least likely to affect the infant (Table 9-4)
- Avoiding drugs that are known to be hazardous (see Table 9-3)
- Using the lowest effective dosage for the shortest possible time

TABLE 9-4 ■ Drugs of Choice for Breast-Feeding Women*

Drug Category	Drugs and Drug Groups of Choice	Comments
Analgesic drugs	Acetaminophen, ibuprofen, flurbiprofen, ketorolac, mefenamic acid, sumatriptan, morphine	Sumatriptan may be given for migraine. Morphine may be given for severe pain.
Anticoagulant drugs	Warfarin, acenocoumarol, heparin (unfractionated and low molecular weight)	Among breast-fed infants whose mothers were taking warfarin, the drug was undetectable in plasma and bleeding time was not affected.
Antidepressant drugs	Sertraline, tricyclic antidepressants	Other antidepressants, such as fluoxetine [Prozac], may be given with caution.
Antiepileptic drugs	Carbamazepine, phenytoin, valproic acid	The estimated level of exposure to these drugs in infants is less than 10% of the therapeutic dose standardized by weight.
Antihistamines (histamine blockers)	Loratadine	Other antihistamines may be given, but data on the concentrations of these drugs in breast milk are lacking.
Antimicrobial drugs	Penicillins, cephalosporins, aminoglycosides, macrolides	Avoid chloramphenicol and tetracycline
Beta-adrenergic antagonists	Labetalol, propranolol	Angiotensin-converting enzyme inhibitors and calcium channel-blocking agents are also considered safe.
Endocrine drugs	Propylthiouracil, insulin, levothyroxine	The estimated level of exposure to propylthiouracil in breast-feeding infants is less than 1% of the therapeutic dose standardized by weight; thyroid function of the infants is not affected.
Glucocorticoids	Prednisolone and prednisone	The amount of prednisolone the infant would ingest in breast milk is less than 0.1% of the therapeutic dose standardized by weight.

*This list is not exhaustive. Cases of overdoses of these drugs must be assessed on an individual basis. Adapted from Shinya I: Drug therapy for breast-feeding women. *N Engl J Med* 343:118-126, 2000.

KEY POINTS

- Because hepatic metabolism and glomerular filtration increase during pregnancy, dosages of some drugs may need to be increased.
- Lipid-soluble drugs cross the placenta readily, whereas drugs that are ionized, polar, or protein bound cross with difficulty. Nonetheless, all drugs cross to some extent.
- When prescribing drugs during pregnancy, the clinician must try to balance the benefits of treatment versus the risks—often without knowing what the risks really are.
- About 3% of all babies are born with gross structural malformations.
- Less than 1% of birth defects are caused by drugs.
- Teratogen-induced gross malformations result from exposure early in pregnancy (weeks 3 through 8 of gestation), the time of organogenesis.
- Functional impairments (eg, mental retardation) result from exposure to teratogens later in pregnancy.
- For most drugs, we lack reliable data on the risks of use during pregnancy.
- Lack of teratogenicity in animals is not proof of safety in humans.
- Some drugs (eg, thalidomide) cause birth defects with just one dose, whereas others (eg, alcohol) require prolonged exposure.
- FDA Pregnancy Risk Categories indicate the relative risks of drug use. Drugs in Category X pose the highest risk of fetal harm and are contraindicated during pregnancy.
- Any woman of reproductive age who is taking a known teratogen must be counseled about the teratogenic risk and the necessity of using at least one reliable form of birth control.
- Drugs that are lipid soluble readily enter breast milk, whereas drugs that are ionized, polar, or protein bound tend to be excluded. Nonetheless, all drugs enter to some extent.
- Although most drugs can be detected in breast milk, concentrations are usually too low to harm the nursing infant.
- If possible, drugs should be avoided during breast-feeding.
- If drugs cannot be avoided during breast-feeding, common sense dictates choosing drugs known to be safe (Table 9-4) and avoiding drugs known to be dangerous (Table 9-3).

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Drug Therapy in Pediatric Patients

Pharmacokinetics: Neonates and Infants

Absorption

Distribution

Hepatic Metabolism

Renal Excretion

Pharmacokinetics: Children 1 Year and Older

Adverse Drug Reactions

Dosage Determination

Promoting Adherence

Patients who are very young or very old respond differently to drugs than do the rest of the population. Most differences are *quantitative*. Specifically, patients in both age groups are more sensitive to drugs than other patients, and they show greater individual variation. Drug sensitivity in the very young results largely from *organ system immaturity*. Drug sensitivity in the elderly results largely from *organ system degeneration*. Because of heightened drug sensitivity, patients in both age groups are at increased risk of adverse drug reactions. In this chapter we discuss the physiologic factors that underlie heightened drug sensitivity in pediatric patients, as well as ways to promote safe and effective drug use. Drug therapy in geriatric patients is discussed in Chapter 11.

Pediatrics covers all patients up to the age of 16. Because of ongoing growth and development, pediatric patients in different age groups present different therapeutic challenges. Traditionally, the pediatric population is subdivided into six groups:

- Premature infants (less than 36 weeks' gestational age)
- Full-term infants (36 to 40 weeks' gestational age)
- Neonates (first 4 postnatal weeks)
- Infants (weeks 5 to 52 postnatal)
- Children (1 to 12 years)
- Adolescents (12 to 16 years)

Not surprisingly, as young patients grow older, they become more like adults physiologically, and hence more like adults with regard to drug therapy. Conversely, the very young—those less than 1 year old, and especially those less than 1 month old—are very different from adults. If drug therapy in these patients is to be safe and effective, we must account for these differences.

Pediatric drug therapy is made even more difficult by insufficient drug information: Fully two-thirds of drugs used in pediatrics have never been tested in children. As a result, we lack reliable information on dosing, pharmacokinetics, and effects, both therapeutic and adverse. Is this lack of knowledge causing adverse events and even death? Possibly, but no one knows. Is it preventing optimal treatment? Probably, but again, we just don't know. To help expand our knowledge, Congress enacted two important laws: the *Best Pharmaceuti-*

als for Children Act, passed in 2002, and the *Pediatric Research Equity Act of 2003*. Both are designed to promote drug research in children. What we have learned so far underscores both the state of our ignorance and the need for much more work. For example, of the drugs studied to date:

- About 20% were ineffective in children, even though they were effective in adults.
- About 30% caused unanticipated side effects, some of them potentially lethal.
- About 20% required dosages different from those that had been extrapolated from dosages used in adults.

As more studies are done, the huge gaps in our knowledge will shrink. In the meantime, we must still treat children with drugs—even though we lack the information needed to prescribe rationally. Hence, similar to drug therapy during pregnancy, prescribers must try to balance benefits versus risks, without knowing with precision what the benefits and risks really are.

PHARMACOKINETICS: NEONATES AND INFANTS

As we discussed in Chapter 4, pharmacokinetic factors determine the concentration of a drug at its sites of action, and hence determine the intensity and duration of responses. If drug levels are elevated, responses will be more intense. If drug elimination is delayed, responses will be prolonged. Because the organ systems that regulate drug levels are not fully developed in the very young, these patients are at risk of both possibilities: drug effects that are unusually intense *and* prolonged. By accounting for pharmacokinetic differences in the very young, we can increase the chances that drug therapy will be both effective and safe.

Figure 10-1 illustrates how drug levels differ between infants and adults following administration of equivalent doses (ie, doses adjusted for body weight). When a drug is administered *intravenously* (Fig. 10-1A), levels decline more slowly in the infant than in the adult. As a result, drug levels in the infant remain above the minimum effective concentration (MEC) longer than in the adult, thereby causing effects to be prolonged. When a drug is administered *subcutaneously* (Fig. 10-1B), not only do levels in the infant remain above the MEC *longer* than in the adult, but these levels also rise *higher*, causing effects to be more intense as well as prolonged. From these illustrations, it is clear that adjustment of dosage for infants on the basis of body size alone is not sufficient to achieve safe results.

If small body size is not the major reason for heightened drug sensitivity in infants, what is? The increased sensitivity of infants is due largely to the immature state of five pharmacokinetic processes: (1) drug absorption, (2) protein binding of drugs, (3) exclusion of drugs from the central nervous sys-

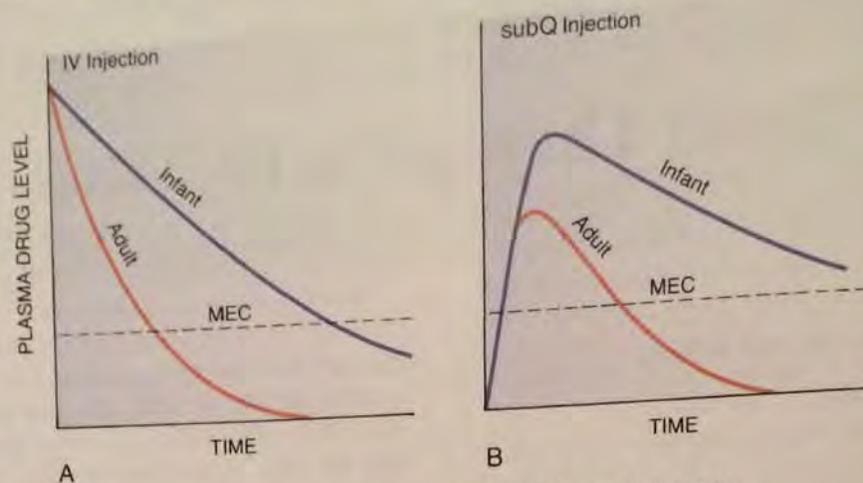


Figure 10-1 ■ Comparison of plasma drug levels in adults and infants. Note that **A**, Plasma drug levels following IV injection. Dosage was adjusted for body weight. Note that plasma levels remain above the minimum effective concentration (MEC) much longer in the infant. **B**, Plasma drug levels following subQ injection. Dosage was adjusted for body weight. Note that both the maximum drug level and the duration of action are greater in the infant. (Redrawn from Levine RR: *Pharmacology: Drug Actions and Reactions*. Boston: Little, Brown, 1973:238.)

tem (CNS) by the blood-brain barrier, (4) hepatic drug metabolism, and (5) renal drug excretion.

Absorption

Oral Administration. Gastrointestinal physiology in the infant is very different from that in the adult. As a result, drug absorption may be enhanced or impeded, depending on the physicochemical properties of the drug involved.

Gastric emptying time is both prolonged and irregular in early infancy, and then gradually reaches adult values by 6 to 8 months. For drugs that are absorbed primarily from the stomach, delayed gastric emptying enhances absorption. On the other hand, for drugs that are absorbed primarily from the intestine, absorption is delayed. Because gastric emptying time is irregular, the precise impact on absorption is not predictable.

Gastric acidity is very low 24 hours after birth and does not reach adult values for 2 years. Because of low acidity, absorption of acid-labile drugs is increased.

Intramuscular Administration. Drug absorption following IM injection in the neonate is slow and erratic. Delayed absorption is due in part to low blood flow through muscle during the first days of postnatal life. By early infancy, absorption of IM drugs becomes more rapid than in neonates and adults.

Transdermal Absorption. Drug absorption through the skin is more rapid and complete with infants than with older children and adults. Why? Because (1) the stratum corneum of the infant's skin is very thin and (2) blood flow to the skin is greater in infants than in older patients. Because of this enhanced absorption, infants are at increased risk of toxicity from topical drugs.

Distribution

Protein Binding. Binding of drugs to albumin and other plasma proteins is limited in the infant. Why? Because (1) the amount of albumin is relatively low and (2) endogenous compounds (eg, fatty acids, bilirubin) compete with drugs for available binding sites. Consequently, drugs that ordinarily undergo extensive protein binding in adults undergo much

less binding in infants. As a result, the concentration of free levels of such drugs is relatively high in the infant, thereby intensifying effects. To ensure that effects are not too intense, dosages in infants should be reduced. Protein-binding capacity reaches adult values within 10 to 12 months.

Blood-Brain Barrier. The blood-brain barrier is not fully developed at birth. As a result, drugs and other chemicals have relatively easy access to the central nervous system (CNS), making the infant especially sensitive to drugs that affect CNS function. Accordingly, all medicines employed for their CNS effects (eg, morphine, phenobarbital) should be given in reduced dosage. Dosage should also be reduced for drugs used for actions outside the CNS if those drugs are capable of producing CNS toxicity as a side effect.

Hepatic Metabolism

The drug-metabolizing capacity of newborns is low. As a result, neonates are especially sensitive to drugs that are eliminated primarily by hepatic metabolism. When these drugs are used, dosages must be reduced. The capacity of the liver to metabolize many drugs increases rapidly about 1 month after birth, and approaches adult levels a few months later. Complete maturation of the liver develops by 1 year.

The data in Table 10-1 illustrate the limited drug-metabolizing capacity of newborns. These data are from experiments on the metabolism and effects of hexobarbital (a CNS depressant) in newborn and adult animals. Metabolism was measured in microsomal enzyme preparations made from the livers of guinea pigs. The effect of hexobarbital—CNS depression—was assessed in mice. Duration of sleeping time following hexobarbital injection was used as the index of CNS depression.

As indicated in Table 10-1, the drug-metabolizing capacity of the adult liver is much greater than the drug-metabolizing capacity of the newborn liver. Whereas the adult liver preparation metabolized an average of 33% of the hexobarbital presented to it, there was virtually no measurable metabolism by the newborn preparation.

The physiologic impact of limited drug-metabolizing capacity is indicated by observing sleeping time in newborns versus sleeping time in adults following injection of hexobarbital. As shown in Table 10-1, a low dose (10 mg/kg) of hexobarbital caused adult mice to sleep less than 5 minutes. In contrast, the same dose caused newborns to sleep 6 hours. The differential effects on adults and newborns are much more dramatic at a higher dose (50 mg/kg): Whereas the adults merely slept longer, the newborns died.

TABLE 10-1 ■ Comparison of the Metabolism and Effect of Hexobarbital in Adult Versus Newborn Animals

Age	Percentage of Hexobarbital Metabolized (in 1 hr)	Duration of Drug-Induced Sleep	
		Dose: 10 mg/kg	Dose: 50 mg/kg
Newborn	"0"	6 hr	Eternal*
Adult	28-39	Less than 5 min	12-22 min

*The 50-mg/kg dose was lethal to newborn animals.

Data from Jondorf WR, Maickel RP, Brodie BB: Inability of newborn mice and guinea pigs to metabolize drugs. *Biochem Pharmacol* 1:352, 1958.

Renal Excretion

Renal drug excretion is significantly reduced at birth. Renal blood flow, glomerular filtration, and active tubular secretion are all low during infancy. Because the drug-excreting capacity of infants is limited, drugs that are eliminated primarily by renal excretion must be given in reduced dosage and/or at longer dosing intervals. Adult levels of renal function are achieved by 1 year.

The data in Table 10-2 illustrate the limited ability of the infant kidney to excrete foreign compounds. These data show rates of renal excretion for two compounds: inulin and *para*-aminohippuric acid (PAH). Inulin is excreted entirely by glomerular filtration. PAH is excreted by a combination of glomerular filtration and active tubular secretion. Note that the half-life for inulin is 630 minutes in infants but only 120 minutes in adults. Since inulin is eliminated by glomerular filtration alone, these data tell us that the glomerular filtration rate in the infant is much slower than in the adult. From the data for clearance of PAH, taken together with the data for clearance of inulin, we can conclude that tubular secretion in infants is also much slower than in adults.

PHARMACOKINETICS: CHILDREN 1 YEAR AND OLDER

By the age of 1 year, most pharmacokinetic parameters in children are similar to those in adults. Hence, drug sensitivity in children over the age of 1 is more like that of adults than that of the very young. Although pharmacokinetically similar to adults, children do differ in one important way: They metabolize drugs *faster* than adults. Drug-metabolizing capacity is markedly elevated until the age of 2 years, and then gradually declines. A further sharp decline takes place at puberty, when adult values are reached. Because of enhanced drug metabolism in children, an increase in dosage or a reduction in dosing interval may be needed for drugs that are eliminated by hepatic metabolism.

ADVERSE DRUG REACTIONS

Like adults, pediatric patients are subject to adverse reactions when drug levels rise too high. In addition, pediatric patients are vulnerable to unique adverse effects related to organ system immaturity and to ongoing growth and development. Among

TABLE 10-2 ■ Renal Function in Adults Versus Infants

	Average Infant	Average Adult
Body Weight (kg)	3.5	70
Inulin Clearance		
Rate (mL/min)	3 (approximate)	130
Half-time (min)	630	120
<i>Para</i>-aminohippuric Acid (PAH) Clearance		
Rate (mL/min)	12 (approximate)	650
Half-time (min)	160	43

Adapted from Goldstein A, Aronow L, Kalman SM: *Principles of Drug Action: The Basis of Pharmacology*, 2nd ed. New York: Churchill Livingstone, 1974:215.

TABLE 10-3 ■ Adverse Drug Reactions Unique to Pediatric Patients

Drug	Adverse Effect
Androgens	Premature puberty in males; reduced adult height from premature epiphyseal closure
Aspirin and other salicylates	Severe intoxication from acute overdose (acidosis, hyperthermia, respiratory depression); Reye's syndrome in children with chickenpox or influenza
Chloramphenicol	Gray syndrome (neonates and infants)
Glucocorticoids	Growth suppression with prolonged use
Fluoroquinolones	Tendon rupture
Hexachlorophene	CNS toxicity (infants)
Nalidixic acid	Cartilage erosion
Phenothiazines	Sudden infant death syndrome
Promethazine	Pronounced respiratory depression in children under 2 years old
Sulfonamides	Kernicterus (neonates)
Tetracyclines	Staining of developing teeth

CNS = central nervous system.

these age-related effects are growth suppression (caused by glucocorticoids), discoloration of developing teeth (caused by tetracyclines), and kernicterus (caused by sulfonamides). Table 10-3 presents a list of drugs that can cause unique adverse effects in pediatric patients of various ages. These drugs should be avoided in patients whose age puts them at risk.

DOSAGE DETERMINATION

Because of the pharmacokinetic factors discussed above, dosage selection for pediatric patients is difficult. Selecting a dosage is especially difficult in the very young, since pharmacokinetic factors are undergoing rapid change.

Pediatric doses have been established for a few drugs but not for most. For drugs that do not have an established pediatric dose, dosage can be extrapolated from adult doses. The

method of conversion employed most commonly is based on body surface area:

$$\text{Approximate child's dose} = \frac{\text{Body surface area of the child} \times \text{Adult dose}}{1.73 \text{ m}^2}$$

Please note that initial pediatric doses—whether based on established pediatric doses or extrapolated from adult doses—are at best an *approximation*. Subsequent doses must be adjusted on the basis of clinical outcome and plasma drug concentrations. These adjustments are especially important in neonates and younger infants. Clearly, if dosage adjustments are to be optimal, it is essential that we monitor the patient for therapeutic and adverse responses.

PROMOTING ADHERENCE

Achieving accurate and timely dosing requires informed participation of the child's caregiver and, to the extent possible, active involvement of the child as well. Effective education is critical. The following issues should be addressed:

- Dosage size and timing
- Route and technique of administration

- Duration of treatment
- Drug storage
- The nature and time course of desired responses
- The nature and time course of adverse responses

Written instructions should be provided. For techniques of administration that are difficult, a demonstration should be made, after which the parents should repeat the procedure to ensure they understand. With young children, spills and spitting out are common causes of inaccurate dosing; parents should be taught to estimate the amount of drug lost and to re-administer that amount, being careful not to overcompensate. When more than one person is helping medicate a child, all participants should be warned against multiple dosing. Multiple dosing can be avoided by maintaining a drug administration chart. With some disorders—especially infections—symptoms may resolve before the prescribed course of treatment has been completed. Parents should be instructed to complete the full course nonetheless. Additional ways to promote adherence include (1) selecting the most convenient dosage form and dosing schedule, (2) suggesting mixing oral drugs with food or juice (when allowed) to improve palatability, (3) providing a calibrated medicine spoon or syringe for measuring liquid formulations, and (4) taking extra time with young or disadvantaged parents to help ensure conscientious and skilled participation.

KEY POINTS

- The majority of drugs used in pediatrics have never been tested in children. As a result, we lack reliable information on which to base drug selection or dosage.
- Because of organ system immaturity, very young patients are highly sensitive to drugs.
- In neonates and young infants, drug responses may be unusually intense and prolonged.
- Absorption of IM drugs in *neonates* is slower than in adults. In contrast, absorption of IM drugs in *infants* is more rapid than in adults.
- Protein-binding capacity is limited early in life. Hence, free concentrations of some drugs may be especially high.
- The blood-brain barrier is not fully developed at birth. Hence, neonates are especially sensitive to drugs that affect the CNS.
- The drug-metabolizing capacity of neonates is low. Hence, neonates are especially sensitive to drugs that are eliminated primarily by hepatic metabolism.
- Renal excretion of drugs is low in neonates. Hence, drugs that are eliminated primarily by the kidney must be given in reduced dosage and/or at longer dosing intervals.
- In children 1 year and older, most pharmacokinetic parameters are similar to those in adults. Hence, drug sensitivity is more like that of adults than the very young.
- Children (1 to 12 years) differ pharmacokinetically from adults in that children metabolize drugs *faster*.
- Initial pediatric doses are at best an approximation. Hence, subsequent doses must be adjusted on the basis of clinical outcome and plasma drug levels.

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Drug Therapy in Geriatric Patients

Pharmacokinetic Changes in the Elderly Pharmacodynamic Changes in the Elderly Adverse Drug Reactions and Drug Interactions Promoting Adherence

Drug use among the elderly (those 65 years and older) is disproportionately high. Whereas the elderly constitute only 12% of the U.S. population, they consume 31% of the nation's prescribed drugs. Reasons for this intensive use of drugs include increased severity of illness, multiple pathologies, and excessive prescribing.

Drug therapy in the elderly represents a special therapeutic challenge. As a rule, older patients are more sensitive to drugs than are younger adults, and they show wider individual variation. In addition, the elderly experience more adverse drug reactions and drug-drug interactions. The principal factors underlying these complications are (1) altered pharmacokinetics (secondary to organ system degeneration), (2) multiple and severe illnesses, (3) multidrug therapy, and (4) poor adherence. To help ensure that drug therapy is as safe and effective as possible, *individualization of treatment is essential: Each patient must be monitored for desired and adverse responses, and the regimen must be adjusted accordingly.* Because the elderly typically suffer from chronic illnesses, the usual objective is to reduce symptoms and improve quality of life, since cure is generally impossible.

PHARMACOKINETIC CHANGES IN THE ELDERLY

The aging process can affect all phases of pharmacokinetics. From early adulthood on, there is a gradual, progressive decline in organ function. This decline can alter the absorption, distribution, metabolism, and excretion of drugs. As a rule, these pharmacokinetic changes increase drug sensitivity (largely from reduced hepatic and renal drug elimination). It should be noted, however, that the extent of change varies greatly among patients; Pharmacokinetic changes may be minimal in patients who have remained physically fit, whereas they may be dramatic in patients who have aged less fortunately. Accordingly, you should keep in mind that age-related changes in pharmacokinetics are not only a potential source of increased sensitivity to drugs, they are also a potential source of increased variability. The physiologic changes that underlie alterations in pharmacokinetics are summarized in Table 11-1.

TABLE 11-1 ■ Physiologic Changes That Can Affect Pharmacokinetics in the Elderly

Absorption of Drugs

- Increased gastric pH
- Decreased absorptive surface area
- Decreased splanchnic blood flow
- Decreased GI motility
- Delayed gastric emptying

Distribution of Drugs

- Increased body fat
- Decreased lean body mass
- Decreased total body water
- Decreased serum albumin
- Decreased cardiac output

Metabolism of Drugs

- Decreased hepatic blood flow
- Decreased hepatic mass
- Decreased activity of hepatic enzymes

Excretion of Drugs

- Decreased renal blood flow
- Decreased glomerular filtration rate
- Decreased tubular secretion
- Decreased number of nephrons

Absorption

Altered GI absorption is not a major factor in drug sensitivity in the elderly. As a rule, the *percentage* of an oral dose that becomes absorbed does not change with age. However, the *rate* of absorption may be slowed (because of delayed gastric emptying and reduced splanchnic blood flow). As a result, drug responses may be somewhat delayed. Gastric acidity is reduced in the elderly and may alter the absorption of certain drugs. For example, some drug formulations require high acidity to dissolve, and hence their absorption may be reduced.

Distribution

Four major factors can alter drug distribution in the elderly: (1) increased percent body fat, (2) decreased percent lean body mass, (3) decreased total body water, and (4) reduced concentration of serum albumin. The increase in body fat seen in the elderly provides a storage depot for *lipid-soluble* drugs (eg, thiopental). As a result, plasma levels of these drugs are reduced, causing a reduction in responses. Because of the decline in lean body mass and total body water, *water-soluble* drugs (eg, ethanol) become distributed in a smaller volume than in younger adults. As a result, the con-

centration of these drugs is increased, causing effects to be more intense. Although albumin levels are only slightly reduced in healthy adults, these levels can be significantly reduced in adults who are malnourished. Because of reduced albumin levels, protein binding of drugs decreases, causing levels of free drug to rise. As a result, drug effects may be more intense.

Metabolism

Rates of hepatic drug metabolism tend to decline with age. Principal reasons are reduced hepatic blood flow, reduced liver mass, and decreased activity of some hepatic enzymes. Because liver function is diminished, the half-lives of certain drugs may be increased, thereby prolonging responses. Responses to oral drugs that ordinarily undergo extensive first-pass metabolism may be enhanced. Please note, however, that the degree of decline in drug metabolism varies greatly among individuals. As a result, we cannot predict whether drug responses will be significantly reduced in any particular patient.

Excretion

Renal function, and hence renal drug excretion, undergoes progressive decline beginning in early adulthood. *Drug accumulation secondary to reduced renal excretion is the most important cause of adverse drug reactions in the elderly.* The decline in renal function is the result of reductions in renal blood flow, glomerular filtration rate, active tubular secretion, and number of nephrons. Renal pathology can further compromise kidney function. The degree of decline in renal function varies greatly among individuals. Accordingly, when patients are taking drugs that are eliminated primarily by the kidneys, renal function should be assessed. In the elderly, the proper index of renal function is *creatinine clearance*, not *serum creatinine levels*. Creatinine levels do not reflect kidney function in the elderly because the source of serum creatinine—lean muscle mass—declines in parallel with the decline in kidney function. As a result, creatinine levels may be normal even though renal function is greatly reduced.

PHARMACODYNAMIC CHANGES IN THE ELDERLY

Alterations in receptor properties may underlie altered sensitivity to some drugs. However, information on such pharmacodynamic changes is limited. In support of the possibility of altered pharmacodynamics is the observation that beta-adrenergic blocking agents (drugs used primarily for cardiac disorders) are *less* effective in the elderly than in younger adults, even when present in the same concentrations. Possible explanations for this observation include (1) a reduction in the number of beta receptors and (2) a reduction in the affinity of beta receptors for beta-receptor blocking agents. Other drugs (warfarin, certain central nervous system depressants) produce effects that are more intense in the elderly, suggesting a possible increase in receptor number, receptor affinity, or both. Unfortunately, our knowledge of pharmacodynamic changes in the elderly is restricted to a few families of drugs.

ADVERSE DRUG REACTIONS AND DRUG INTERACTIONS

Adverse drug reactions (ADRs) are 7 times more common in the elderly than in younger adults, accounting for about 16% of hospital admissions among older individuals and 50% of all medication-related deaths. The vast majority of these reactions are dose related, not idiosyncratic. Symptoms in the elderly are often nonspecific (eg, dizziness, cognitive impairment), making identification of ADRs difficult.

Perhaps surprisingly, the increase in ADRs seen in the elderly is not the direct result of aging per se. Rather, multiple factors predispose older patients to ADRs. The most important are:

- Drug accumulation secondary to reduced renal function
- Polypharmacy (treatment with multiple drugs)
- Greater severity of illness
- The presence of multiple pathologies
- Greater use of drugs that have a low therapeutic index (eg, digoxin, a drug for heart failure)
- Increased individual variation secondary to altered pharmacokinetics
- Inadequate supervision of long-term therapy
- Poor patient adherence

The majority of ADRs in the elderly are avoidable. Measures that can reduce their incidence include:

- Taking a thorough drug history, including over-the-counter medications
- Accounting for the pharmacokinetic and pharmacodynamic changes that occur with aging
- Initiating therapy with low doses
- Monitoring clinical responses and plasma drug levels to provide a rational basis for dosage adjustment
- Employing the simplest regimen possible
- Monitoring for drug-drug interactions and iatrogenic illness
- Periodically reviewing the need for continued drug therapy, and discontinuing medications as appropriate
- Encouraging the patient to dispose of old medications
- Taking steps to promote adherence (see below)
- Avoiding drugs on the Beers list (see below)

The *Beers list* identifies drugs with a high likelihood of causing adverse effects in the elderly. Accordingly, drugs on this list should generally be avoided. A partial listing of these drugs appears in Table 11-2. The full list, updated in 2003, is available online at <http://archinte.ama-assn.org/cgi/reprint/163/22/2716>.

PROMOTING ADHERENCE

Between 26% and 59% of elderly patients fail to take their medicines as prescribed. Some patients never fill their prescriptions, some fail to refill their prescriptions, and some don't follow the prescribed dosing schedule. Nonadherence can result in therapeutic failure (from underdosing or erratic dosing) or toxicity (from overdosing). Of the two possibilities, underdosing with resulting therapeutic failure is by far (90%) the more common. Problems arising from nonadherence account for up to 10% of all hospital admissions, and their management may cost over \$100 billion a year.

TABLE 11-2 • Some Drugs to Generally Avoid in the Elderly

Drugs	Reason for Concern	Alternative Treatments
Analgesics		
Ketorolac [Toradol]	GI bleeding	Mild pain: acetaminophen, ibuprofen
Meperidine [Demerol]	Not effective at usual doses, confusion	Moderate to severe pain: morphine, oxycodone
Propoxyphene* [Darvon]	No better than acetaminophen, but has the ADRs of an opioid	
Antidepressants		
Amitriptyline	Anticholinergic effects (constipation, urinary retention, blurred vision)	SSRIs (other than daily fluoxetine) or other antidepressants
Doxepin [Sinequan]	Long half-life; agitation, insomnia, anorexia	SSRI with a shorter half-life (eg, sertraline [Zoloft])
Fluoxetine [Prozac], taken daily		
Antihistamines, first generation		
Chlorpheniramine [Chlor-Trimeton ♣, Chlor-tripolon, others]	Anticholinergic effects: constipation, urinary retention, blurred vision	Second-generation antihistamines, such as cetirizine [Zyrtec], fexofenadine [Allegra], or loratadine [Claritin]
Diphenhydramine [Benadryl, others]		
Hydroxyzine [Vistaril, Atarax ♣]		
Promethazine [Phenergan, others]		
Antihypertensives		
Alpha-adrenergic blocking agents	Hypotension, dry mouth, incontinence	Thiazide diuretic, ACE inhibitor, beta-adrenergic blocker, calcium channel blocker
Doxazosin [Cardura]		
Prazosin [Minipress]		
Terazosin [Hytrin]		
Clonidine [Catapres]	Orthostatic hypotension, adverse CNS effects	
Guanethidine	Orthostatic hypotension, depression	
Methyldopa	Bradycardia, depression	
Reserpine	Depression, impotence, sedation, orthostatic hypotension	
Sedative-Hypnotics		
Barbiturates	Physical dependence; compared with other hypnotics, higher risk of falls, confusion, cognitive impairment	Temazepam [Restoril], zolpidem [Ambien], zaleplon [Sonata], ramelteon [Rozerem], eszopiclone [Lunesta]
Benzodiazepines, long acting	Prolonged sedation	A short-acting benzodiazepine, such as lorazepam [Ativan], given in low dosage
Chlordiazepoxide [Librium]		
Diazepam [Valium, others]		
Flurazepam		
Drugs for Urge Incontinence		
Oxybutynin [Ditropan]	Urinary retention, confusion, hallucinations, sedation	Behavioral therapy (eg, bladder retraining, urge suppression)
Tolterodine [Detrol]		
Muscle Relaxants		
Carisoprodol [Soma]	Anticholinergic effects, sedation, cognitive impairment; may not be effective at tolerable dosage	For spasticity, use nerve block, or an antispasmodic, such as baclofen [Lioresal]
Cyclobenzaprine [Flexeril, others]		
Metaxalone [Skelaxin]		
Methocarbamol [Robaxin]		

*No longer available in the United States or Canada.

ACE = angiotensin-converting enzyme, ADR = adverse drug reaction, CNS = central nervous system, GI = gastrointestinal, SSRI = selective serotonin reuptake inhibitor.

Adapted from Fick DM, Cooper JW, Wade WE, et al: Updating the Beers criteria for potentially inappropriate medication use in older adults. *Arch Intern Med* 163:2716-2724, 2003. (Note: The paper by Fick et al. lists many drugs in addition to those in this table.)

Multiple factors underlie nonadherence to the prescribed regimen (Table 11-3). Among these are forgetfulness; failure to comprehend instructions (because of intellectual, visual, or auditory impairment); inability to pay for medications; and use of complex regimens (several drugs taken several times a day). All of these factors can contribute to *unintentional* nonadherence. However, in the majority of cases (about 75%), nonadherence among the elderly is *intentional*. The principal reason given for intentional nonadherence is the patient's con-

viction that the drug was simply not needed in the dosage prescribed. Unpleasant side effects and expense also contribute to intentional nonadherence.

Several measures can promote adherence, including:

- Simplifying the regimen so that the number of drugs and doses per day is as small as possible
- Explaining the treatment plan using clear, concise verbal and written instructions

TABLE 11-3 ■ Factors That Contribute to Poor Adherence in the Elderly

- Multiple chronic disorders
- Multiple prescription medications
- Multiple doses/day for each medication
- Drug packaging that is difficult to open
- Multiple prescribers
- Changes in the regimen (addition of drugs, changes in dosage size or timing)
- Cognitive or physical impairment (reduction in memory, hearing, visual acuity, color discrimination, or manual dexterity)
- Living alone
- Recent discharge from hospital
- Low literacy
- Inability to pay for drugs
- Personal conviction that a drug is unnecessary or the dosage too high
- Presence of side effects

- Choosing an appropriate dosage form (eg, a liquid formulation if the patient has difficulty swallowing)
- Labeling drug containers clearly, and avoiding containers that are difficult to open by patients with impaired dexterity (eg, those with arthritis)
- Suggesting the use of a calendar, diary, or pill counter to record drug administration
- Asking the patient if he or she has access to a pharmacy and can afford the medication
- Enlisting the aid of a friend, relative, or visiting healthcare professional
- Monitoring for therapeutic responses, adverse reactions, and plasma drug levels

It must be noted, however, that the benefits of these measures will be restricted primarily to patients whose nonadherence is *unintentional*. Unfortunately, these measures are generally inapplicable to the patient whose nonadherence is *intentional*. For these patients, intensive education may help.

KEY POINTS

- Older patients are generally more sensitive to drugs than are younger adults, and they show wider individual variation.
- Individualization of therapy for the elderly is essential: Each patient must be monitored for desired and adverse responses, and the regimen must be adjusted accordingly.
- Aging-related organ decline can change drug absorption, distribution, metabolism, and (especially) excretion.
- The *rate* of drug absorption may be slowed in the elderly, although the *extent* of absorption is usually unchanged.
- Plasma concentrations of lipid-soluble drugs may be low in the elderly, and concentrations of water-soluble drugs may be high.
- Reduced liver function may prolong drug effects.
- Reduced renal function, with resultant drug accumulation, is the most important cause of adverse drug reactions in the elderly.
- Because the degree of renal impairment among the elderly varies, creatinine clearance (a test of renal function)

should be determined for all patients taking drugs that are eliminated primarily by the kidneys.

- Adverse drug reactions are much more common in the elderly than in younger adults.
- Factors underlying the increase in adverse reactions include polypharmacy, severe illness, multiple pathologies, and treatment with dangerous drugs.
- Nonadherence is common among the elderly.
- Reasons for *unintentional* nonadherence include complex regimens, awkward drug packaging, forgetfulness, side effects, low income, and failure to comprehend instructions.
- Most cases (75%) of nonadherence among the elderly are *intentional*. Reasons include expense, side effects, and the patient's conviction that the drug is unnecessary or the dosage too high.

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Basic Principles of Neuropharmacology

How Neurons Regulate Physiologic Processes Basic Mechanisms by Which Neuropharmacologic Agents Act

Sites of Action: Axons Versus Synapses

Steps in Synaptic Transmission

Effects of Drugs on the Steps of Synaptic Transmission

Multiple Receptor Types and Selectivity of Drug Action

An Approach to Learning About Peripheral Nervous System Drugs

Neuropharmacology can be defined as *the study of drugs that alter processes controlled by the nervous system*. Neuropharmacologic drugs produce effects equivalent to those produced by excitation or suppression of neuronal activity. Neuropharmacologic agents can be divided into two broad categories: (1) peripheral nervous system (PNS) drugs and (2) central nervous system (CNS) drugs.

The neuropharmacologic drugs constitute a large and important family of therapeutic agents. These drugs are used to treat conditions ranging from depression to epilepsy to hypertension to asthma. The clinical significance of these agents is reflected in the fact that over 25% of this text is dedicated to them.

Why do we have so many neuropharmacologic drugs? The answer lies in a concept discussed in Chapter 5: Most therapeutic agents act by helping the body help itself. That is, most drugs produce their therapeutic effects by coaxing the body to perform normal processes in a fashion that benefits the patient. Since the nervous system participates in the regulation of practically all bodily processes, practically all bodily processes can be influenced by drugs that alter neuronal regulation. By mimicking or blocking neuronal regulation, neuropharmacologic drugs can modify such diverse processes as skeletal muscle contraction, cardiac output, vascular tone, respiration, GI function, uterine motility, glandular secretion, and functions unique to the CNS, such as ideation, mood, and perception of pain. Given the broad spectrum of processes that neuropharmacologic drugs can alter, and given the potential benefits to be gained by manipulating those processes, it should be no surprise that neuropharmacologic drugs have widespread clinical applications.

We begin our study of neuropharmacology by discussing PNS drugs (Chapters 14 through 19), after which we discuss CNS drugs (Chapters 20 through 40). The principal rationale for this order of presentation is that our understanding of PNS pharmacology is much clearer than our understanding of CNS

pharmacology. Why? Because the PNS is less complex than the CNS, and more accessible to experimentation. By placing our initial focus on the PNS, we can establish a firm knowledge base in neuropharmacology before proceeding to the less definitive and vastly more complex realm of CNS pharmacology.

HOW NEURONS REGULATE PHYSIOLOGIC PROCESSES

As a rule, if we want to understand the effects of a drug on a particular physiologic process, we must first understand the process itself. Accordingly, if we wish to understand the impact of drugs on neuronal regulation of bodily function, we must first understand how neurons regulate bodily function when drugs are absent.

Figure 12-1 illustrates the basic process by which neurons elicit responses from other cells. The figure depicts two cells: a neuron and a postsynaptic cell. The postsynaptic cell might be another neuron, a muscle cell, or a cell within a secretory gland. As indicated, there are two basic steps—*axonal conduction* and *synaptic transmission*—in the process by which the neuron influences the behavior of the postsynaptic cell. Axonal conduction is simply the process of conducting an action potential down the axon of the neuron. Synaptic transmission is the process by which information is carried across the gap between the neuron and the postsynaptic cell. As shown in the figure, synaptic transmission requires the release of neurotransmitter molecules from the axon terminal followed by binding of these molecules to receptors on the postsynaptic cell. As a result of transmitter-receptor binding, a series of events is initiated in the postsynaptic cell, leading to a change in its behavior. The precise nature of the change depends on the identity of the neurotransmitter and the type of cell involved. If the postsynaptic cell is another neuron, it

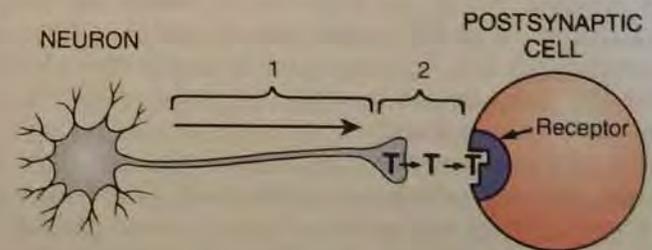


Figure 12-1 ■ How neurons regulate other cells.

There are two basic steps in the process by which neurons elicit responses from other cells: (1) axonal conduction and (2) synaptic transmission. (T = neurotransmitter.)

may increase or decrease its firing rate; if the cell is part of a muscle, it may contract or relax; and if the cell is glandular, it may increase or decrease secretion.

BASIC MECHANISMS BY WHICH NEUROPHARMACOLOGIC AGENTS ACT

Sites of Action: Axons Versus Synapses

In order to influence a process under neuronal control, a drug can alter one of two basic neuronal activities: axonal conduction or synaptic transmission. Most neuropharmacologic agents act by altering synaptic transmission. Only a few alter axonal conduction. Why do drugs usually target synaptic transmission? Because drugs that alter synaptic transmission can produce effects that are much more selective than those produced by drugs that alter axonal conduction.

Axonal Conduction

Drugs that act by altering axonal conduction are not very selective. Recall that the process of conducting an impulse along an axon is essentially the same in all neurons. As a consequence, a drug that alters axonal conduction will affect conduction in all nerves to which it has access. Such a drug cannot produce selective effects.

Local anesthetics are the only drugs proved to work by altering (decreasing) axonal conduction. Because these agents produce nonselective inhibition of axonal conduction, they suppress transmission in any nerve they reach. Hence, although local anesthetics are certainly valuable, their indications are limited.

Synaptic Transmission

In contrast to drugs that alter axonal conduction, drugs that alter synaptic transmission can produce effects that are highly selective. Why? Because synapses, unlike axons, differ from one another. Synapses at different sites employ different transmitters. In addition, for most transmitters, the body employs more than one type of receptor. Hence, by using a drug that selectively influences a specific type of neurotransmitter or receptor, we can alter one neuronally regulated process while leaving most others unchanged. Because of their relative selectivity, drugs that alter synaptic transmission have many uses.

Receptors

The ability of a neuron to influence the behavior of another cell depends, ultimately, upon the ability of that neuron to alter receptor activity on the target cell. As discussed, neurons alter receptor activity by releasing transmitter molecules, which diffuse across the synaptic gap and bind to receptors on the postsynaptic cell. If the target cell lacked receptors for the transmitter that a neuron released, that neuron would be unable to affect the target cell.

The effects of neuropharmacologic drugs, like those of neurons, depend on altering receptor activity. That is, no matter what its precise mechanism of action, a neuropharmacologic drug ultimately works by influencing receptor activity on target cells. This commonsense concept is central to understanding the actions of neuropharmacologic drugs. In fact, this concept is so critical to our understanding of neuropharmacologic agents that I will repeat it: *The impact of a drug on*

a neuronally regulated process is dependent on the ability of that drug to directly or indirectly influence receptor activity on target cells.

Steps in Synaptic Transmission

To understand how drugs alter receptor activity, we must first understand the steps by which synaptic transmission takes place—since it is by modifying these steps that neuropharmacologic drugs influence receptor function. The steps in synaptic transmission are summarized in Figure 12-2.

Step 1: Transmitter Synthesis. For synaptic transmission to take place, molecules of transmitter must be present in the nerve terminal. Hence, we can look upon transmitter synthesis as the first step in transmission. In the figure, the letters Q, R, and S represent the precursor molecules from which the transmitter (T) is made.

Step 2: Transmitter Storage. Once transmitter is synthesized, it must be stored until the time of its release. Transmitter storage takes place within vesicles—tiny packets present in the axon terminal. Each nerve terminal contains a large number of transmitter-filled vesicles.

Step 3: Transmitter Release. Release of transmitter is triggered by the arrival of an action potential at the axon terminal. The action potential initiates a process in which vesicles undergo fusion with the terminal membrane, causing release of their contents into the synaptic gap. Each action potential causes only a small fraction of all vesicles present in the axon terminal to discharge their contents.

Step 4: Receptor Binding. Following release, transmitter molecules diffuse across the synaptic gap and then un-

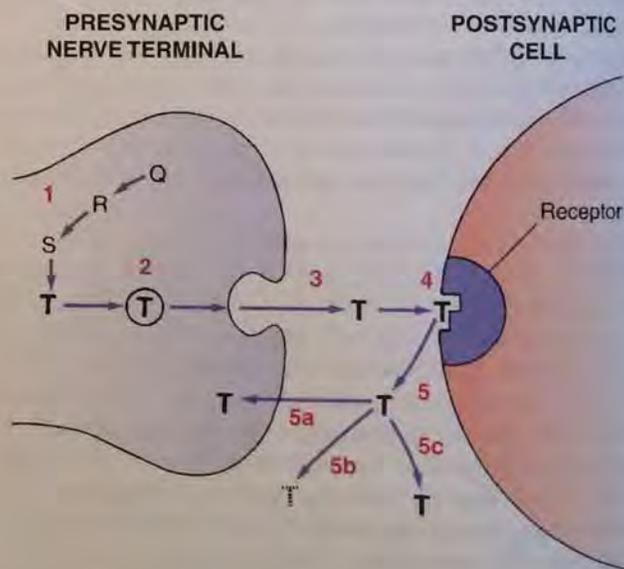


Figure 12-2 • Steps in synaptic transmission.

Step 1, Synthesis of transmitter (T) from precursor molecules (Q, R, and S). Step 2, Storage of transmitter in vesicles. Step 3, Release of transmitter: In response to an action potential, vesicles fuse with the terminal membrane and discharge their contents into the synaptic gap. **Step 4, Action at receptor:** Transmitter binds (reversibly) to its receptor on the postsynaptic cell, causing a response in that cell. **Step 5, Termination of transmission:** Transmitter dissociates from its receptor and is then removed from the synaptic gap by (a) reuptake into the nerve terminal, (b) enzymatic degradation, or (c) diffusion away from the gap.

dergo reversible binding to receptors on the postsynaptic cell. This binding initiates a cascade of events that result in altered behavior of the postsynaptic cell.

Step 5: Termination of Transmission. Transmission is terminated by dissociation of transmitter from its receptors, followed by removal of free transmitter from the synaptic gap. Transmitter can be removed from the synaptic gap by three processes: (1) reuptake, (2) enzymatic degradation, and (3) diffusion. In those synapses where transmission is terminated by reuptake, axon terminals contain "pumps" that transport transmitter molecules back into the neuron from which they were released (Step 5a in Fig. 12-2). Following reuptake, molecules of transmitter may be degraded, or they may be packaged in vesicles for reuse. In synapses where transmitter is cleared by enzymatic degradation (Step 5b), the synapse contains large quantities of transmitter-inactivating enzymes. Although simple diffusion away from the synaptic gap (Step 5c) is a potential means of terminating transmitter action, this process is very slow and generally of little significance.

Effects of Drugs on the Steps of Synaptic Transmission

As emphatically noted, all neuropharmacologic agents (except local anesthetics) produce their effects by directly or indirectly altering receptor activity. We also noted that the way in which drugs alter receptor activity is by interfering with synaptic transmission. Because synaptic transmission has multiple steps, the process offers a number of potential targets for drugs. In this section, we examine the specific ways in which drugs can alter the steps of synaptic transmission. By way of encouragement, although this information may appear complex, it isn't. In fact, it's largely self-evident.

Before discussing specific mechanisms by which drugs can alter receptor activity, we need to understand what drugs are capable of doing to receptors in general terms. From the broadest perspective, when a drug influences receptor function, that drug can do just one of two things: it can enhance receptor activation or it can reduce receptor activation. What do we mean by receptor activation? For our purposes, we can define *activation* as an effect on receptor function equivalent to that produced by the natural neurotransmitter at a particular synapse. Hence, a drug whose effects mimic the effects of a natural transmitter would be said to *increase* receptor activation. Conversely, a drug whose effects were equivalent to reducing the amount of natural transmitter available for receptor binding would be said to *decrease* receptor activation.

Please note that activation of a receptor does not necessarily mean that a physiologic process will go faster; receptor activation can also make a process go slower. For example, a drug that mimics acetylcholine at receptors on the heart will cause the heart to beat more slowly. Since the effect of this drug on receptor function mimicked the effect of the natural neurotransmitter, we would say that the drug activated acetylcholine receptors, even though activation caused heart rate to decline.

Having defined receptor activation, we are ready to discuss the mechanisms by which drugs, acting on specific steps of synaptic transmission, can increase or decrease receptor activity. These mechanisms are summarized in Table 12-1. As we

TABLE 12-1 • Effects of Drugs on Synaptic Transmission and the Resulting Impact on Receptor Activation

Step of Synaptic Transmission	Drug Action	Impact on Receptor Activation*
1. Synthesis of transmitter	Increased synthesis of T	Increase
	Decreased synthesis of T	Decrease
	Synthesis of "super" T	Increase
2. Storage of transmitter	Reduced storage of T	Decrease
3. Release of transmitter	Promotion of T release	Increase
	Inhibition of T release	Decrease
4. Binding to receptor	Direct receptor activation	Increase
	Enhanced response to T	Increase
	Blockade of T binding	Decrease
5. Termination of transmission	Blockade of T reuptake	Increase
	Inhibition of T breakdown	Increase

T = transmitter.

*Receptor activation is defined as producing an effect equivalent to that produced by the natural transmitter that acts on a particular receptor.

consider these mechanisms one by one, their commonsense nature should become apparent.

Transmitter Synthesis. There are three different effects that drugs are known to have on transmitter synthesis. They can (1) increase transmitter synthesis, (2) decrease transmitter synthesis, or (3) cause the synthesis of transmitter molecules that are more effective than the natural transmitter itself.

The impact of increased or decreased transmitter synthesis on receptor activity should be obvious. A drug that increases transmitter synthesis will cause receptor activation to increase. The process is this: As a result of increased transmitter synthesis, storage vesicles will contain transmitter in abnormally high amounts. Hence, when an action potential reaches the axon terminal, more transmitter will be released, and therefore more transmitter will be available to receptors on the postsynaptic cell, causing activation of those receptors to increase. Conversely, a drug that decreases transmitter synthesis will cause the transmitter content of vesicles to decline, resulting in reduced transmitter release and decreased receptor activation.

Some drugs can cause neurons to synthesize transmitter molecules whose structure is different from that of normal transmitter molecules. For example, by acting as substrates for enzymes in the axon terminal, drugs can be converted into "super" transmitters (molecules whose ability to activate receptors is greater than that of the naturally occurring transmitter at a particular site). Release of these supertransmitters will cause receptor activation to increase. In theory, it should be possible to cause the synthesis of *faulty* transmitter molecules (ie, molecules with a reduced ability to activate a particular receptor). However, we have no medicines that are known to act this way.

Transmitter Storage. Drugs that interfere with transmitter storage will cause receptor activation to decrease. Why? Because disruption of storage depletes vesicles of their transmitter content, thereby decreasing the amount of transmitter available for release.

Transmitter Release. Drugs can either *promote* or *inhibit* transmitter release. Drugs that promote release will increase receptor activation. Conversely, drugs that inhibit release will reduce receptor activation. The amphetamines (CNS stimulants) represent drugs that act by promoting transmitter release. Botulinum toxin, in contrast, acts by inhibiting transmitter release.*

Receptor Binding. Many drugs act directly at receptors. These agents can either (1) bind to receptors and cause activation, (2) bind to receptors and thereby block receptor activation by other agents, or (3) bind to receptor components and thereby enhance receptor activation by the natural transmitter at the site.

In the terminology introduced in Chapter 5, drugs that directly activate receptors are called *agonists*, whereas drugs that prevent receptor activation are called *antagonists*. We have no special name for drugs that bind to receptors and thereby enhance the effects of the natural transmitter. The direct-acting receptor agonists and antagonists constitute the largest and most important groups of neuropharmacologic drugs.

Examples of drugs that act directly at receptors are numerous. Drugs that bind to receptors and cause *activation* include morphine (used for its effects on the CNS), epinephrine (used mainly for its effects on the cardiovascular system), and insulin (used for its effects in diabetes). Drugs that bind to receptors and *prevent* their activation include naloxone (used to treat overdose with morphine-like drugs), antihistamines (used to treat allergic disorders), and propranolol (used to treat hypertension, angina pectoris, and cardiac dysrhythmias). The principal examples of drugs that bind to receptors and thereby enhance the actions of a natural transmitter are the benzodiazepines. Drugs in this family, which includes diazepam [Valium] and related agents, are used to treat anxiety, seizure disorders, and muscle spasm.

*Botulinum toxin blocks release of acetylcholine from the neurons that control skeletal muscles, including the muscles of respiration. The potential for disaster is obvious.

Termination of Transmitter Action. Drugs can interfere with the termination of transmitter action by two mechanisms: (1) blockade of transmitter reuptake and (2) inhibition of transmitter degradation. Drugs that act by either mechanism will increase transmitter availability, thereby causing receptor activation to increase.

MULTIPLE RECEPTOR TYPES AND SELECTIVITY OF DRUG ACTION

As we discussed in Chapter 1, selectivity is one of the most desirable qualities a drug can have. Why? Because a selective drug is able to alter a specific disease process while leaving other physiologic processes largely unaffected.

Many neuropharmacologic agents display a high degree of selectivity. This selectivity is possible because the nervous system works through multiple types of receptors to regulate processes under its control. If neurons had only one or two types of receptors through which to act, selective effects by neuropharmacologic drugs could not be achieved.

The relationship between multiple receptor types and selective drug action is illustrated by Mort and Merv, whose unique physiologies are depicted in Figure 12-3. Let's begin with Mort. Mort can perform four functions: he can pump blood, digest food, shake hands, and empty his bladder. As indicated in the figure, all four functions are under neuronal control, and, in all cases, that control is exerted by activation of the same type of receptor (designated A).

As long as Mort remains healthy, having only one type of receptor to regulate his various functions is no problem. Selective *physiologic* regulation can be achieved simply by sending impulses down the appropriate nerves. When there is a need to increase cardiac output, impulses are sent down the nerve to his heart; when digestion is needed, impulses are sent down the nerve to his stomach; and so forth.

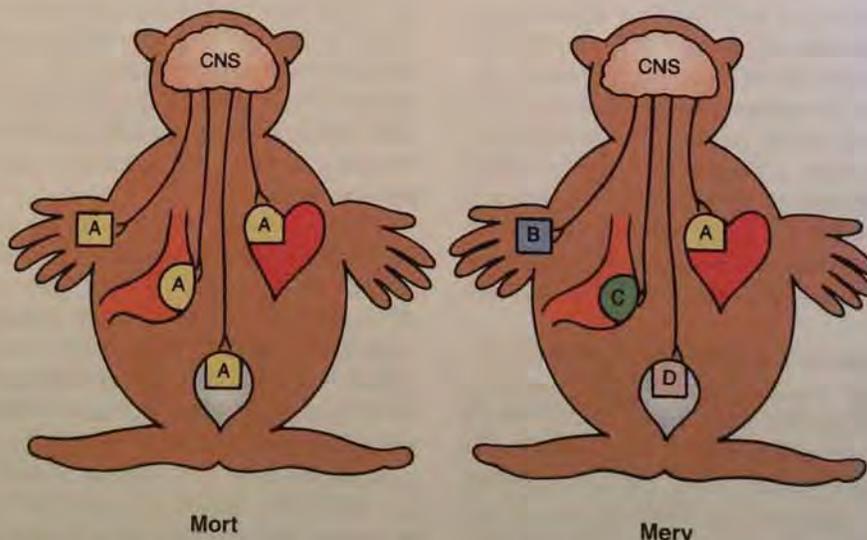


Figure 12-3 ■ Multiple drug receptors and selective drug action.

Mort. All of Mort's organs are regulated through activation of type A receptors. Drugs that affect type A receptors on one organ will affect type A receptors on all other organs. Hence, selective drug action is impossible. **Merv.** Merv has four types of receptors (A, B, C, and D) to regulate his four organs. A drug that acts at one type of receptor will not affect the others. Hence, selective drug action is possible.

- Drugs that decrease transmitter synthesis decrease receptor activation.
- Drugs that promote synthesis of "super" transmitters increase receptor activation.
- Drugs that impede transmitter storage decrease receptor activation.
- Drugs that promote transmitter release increase receptor activation.
- Drugs that suppress transmitter release decrease receptor activation.
- Agonist drugs increase receptor activation.
- Antagonist drugs decrease receptor activation.
- Drugs that bind to receptors and enhance the actions of the natural transmitter at the receptor increase receptor activation.

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CHAPTER 12 Basic Principles of Neuropharmacology

ingly, when preparing to study PNS pharmacology, you must first establish a working knowledge of the PNS itself. In particular, you need to know two basic types of information about PNS function. First, you need to know the types of receptors through which the PNS works when influencing the function of a specific organ. Second, you need to know what the normal response to activation of those receptors is. All of the information you need about PNS function is reviewed in Chapter 13.

Once you understand the PNS itself, you can go on to learn about PNS drugs. Although learning about these drugs will require significant effort, the learning process itself is straightforward. To understand any particular PNS drug, you need three types of information: (1) the type (or types) of receptor through which the drug acts; (2) the normal response to activation of those receptors; and (3) what the drug in question does to receptor function (ie, does it increase or decrease receptor activation?). Armed with these three types of information, you can predict the major effects of any PNS drug.

An example will illustrate this process. Let's consider a drug named *isoproterenol*. The first information we need is the identity of the receptors at which isoproterenol acts. Isoproterenol acts at two types of receptors, named beta₁ and beta₂. Next, we need to know the normal responses to activation of these receptors. The most prominent responses to activation of beta₁ receptors are *increased heart rate and increased force of cardiac contraction*. The primary responses to activation of beta₂ receptors are *bronchial dilation and elevation of blood glucose levels*. Lastly, we need to know whether isoproterenol increases or decreases the activation of beta₁ and beta₂ receptors. At both types of receptor, isoproterenol causes *activation*. Armed with these three primary pieces of information about isoproterenol, we can now predict the principal effects of this drug. By activating beta₁ and beta₂ receptors, isoproterenol can elicit three major responses: (1) increased cardiac output (by increasing heart rate and force of contraction); (2) dilation of the bronchi; and (3) elevation of blood glucose. Depending on the patient to whom this drug is given, these responses may be beneficial or detrimental.

From this example, you can see how easy it is to predict the effects of a PNS drug. Accordingly, I strongly encourage you to take the approach suggested when studying these agents. That is, for each PNS drug, you should learn (1) the identity of the receptors at which that drug acts, (2) the normal responses to activation of those receptors, and (3) whether the drug increases or decreases receptor activation.

Although having only one receptor type is no disadvantage when all is well, if Mort gets sick, having only one receptor type creates a therapeutic challenge. Let's assume he develops heart disease and we need to give a drug that will help increase cardiac output. To stimulate cardiac function, we need to administer a drug that will activate receptors on his heart. Unfortunately, since the receptors on his heart are the same as the receptors on his other organs, a drug that stimulates cardiac function will stimulate his other organs too. Consequently any attempt to improve cardiac output with drugs will necessarily be accompanied by side effects. These will range from silly (compulsive handshaking) to embarrassing (tenures) to hazardous (gastric ulcers). Such side effects are not likely to elicit either gratitude or adherence. Please note that all of these undesirable effects are the direct result of Mort having a nervous system that works through just one type of receptor to regulate all organs. That is, the presence of only one receptor type has made selective drug action impossible.

Now let's consider Merv. Although Merv appears to be Mort's twin, Merv differs in one important way: Whereas all functions in Mort are regulated through just one type of receptor, Merv employs different receptors to control each of his four functions. Because of this simple but important difference, the selective drug action that was impossible with Mort can be achieved easily with Merv. We can, for example, selectively enhance cardiac function in Merv without risking the side effects to which Mort was predisposed. This can be done simply by administering an agonist agent that binds selectively to receptors on the heart (type A receptors). If this medication is sufficiently selective for type A receptors, it will not interact with receptor types B, C, or D. Hence, function in structures regulated by those receptors will be unaffected. Note that our ability to produce selective drug action in Merv is made possible because his nervous system works through different types of receptors to regulate function in his various organs. The message from this example is clear: *The more types of receptors we have to work with, the greater our chances of producing selective drug effects.*

AN APPROACH TO LEARNING ABOUT PERIPHERAL NERVOUS SYSTEM DRUGS

As discussed, to understand the ways in which drugs can alter a process under neuronal control, we must first understand how the nervous system itself regulates that process. Accord-

KEY POINTS

- Except for local anesthetics, which suppress axonal conduction, all neuropharmacologic drugs act by altering synaptic transmission.
- Synaptic transmission consists of five basic steps: transmitter synthesis, transmitter storage, transmitter release, binding of transmitter to its receptors, and termination of transmitter action by dissociation of transmitter from the receptor followed by transmitter reuptake or degradation.
- Ultimately, the impact of a drug on a neuronally regulated process depends on that drug's ability to directly or indirectly alter receptor activity on target cells.
- Drugs can do one of two things to receptor function: they can increase receptor activation or they can decrease receptor activation.
- Drugs that increase transmitter synthesis increase receptor activation.

Physiology of the Peripheral Nervous System

Divisions of the Nervous System

Overview of Autonomic Nervous System Functions

Functions of the Parasympathetic Nervous System

Functions of the Sympathetic Nervous System

Basic Mechanisms by Which the Autonomic Nervous System Regulates Physiologic Processes

Anatomic Considerations

Introduction to Transmitters of the Peripheral Nervous System

Introduction to Receptors of the Peripheral Nervous System

Exploring the Concept of Receptor Subtypes

Locations of Receptor Subtypes

Functions of Cholinergic and Adrenergic Receptor Subtypes

Functions of Cholinergic Receptor Subtypes

Functions of Adrenergic Receptor Subtypes

Receptor Specificity of the Adrenergic Transmitters

Transmitter Life Cycles

Life Cycle of Acetylcholine

Life Cycle of Norepinephrine

Life Cycle of Epinephrine

To understand peripheral nervous system drugs, we must first understand the peripheral nervous system itself. The purpose of this chapter is to help you develop that understanding.

It's not uncommon for students to be at least slightly apprehensive about studying the peripheral nervous system—especially the autonomic component. In fact, it's not uncommon for students who have studied this subject before to be thoroughly convinced that they will never, ever really understand it. This reaction is unfortunate in that, although there is a lot to learn, the information is not terribly difficult. My approach to teaching this information is untraditional. Hopefully, it will make your work easier.

Since our ultimate goal concerns pharmacology—and not physiology—I do not address everything there is to know about the peripheral nervous system. Rather, I limit the discussion to those aspects of peripheral nervous system physiology that have a direct bearing on your ability to understand drugs.

DIVISIONS OF THE NERVOUS SYSTEM

The nervous system has two main divisions, the *central nervous system* (CNS) and the *peripheral nervous system*. The CNS is subdivided into the brain and spinal cord.

The peripheral nervous system has two major subdivisions: (1) the *somatic motor system* and (2) the *autonomic nervous system*. The autonomic nervous system is further subdivided into the *parasympathetic nervous system* and the *sympathetic nervous system*. The somatic motor system controls voluntary movement of muscles. The two subdivisions of the autonomic nervous system regulate many “involuntary” processes.

The autonomic nervous system is the principal focus of this chapter. The somatic motor system is also considered, but discussion is brief.

OVERVIEW OF AUTONOMIC NERVOUS SYSTEM FUNCTIONS

The autonomic nervous system has three principal functions: (1) regulation of the *heart*; (2) regulation of *secretory glands* (salivary, gastric, sweat, and bronchial glands); and (3) regulation of *smooth muscles* (muscles of the bronchi, blood vessels, urogenital system, and GI tract). These regulatory activities are shared between the sympathetic and parasympathetic divisions of the autonomic nervous system.

Functions of the Parasympathetic Nervous System

The parasympathetic nervous system performs seven regulatory functions that have particular relevance to drugs. Specifically, stimulation of appropriate parasympathetic nerves causes

- Slowing of heart rate
- Increased gastric secretion
- Emptying of the bladder
- Emptying of the bowel
- Focusing the eye for near vision
- Constricting the pupil
- Contracting bronchial smooth muscle

Just how the parasympathetic nervous system elicits these responses is discussed later under *Functions of Cholinergic Receptor Subtypes*.

From the above we can see that the parasympathetic nervous system is concerned primarily with what might be called the “housekeeping” chores of the body (digestion of food and excretion of wastes). In addition, the system helps control vision and conserve energy (by reducing cardiac work).

Therapeutic agents that alter parasympathetic nervous system function are used primarily for their effects on the GI

tract, bladder, and eye. Occasionally, these drugs are also used for effects on the heart and lungs.

A variety of poisons act by mimicking or blocking effects of parasympathetic stimulation. Among these are insecticides, nerve gases, and toxic compounds found in certain mushrooms and plants.

Functions of the Sympathetic Nervous System

The sympathetic nervous system has three main functions:

- Regulating the cardiovascular system
- Regulating body temperature
- Implementing the “fight-or-flight” reaction

The sympathetic nervous system exerts multiple influences on the heart and blood vessels. Stimulation of sympathetic nerves to the heart increases cardiac output. Stimulation of sympathetic nerves to arterioles and veins causes vasoconstriction. Release of epinephrine from the adrenal medulla results in vasoconstriction in most vascular beds and vasodilation in certain others. By influencing the heart and blood vessels, the sympathetic nervous system can achieve three homeostatic objectives:

- Maintenance of blood flow to the brain
- Redistribution of blood flow during exercise
- Compensation for loss of blood, primarily by causing vasoconstriction

The sympathetic nervous system helps regulate body temperature in three ways: (1) By regulating blood flow to the skin, sympathetic nerves can increase or decrease heat loss. By *dilating* surface vessels, sympathetic nerves increase blood flow to the skin and thereby accelerate heat loss. Conversely, *constricting* cutaneous vessels conserves heat. (2) Sympathetic nerves to sweat glands promote secretion of sweat, thereby helping the body cool. (3) By inducing piloerection (erection of hair), sympathetic nerves can promote heat conservation.

When we are faced with adversity, the sympathetic nervous system orchestrates the fight-or-flight response, which consists of

- Increasing heart rate and blood pressure
- Shunting blood away from the skin and viscera and into skeletal muscles
- Dilating the bronchi to improve oxygenation
- Dilating the pupils (perhaps to enhance visual acuity)
- Mobilizing stored energy, thereby providing glucose for the brain and fatty acids for muscles

The sensation of being “cold with fear” is brought on by shunting of blood away from the skin. The phrase “wide-eyed with fear” may be based on pupillary dilation.

Many therapeutic agents produce their effects by altering functions under sympathetic control. These drugs are used primarily for effects on the heart, blood vessels, and lungs. Agents that alter cardiovascular function are used to treat hypertension, heart failure, angina pectoris, and other disorders. Drugs affecting the lungs are used primarily for asthma.

BASIC MECHANISMS BY WHICH THE AUTONOMIC NERVOUS SYSTEM REGULATES PHYSIOLOGIC PROCESSES

To understand how drugs influence processes under autonomic control, we must first understand how the autonomic nervous system itself regulates those activities. The basic mechanisms by which the autonomic nervous system regulates physiologic processes are discussed below.

Patterns of Innervation and Control

Most structures under autonomic control are innervated by sympathetic nerves *and* parasympathetic nerves. The relative influence of sympathetic and parasympathetic nerves depends on the organ under consideration.

In many organs that receive dual innervation, the influence of sympathetic nerves *opposes* that of parasympathetic nerves. For example, in the heart, *sympathetic* nerves *increase* heart rate, whereas *parasympathetic* nerves *slow* heart rate (Fig. 13-1).

In some organs that receive nerves from both divisions of the autonomic nervous system, the effects of sympathetic and parasympathetic nerves are *complementary*, rather than opposite. For example, in the male reproductive system, erection is regulated by parasympathetic nerves while ejaculation is controlled by sympathetic nerves. If attempts at reproduction are to succeed, cooperative interaction of both systems is needed.

A few structures under autonomic control receive innervation from only one division. The principal example is blood vessels, which are innervated exclusively by sympathetic nerves.

In summary, there are three basic patterns of autonomic innervation and regulation:

- Innervation by *both* divisions of the autonomic nervous system in which the effects of the two divisions are *opposed*
- Innervation by *both* divisions of the autonomic nervous system in which the effects of the two divisions are *complementary*
- Innervation and regulation by *only one* division of the autonomic nervous system

Feedback Regulation

Feedback regulation is a process that allows a system to adjust itself by responding to incoming information. Practically all physiologic processes are regulated at least in part by feedback control.

Figure 13-2 depicts a feedback loop typical of those used by the autonomic nervous system. The main elements of this loop are (1) a *sensor*; (2) an *effector*; and (3) neurons connecting the sensor to the effector. The purpose of the sensor is to monitor the status of a physiologic process. Information

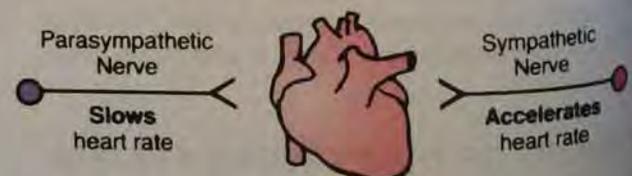


Figure 13-1 • Opposing effects of parasympathetic and sympathetic nerves.

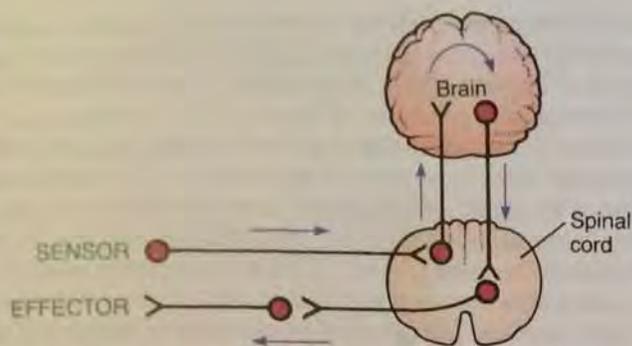


Figure 13-2 • Feedback loop of the autonomic nervous system.

picked up by the sensor is sent to the central nervous system (spinal cord and brain), where it is integrated with other relevant information. Signals (instructions for change) are then sent from the central nervous system along nerves of the autonomic system to the effector. In response to these instructions, the effector makes appropriate adjustments in the process. The entire procedure is called a *reflex*.

Baroreceptor Reflex. From a pharmacologic perspective, the most important feedback loop of the autonomic nervous system is one that helps regulate blood pressure. This system is referred to as the *baroreceptor reflex*. (Baroreceptors are receptors that sense blood pressure.) This reflex is important to us because it frequently opposes our attempts to modify blood pressure with drugs.

Feedback (reflex) control of blood pressure is achieved as follows: (1) Baroreceptors located in the carotid sinus and aortic arch monitor changes in blood pressure and send this information to the brain. (2) In response, the brain sends impulses along nerves of the autonomic nervous system, instructing the heart and blood vessels to behave in a way that restores blood pressure to normal. Accordingly, when blood pressure *falls*, the baroreceptor reflex causes vasoconstriction and increases cardiac output. Both actions help bring blood pressure back up. Conversely, when blood pressure *rises* too high, the baroreceptor reflex

causes vasodilation and reduces cardiac output, thereby causing blood pressure to drop. The baroreceptor reflex is discussed in greater detail in Chapter 43 (Review of Hemodynamics).

Autonomic Tone

The term *autonomic tone* refers to the steady, day-to-day influence exerted by the autonomic nervous system on a particular organ or organ system. Autonomic tone provides a basal level of control over which reflex regulation is superimposed.

When an organ is innervated by both divisions of the autonomic nervous system, one division—either sympathetic or parasympathetic—provides most of the basal control, thereby obviating conflicting instruction. Recall that, when an organ receives nerves from both divisions of the autonomic nervous system, those nerves frequently exert opposing influences. If both divisions were to send impulses simultaneously, the resultant conflicting instructions would be counterproductive (like running heating and air conditioning simultaneously). By having only one division of the autonomic nervous system provide the basal control to an organ, conflicting signals are avoided.

The branch of the autonomic nervous system that controls organ function most of the time is said to provide the *predominant tone* to that organ. *In most organs, the parasympathetic nervous system provides the predominant tone.* The vascular system, which is regulated almost exclusively by the *sympathetic nervous system*, is the principal exception.

ANATOMIC CONSIDERATIONS

Although we know a great deal about the anatomy of the peripheral nervous system, very little of this information helps us understand peripheral nervous system drugs. The few details that *do* pertain to pharmacology are summarized in Figure 13-3.

Parasympathetic Nervous System

Pharmacologically relevant aspects of parasympathetic anatomy are shown in Figure 13-3. Note that there are *two* neurons in the pathway leading from the spinal cord to organs innervated by

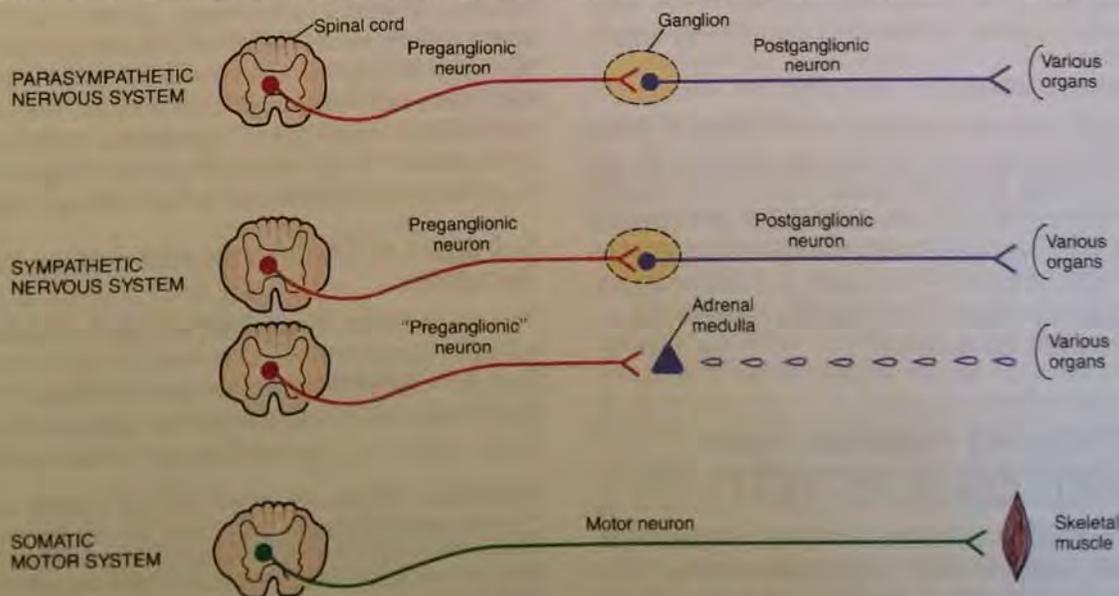


Figure 13-3 • The basic anatomy of the parasympathetic and sympathetic nervous systems and the somatic motor system.

parasympathetic nerves. The junction (synapse) between these two neurons occurs within a structure called a *ganglion*. (A ganglion is simply a lump created by a group of nerve cell bodies.) Not surprisingly, the neurons that go from the spinal cord to the parasympathetic ganglia are called *preganglionic neurons*, whereas the neurons that go from the ganglia to effector organs are called *postganglionic neurons*. The anatomy of the parasympathetic nervous system offers two general sites at which drugs can act: (1) the synapses between preganglionic neurons and postganglionic neurons and (2) the junctions between postganglionic neurons and their effector organs.

Sympathetic Nervous System

Pharmacologically relevant aspects of sympathetic nervous system anatomy are illustrated in Figure 13-3. As you can see, these features are nearly identical to those of the parasympathetic nervous system. Like the parasympathetic nervous system, the sympathetic nervous system employs two neurons in the pathways leading from the spinal cord to organs under its control. As with the parasympathetic nervous system, the junctions between those neurons are located in *ganglia*. Neurons leading from the spinal cord to the sympathetic ganglia are termed *preganglionic neurons*, and neurons leading from ganglia to effector organs are termed *postganglionic neurons*.

The *medulla of the adrenal gland* is a feature of the sympathetic nervous system that requires comment. Although not a neuron per se, the adrenal medulla can be looked on as the functional equivalent of a postganglionic neuron of the sympathetic nervous system. (The adrenal medulla influences the body by releasing epinephrine into the bloodstream, which then produces effects much like those that occur in response to stimulation of postganglionic sympathetic nerves.) Because the adrenal medulla is similar in function to a postganglionic neuron, it is appropriate to refer to the nerve leading from the spinal cord to the adrenal as preganglionic, even though there is no ganglion, as such, in this pathway.

As with the parasympathetic nervous system, drugs that affect the sympathetic nervous system have two general sites of action: (1) the synapses between preganglionic and postganglionic neurons (including the adrenal medulla), and (2) the junctions between postganglionic neurons and their effector organs.

Somatic Motor System

Pharmacologically relevant anatomy of the somatic motor system is depicted in Figure 13-3. Note that there is *only one* neuron in the pathway from the spinal cord to the muscles innervated by somatic motor nerves. Because this pathway contains only one neuron, peripherally acting drugs that affect somatic motor system function have only one site of action: the *neuromuscular junction* (ie, the junction between the somatic motor nerve and the muscle).

INTRODUCTION TO TRANSMITTERS OF THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system employs three neurotransmitters: *acetylcholine*, *norepinephrine*, and *epinephrine*. Any given junction in the peripheral nervous system uses only one of these transmitter substances. A fourth compound—*dopamine*—may also serve as a peripheral nervous system transmitter, but this role has not been demonstrated conclusively.

To understand peripheral nervous system pharmacology, it is necessary to know the identity of the transmitter employed at each of the junctions of the peripheral nervous system. This information is summarized in Figure 13-4. As indicated, *acetylcholine* is the transmitter employed at most junctions of the peripheral nervous system. Acetylcholine is the transmitter released by (1) all preganglionic neurons of the parasympathetic nervous system, (2) all preganglionic neurons of the sympathetic nervous system, (3) all postganglionic neurons of the parasympathetic nervous system, (4) all motor neurons of skeletal muscles, and (5) most postganglionic neurons of the sympathetic nervous system that go to sweat glands.

Norepinephrine is the transmitter released by practically all postganglionic neurons of the sympathetic nervous system. The only exceptions are the postganglionic sympathetic neurons that go to sweat glands, which employ acetylcholine as their transmitter.

Epinephrine is the major transmitter released by the adrenal medulla. (The adrenal medulla also releases some norepinephrine.)

Much of what follows in this chapter is based on the information summarized in Figure 13-4. Accordingly, I strongly urge you to learn (memorize) this information now.

INTRODUCTION TO RECEPTORS OF THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system works through several different types of receptors. Understanding these receptors is central to understanding peripheral nervous system pharmacology. All effort that you invest in learning about these receptors now will be richly rewarded as we discuss peripheral nervous system drugs in the chapters to come.

Primary Receptor Types: Cholinergic Receptors and Adrenergic Receptors

There are two basic categories of receptors associated with the peripheral nervous system: *cholinergic receptors* and *adrenergic receptors*. Cholinergic receptors are defined as receptors that mediate responses to acetylcholine. These receptors mediate responses at all junctions where acetylcholine is the transmitter. Adrenergic receptors are defined as receptors that mediate responses to epinephrine (adrenaline) and norepinephrine. These receptors mediate responses at all junctions where norepinephrine or epinephrine is the transmitter.

Subtypes of Cholinergic and Adrenergic Receptors

Not all cholinergic receptors are the same; likewise, not all adrenergic receptors are the same. For each of these two major receptor classes there are receptor subtypes. There are three major subtypes of cholinergic receptors, referred to as nicotinic_N, nicotinic_M, and muscarinic.* And there are four major

*Evidence gathered over the last 15 years indicates that muscarinic receptors like nicotinic receptors, come in subtypes. Five have been identified. Of these, only three—designated M₁, M₂, and M₃—have clearly identified functions. At this time, practically all drugs that affect muscarinic receptors are nonselective. Accordingly, since our understanding of these receptors is limited, and since drugs that can selectively alter their function are few, we will not discuss muscarinic receptor subtypes further in this chapter. However, we will discuss them in Chapter 14, in the context of drugs for overactive bladder.

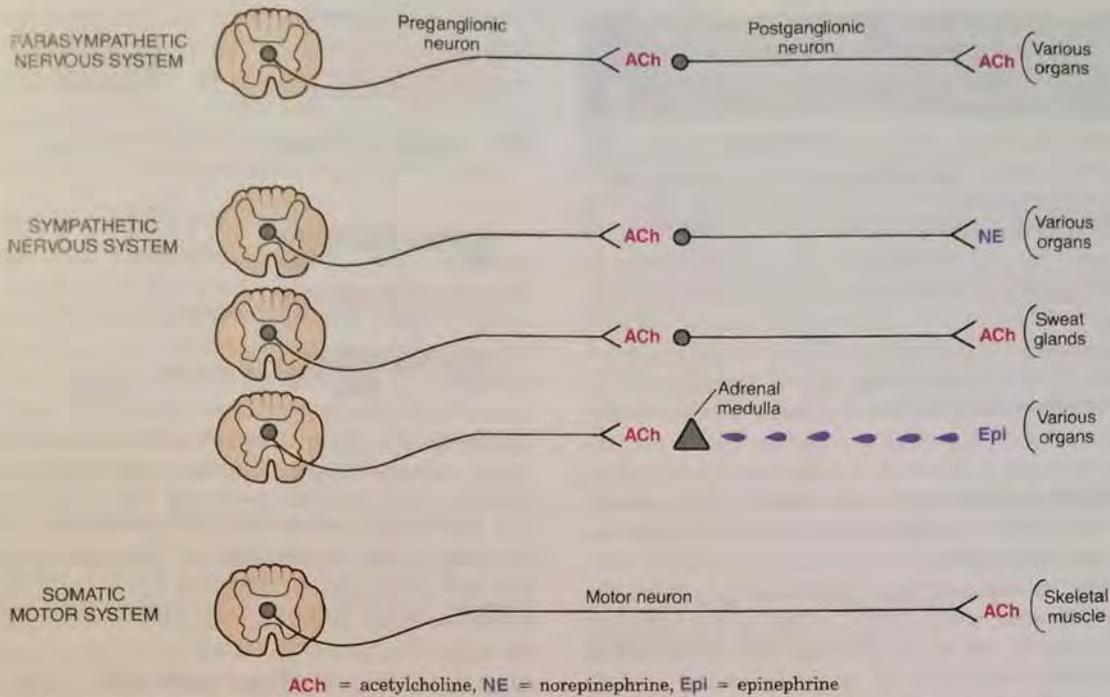


Figure 13-4 Transmitters employed at specific junctions of the peripheral nervous system.

Summary:

1. All preganglionic neurons of the parasympathetic and sympathetic nervous systems release acetylcholine as their transmitter.
2. All postganglionic neurons of the parasympathetic nervous system release acetylcholine as their transmitter.
3. Most postganglionic neurons of the sympathetic nervous system release norepinephrine as their transmitter.
4. Postganglionic neurons of the sympathetic nervous system that innervate sweat glands release acetylcholine as their transmitter.
5. Epinephrine is the principal transmitter released by the adrenal medulla.
6. All motor neurons to skeletal muscles release acetylcholine as their transmitter.

subtypes of adrenergic receptors, referred to as α_1 , α_2 , β_1 , and β_2 .

In addition to the four major subtypes of adrenergic receptors, there is another adrenergic receptor type, referred to as the dopamine receptor. Although dopamine receptors are classified as adrenergic, these receptors do not respond to epinephrine or norepinephrine. Rather, they respond only to dopamine, a neurotransmitter found primarily in the central nervous system.

EXPLORING THE CONCEPT OF RECEPTOR SUBTYPES

The concept of receptor subtypes is important and potentially confusing. In this section we discuss what a receptor subtype is and why receptor subtypes matter.

What Do We Mean by the Term Receptor Subtype?

Receptors that respond to the same transmitter but nonetheless are different from one another would be called receptor subtypes. For example, peripheral receptors that respond to acetylcholine can be found (1) in ganglia of the autonomic nervous system, (2) at neuromuscular junctions, and (3) on organs regulated by the parasympathetic nervous system. However, even

though all of these receptors can be activated by acetylcholine, there is clear evidence that the receptors at these three sites are, in fact, different from one another. Hence, although all of these receptors belong to the same major receptor category (cholinergic), they are sufficiently different as to constitute distinct receptor subtypes.

How Do We Know That Receptor Subtypes Exist?

Historically, our knowledge of receptor subtypes came from observing responses to drugs. In fact, were it not for drugs, receptor subtypes might never have been discovered.

The data in Table 13-1 illustrate the types of drug responses that led to the realization that receptor subtypes exist. These data summarize the results of an experiment designed to study the effects of a natural transmitter (acetylcholine) and a series of drugs (nicotine, muscarine, *d*-tubocurarine, and atropine) on two tissues: skeletal muscle and ciliary muscle. (The ciliary muscle is the muscle responsible for focusing the eye for near vision.) As these data indicate, although skeletal muscle and ciliary muscle both contract in response to acetylcholine, these tissues differ in their responses to drugs. In the discussion below, we examine the selective responses of these tissues to drugs and see how those responses reveal the existence of receptor subtypes.

TABLE 13-1 ■ Responses of Skeletal Muscle and Ciliary Muscle to a Series of Drugs

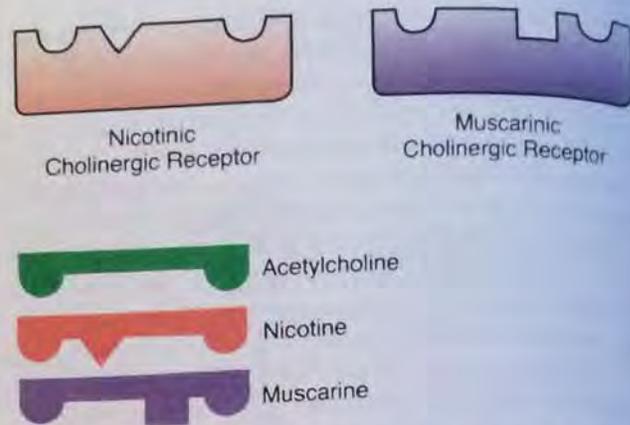
Drug	Response	
	Skeletal Muscle	Ciliary Muscle
Acetylcholine	Contraction	Contraction
Nicotine	Contraction	No response
Muscarine	No response	Contraction
Acetylcholine		
After <i>d</i> -tubocurarine	No response	Contraction
After atropine	Contraction	No response

At synapses on skeletal muscle and ciliary muscle, acetylcholine is the transmitter employed by neurons to elicit contraction. Because both types of muscle respond to acetylcholine, it is safe to conclude that both muscles have receptors for this substance. Because acetylcholine is the natural transmitter for these receptors, we would classify these receptors as *cholinergic*.

What do the effects of nicotine on skeletal muscle and ciliary muscle suggest? The effects of nicotine on these muscles suggest four possible conclusions: (1) Because skeletal muscle contracts when nicotine is applied, we can conclude that skeletal muscle has receptors at which nicotine can act. (2) Because ciliary muscle does *not* respond to nicotine, we can tentatively conclude that ciliary muscle does not have receptors for nicotine. (3) Because nicotine mimics the effects of acetylcholine on skeletal muscle, we can conclude that nicotine may act at the same receptors on skeletal muscle as does acetylcholine. (4) Because both types of muscle have receptors for acetylcholine, and because nicotine appears to act only at the acetylcholine receptors on skeletal muscle, we can tentatively conclude that the acetylcholine receptors on skeletal muscle are different from the acetylcholine receptors on ciliary muscle.

What do the responses to muscarine suggest? The conclusions that can be drawn regarding responses to muscarine are exactly parallel to those drawn for nicotine. These conclusions are: (1) ciliary muscle has receptors that respond to muscarine. (2) skeletal muscle may not have receptors for muscarine. (3) muscarine may be acting at the same receptors on ciliary muscle as does acetylcholine, and (4) the receptors for acetylcholine on ciliary muscle may be different from the receptors for acetylcholine on skeletal muscle.

The responses of skeletal muscle and ciliary muscle to nicotine and muscarine suggest, but do not prove, that the cholinergic receptors on these two tissues are different. However, the responses of these two tissues to *d*-tubocurarine and *atropine*, both of which are receptor *blocking agents*, eliminate any doubts as to the presence of cholinergic receptor subtypes. When both types of muscle are pretreated with *d*-tubocurarine and then exposed to acetylcholine, the response to acetylcholine is blocked—but only in skeletal muscle. Tubocurarine pretreatment does not reduce the ability of acetylcholine to stimulate ciliary muscle. Conversely, pretreatment with atropine selectively blocks the response to acetylcholine in ciliary muscle—but atropine does nothing to prevent acetylcholine from stimulating receptors on skeletal muscle. Because tubocu-

**Figure 13-5 ■ Drug structure and receptor selectivity.**

These cartoon figures illustrate the relationship between structure and receptor selectivity. The structure of acetylcholine allows this transmitter to interact with both receptor subtypes. In contrast, because of their unique structures, nicotine and muscarine are selective for the cholinergic receptor subtypes whose structure complements their own.

arine can selectively block cholinergic receptors in skeletal muscle, whereas atropine can selectively block cholinergic receptors in ciliary muscle, we can conclude with certainty that the receptors for acetylcholine in these two types of muscle must be different.

The data just discussed illustrate the essential role of drugs in revealing the presence of receptor subtypes. If acetylcholine were the only probe that we had, all that we would have been able to observe is that both skeletal muscle and ciliary muscle can respond to this agent. This simple observation would provide no basis for suspecting that the receptors for acetylcholine in these two tissues were different. It is only through the use of selectively acting drugs that the presence of receptor subtypes was initially revealed.

Today, the technology for identifying receptors and their subtypes is extremely sophisticated—not that studies like the one just discussed are no longer of value. In addition to performing traditional drug-based studies, scientists are now cloning receptors using DNA hybridization technology. As you can imagine, this allows us to understand receptors in ways that were unthinkable in the past.*

How Can Drugs Be More Selective Than Natural Transmitters at Receptor Subtypes?

Drugs achieve their selectivity for receptor subtypes by having structures that are different from those of natural transmitters. The relationship between structure and receptor selectivity is illustrated in Figure 13-5. In this figure, cartoon drawings are used to represent drugs (nicotine and muscarine), receptor subtypes (nicotinic and muscarinic), and acetylcholine (the natural transmitter at nicotinic and muscarinic receptors). From the structures shown, we can easily imagine how acetylcholine is able to interact with both kinds of receptor subtypes, whereas

*In addition to revealing exciting new information about receptors previously identified, this spiffy technology is so powerful that new receptors and receptor subtypes are being discovered at a dizzying rate. Which means, of course, that students in the future will have many more receptors to contend with than you do. So, when it seems like you're working awfully hard to master the information on receptors in this chapter and the ones that follow, look on the bright side—you could be studying pharmacology 10 years from now!

nicotine and muscarine can interact only with the receptor subtypes whose structure is complementary to their own. By synthesizing chemicals that are structurally related to natural transmitters, pharmaceutical chemists have been able to produce drugs that are more selective for specific receptor subtypes than are the natural transmitters that act at those sites.

Why Do Receptor Subtypes Exist?

It is not unreasonable for us to wonder why Mother Nature bothered to create more than one type of receptor for any given transmitter. Unfortunately, a definitive answer to that question will have to come from Mother Nature herself. That is, the physiologic benefits of having multiple receptor subtypes for the same transmitter are not immediately obvious. In fact, as noted earlier, were it not for drugs, we probably wouldn't know that receptor subtypes existed at all.

Do Receptor Subtypes Matter to Us? You Bet!

Although receptor subtypes are of uncertain physiologic relevance, from the viewpoint of therapeutics, receptor subtypes are invaluable. The presence of receptor subtypes makes possible a dramatic increase in drug selectivity. For example, thanks to the existence of subtypes of cholinergic receptors (and the development of drugs selective for those receptor subtypes), it is possible to influence the activity of certain cholinergic receptors (eg, receptors of the neuromuscular junction) without altering the activity of all other cholinergic receptors (eg, the cholinergic receptors found in all autonomic ganglia and all target organs of the parasympathetic nervous system). Were it not for the existence of receptor subtypes, a drug that acted on cholinergic receptors at one site would alter the activity of cholinergic receptors at all other sites. Clearly, the existence of receptor subtypes for a particular transmitter makes possible drug actions that are much more selective than could be achieved if all of the receptors for that transmitter were the same. (Recall our discussion of Mort and Merv in Chapter 12.)

LOCATIONS OF RECEPTOR SUBTYPES

Since many of the drugs discussed in the following chapters are selective for specific receptor subtypes, knowledge of the sites at which specific receptor subtypes are located will help us predict which organs a drug will affect. Accordingly, in laying our foundation for studying peripheral nervous system drugs, it is important to learn the sites at which the subtypes of adrenergic and cholinergic receptors are located. This information is summarized in Figure 13-6. You will find it very helpful to master the contents of this figure before proceeding much further. (In the interest of minimizing confusion, subtypes of adrenergic receptors in Figure 13-6 are listed simply as alpha and beta rather than as α_1 , α_2 , β_1 , and β_2 . The locations of all four subtypes of adrenergic receptors are discussed in the section that follows.)

FUNCTIONS OF CHOLINERGIC AND ADRENERGIC RECEPTOR SUBTYPES

Knowledge of receptor function is an absolute requirement for understanding peripheral nervous system drugs. By knowing the receptors at which a drug acts, and by knowing what

those receptors do, we can predict the major effects of any peripheral nervous system drug.

Tables 13-2 and 13-3 summarize the pharmacologically relevant functions of peripheral nervous system receptors. Table 13-2 summarizes responses elicited by activation of *cholinergic* receptor subtypes. Table 13-3 summarizes responses to activation of *adrenergic* receptor subtypes. Before attempting to study specific peripheral nervous system drugs, you should master (memorize) the contents of the appropriate table. Accordingly, you should master Table 13-2 before studying cholinergic drugs (Chapters 14, 15, and 16). And you should master Table 13-3 before studying adrenergic drugs (Chapters 17, 18, and 19). If you master these tables in preparation for learning about peripheral nervous system drugs, you will find the process of learning the pharmacology relatively simple (and perhaps even enjoyable). Conversely, if you attempt to study the pharmacology without first mastering the appropriate table, you are likely to meet with frustration.

Functions of Cholinergic Receptor Subtypes

Table 13-2 summarizes the pharmacologically relevant responses to activation of the three major subtypes of cholinergic receptors: nicotinic_N, nicotinic_M, and muscarinic. Please commit the information in this table to memory.

We can group responses to cholinergic receptor activation into three major categories based on the subtype of receptor involved:

- Activation of *nicotinic_N* (neuronal) receptors promotes *ganglionic transmission* at all ganglia of the sympathetic and parasympathetic nervous systems. In addition, activation of nicotinic_N receptors promotes *release of epinephrine from the adrenal medulla*.
- Activation of *nicotinic_M* (muscle) receptors causes *contraction of skeletal muscle*.
- Activation of *muscarinic* receptors, which are located on target organs of the parasympathetic nervous system, elicits an appropriate response from the organ involved. Specifically, muscarinic activation causes (1) increased glandular secretions (from pulmonary, gastric, intestinal, and sweat glands); (2) contraction of smooth muscle in the bronchi and GI tract; (3) slowing of heart rate; (4) contraction of the sphincter muscle of the iris, resulting in miosis (reduction in pupillary diameter); (5) contraction of the ciliary muscle of the eye, causing the lens to focus for near vision; (6) dilation of blood vessels; and (7) voiding of the urinary bladder (by causing contraction of the detrusor muscle [which forms the bladder wall] and relaxation of the trigone and sphincter muscles [which block the bladder neck when contracted]).

Muscarinic cholinergic receptors on blood vessels require additional comment. These receptors are not associated with the nervous system in any way. That is, no autonomic nerves terminate at vascular muscarinic receptors. It is not at all clear as to how, or even if, these receptors are activated physiologically. However, regardless of their physiologic relevance, the cholinergic receptors on blood vessels do have *pharmacologic* significance. Why? Because drugs that are able to activate these receptors cause vasodilation, which in turn causes blood pressure to fall.

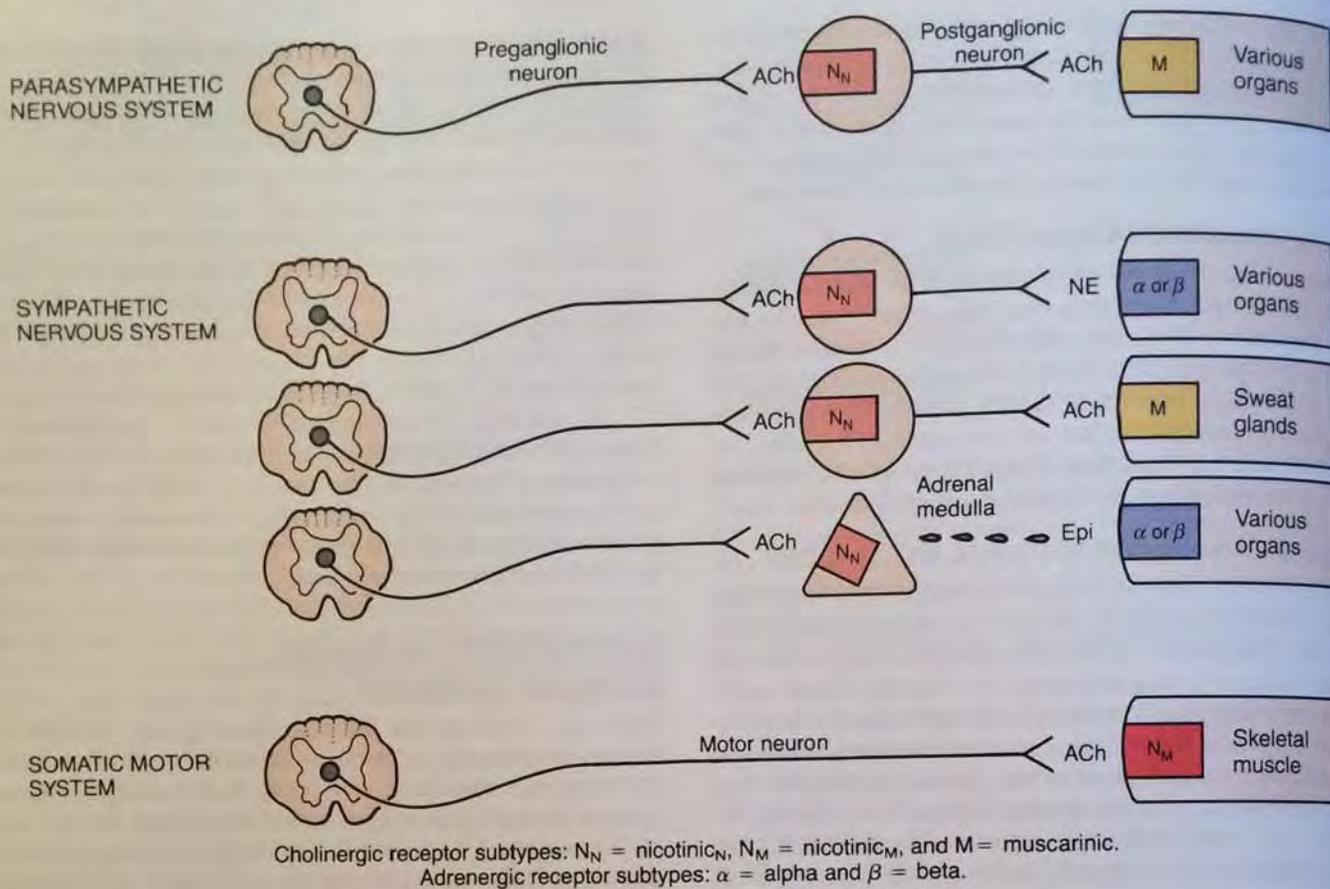


Figure 13-6 ■ Locations of cholinergic and adrenergic receptor subtypes.

Summary:

1. Nicotinic_N receptors are located on the cell bodies of all postganglionic neurons of the parasympathetic and sympathetic nervous systems. Nicotinic_N receptors are also located on cells of the adrenal medulla.
2. Nicotinic_M receptors are located on skeletal muscle.
3. Muscarinic receptors are located on all organs regulated by the parasympathetic nervous system (ie, organs innervated by postganglionic parasympathetic nerves). Muscarinic receptors are also located on sweat glands.
4. Adrenergic receptors—alpha, beta, or both—are located on all organs (except sweat glands) regulated by the sympathetic nervous system (ie, organs innervated by postganglionic sympathetic nerves). Adrenergic receptors are also located on organs regulated by epinephrine released from the adrenal medulla.

Functions of Adrenergic Receptor Subtypes

Adrenergic receptor subtypes and their functions are summarized in Table 13-3. You should commit this information to memory.

Alpha₁ Receptors

Alpha₁ receptors are located in the eyes, blood vessels, male sex organs, prostatic capsule, and bladder (trigone and sphincter).

Ocular alpha₁ receptors are present on the radial muscle of the iris. Activation of these receptors leads to mydriasis (dilation of the pupil). As depicted in Table 13-3, the fibers of the radial muscle are arranged like the spokes of a wheel. Because of this configuration, contraction of the radial muscle causes the pupil to enlarge. (If you have difficulty remembering that *mydriasis* means pupillary enlargement, whereas *miosis* means pupillary constriction, just remember that mydriasis [enlargement] is a bigger word than miosis.)

Activation of alpha₁ receptors in blood vessels produces vasoconstriction. Alpha₁ receptors are present on veins and on arterioles in many capillary beds.

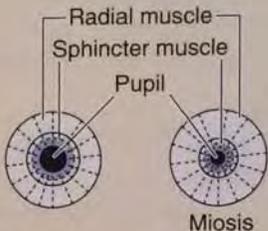
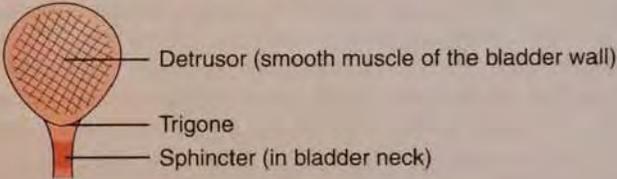
Activation of alpha₁ receptors in the sexual apparatus of males causes ejaculation.

Activation of alpha₁ receptors in smooth muscle of the bladder (trigone and sphincter) and prostatic capsule causes contraction.

Alpha₂ Receptors

Alpha₂ receptors of the peripheral nervous system are located on nerve terminals (see Table 13-3) and not on the organs innervated by the autonomic nervous system. Because alpha₂ receptors are located on nerve terminals, these receptors are referred to as presynaptic or prejunctional. The function of these receptors is to regulate transmitter release. As depicted in Table 13-3, norepinephrine can bind to alpha₂ receptors located on the same neuron from which the norepinephrine

TABLE 33-2 • Functions of Peripheral Cholinergic Receptor Subtypes

Receptor Subtype	Location	Response to Receptor Activation
Nicotinic _γ	All autonomic nervous system ganglia and the adrenal medulla	Stimulation of parasympathetic and sympathetic postganglionic nerves and release of epinephrine from the adrenal medulla
Nicotinic _α	Neuromuscular junction	Contraction of skeletal muscle
Muscarinic	All parasympathetic target organs:	
	Eye	Contraction of the ciliary muscle focuses the lens for near vision Contraction of the iris sphincter muscle causes miosis (decreased pupil diameter)
		
	Heart	Decreased rate
	Lung	Constriction of bronchi
		Promotion of secretions
	Bladder	Contraction of detrusor increases bladder pressure Relaxation of trigone and sphincter allows urine to leave the bladder Coordinated contraction of detrusor and relaxation of trigone and sphincter causes voiding of the bladder
		
	GI tract	Salivation Increased gastric secretions Increased intestinal tone and motility Defecation
	Sweat glands*	Generalized sweating
	Sex organs	Erection
	Blood vessels†	Vasodilation

*Although sweating is due primarily to stimulation of muscarinic receptors by acetylcholine, the nerves that supply acetylcholine to sweat glands belong to the sympathetic nervous system rather than the parasympathetic nervous system.

†Cholinergic receptors on blood vessels are not associated with the nervous system.

was released. The consequence of this norepinephrine-receptor interaction is suppression of further norepinephrine release. Hence, presynaptic α_2 receptors can help reduce transmitter release when too much transmitter has accumulated in the synaptic gap. Drug effects resulting from activation of *peripheral* α_2 receptors are of minimal clinical significance.

α_2 receptors are also present in the CNS. In contrast to peripheral α_2 receptors, central α_2 receptors are therapeutically relevant. We will consider these receptors in later chapters.

Beta₁ Receptors

Beta₁ receptors are located in the heart and the kidney. *Cardiac* beta₁ receptors have great therapeutic significance. Activation of these receptors increases *heart rate*, *force of contraction*, and *velocity of impulse conduction through the atrioventricular (AV) node*.

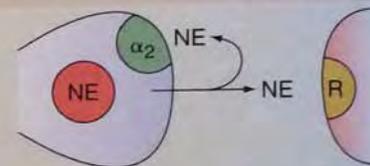
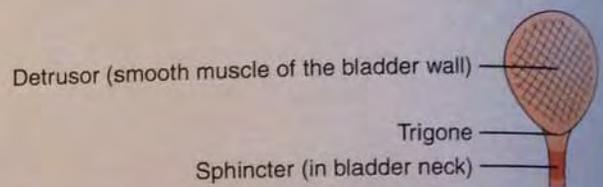
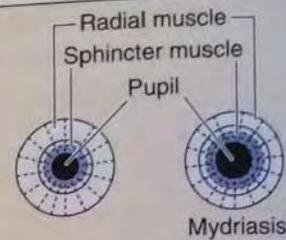
Activation of beta₁ receptors in the *kidney* causes release of *renin* into the blood. Since renin promotes synthesis of angiotensin, a powerful vasoconstrictor, activation of renal beta₁ receptors is a means by which the nervous system helps elevate blood pressure. (The role of renin in the regulation of blood pressure is discussed in depth in Chapter 44.)

Beta₂ Receptors

Beta₂ receptors mediate several important processes. Activation of beta₂ receptors in the lung leads to *bronchial dilation*. Activation of beta₂ receptors in the uterus causes *relaxation of uterine smooth muscle*. Activation of beta₂ receptors in arterioles of the heart, lungs, and skeletal muscles causes *vasodilation* (an effect opposite to that of α_1 activation). Activation of beta₂ receptors in the liver and skeletal muscle promotes *glycogenolysis* (breakdown of glycogen into glucose), thereby increasing blood levels of glucose. In addition, activation of beta₂ receptors in skeletal muscle enhances contraction.

TABLE 13-3 • Functions of Peripheral Adrenergic Receptor Subtypes

Receptor Subtype	Location	Response to Receptor Activation
Alpha ₁	Eye	Contraction of the radial muscle of the iris causes mydriasis (increased pupil size)
	Arterioles	Constriction
	Skin	
	Viscera	
	Mucous membranes	
	Veins	Constriction
	Sex organs, male	Ejaculation
	Prostatic capsule	Contraction
	Bladder	Contraction of trigone and sphincter
Alpha ₂	Presynaptic nerve terminals*	Inhibition of transmitter release
Beta ₁	Heart	Increased rate Increased force of contraction Increased AV conduction velocity
	Kidney	Release of renin
Beta ₂	Arterioles	Dilation
	Heart	
	Lung	
	Skeletal muscle	
	Bronchi	Dilation
	Uterus	Relaxation
	Liver	Glycogenolysis
	Skeletal muscle	Enhanced contraction, glycogenolysis
Dopamine	Kidney	Dilation of kidney vasculature



AV = atrioventricular, NE = norepinephrine, R = receptor.
*Alpha₂ receptors in the central nervous system are postsynaptic.

Dopamine Receptors

In the periphery, the only dopamine receptors of clinical significance are located in the vasculature of the kidney. Activation of these receptors dilates renal blood vessels, thereby enhancing renal perfusion.

In the central nervous system, receptors for dopamine are of great therapeutic significance. The functions of these receptors are discussed in Chapter 21 (Drugs for Parkinson's Disease) and Chapter 31 (Antipsychotic Agents and Their Use in Schizophrenia).

RECEPTOR SPECIFICITY OF THE ADRENERGIC TRANSMITTERS

The receptor specificity of adrenergic transmitters is more complex than the receptor specificity of acetylcholine. Whereas acetylcholine can activate all three subtypes of cholinergic receptors, not every adrenergic transmitter (epinephrine, norepinephrine, dopamine) can interact with each of the five subtypes of adrenergic receptors.

Receptor specificity of adrenergic transmitters is as follows:
(1) epinephrine can activate all alpha and beta receptors, but

not dopamine receptors; (2) *norepinephrine* can activate α_1 , α_2 , and β_1 receptors, but not β_2 or dopamine receptors; and (3) *dopamine* can activate α_1 , β_1 , and dopamine receptors. (Note that dopamine itself is the only transmitter capable of activating dopamine receptors.) Receptor specificity of the adrenergic transmitters is summarized in Table 13-4.

Knowing that epinephrine is the only transmitter that acts at β_2 receptors can serve as an aid to remembering the functions of this receptor subtype. Recall that epinephrine is released from the adrenal medulla—not from neurons—and that the function of epinephrine is to prepare the body for fight or flight. Accordingly, since epinephrine is the only transmitter that activates β_2 receptors, and since epinephrine is released only in preparation for fight or flight, times of fight or flight will be the only occasions on which β_2 receptors will undergo significant physiologic activation. As it turns out, the physiologic changes elicited by β_2 activation are precisely those needed for success in the fight-or-flight response. Specifically, activation of β_2 receptors will (1) dilate blood vessels in the heart, lungs, and skeletal muscles, thereby increasing blood flow to these organs; (2) dilate the bronchi, thereby increasing oxygenation; (3) increase glycogenolysis, thereby increasing available energy; and (4) relax uterine smooth muscle, thereby preventing delivery (a process that would be inconvenient for a

pregnant woman preparing to fight or flee). Accordingly, if you think of the physiologic requirements for success during fight or flight, you will have a good picture of the responses that β_2 activation can cause.

TRANSMITTER LIFE CYCLES

In this section we consider the life cycles of acetylcholine, norepinephrine, and epinephrine. Because a number of drugs produce their effects by interfering with specific phases of the transmitters' life cycles, knowledge of these cycles helps us understand drug actions.

Life Cycle of Acetylcholine

The life cycle of acetylcholine (ACh) is depicted in Figure 13-7. The cycle begins with synthesis of ACh from two precursors: choline and acetylcoenzyme A. Following synthesis, ACh is stored in vesicles and later released in response to an action potential. Following release, ACh binds to receptors (nicotinic_N, nicotinic_M, or muscarinic) located on the post-junctional cell. Upon dissociating from its receptors, ACh is destroyed almost instantaneously by *acetylcholinesterase* (AChE), an enzyme present in abundance on the surface of the postjunctional cell. AChE degrades ACh into two inactive products: acetate and choline. Uptake of choline into the cholinergic nerve terminal completes the life cycle of ACh. Note that an inactive substance (choline), and not the active transmitter (acetylcholine), is taken back up for reuse.

Therapeutic and toxic agents can interfere with the ACh life cycle at several points. Botulinum toxin inhibits ACh release. A number of medicines and poisons act at cholinergic receptors to mimic or block the actions of ACh. Several therapeutic and toxic agents act by inhibiting AChE, thereby causing ACh to accumulate in the junctional gap.

TABLE 13-4 • Receptor Specificity of Adrenergic Transmitters*

Transmitter	Adrenergic Receptor Subtype				
	α_1	α_2	β_1	β_2	Dopamine
Epinephrine	←				→
Norepinephrine	←		→		
Dopamine	↔		↔		↔

*Arrows indicate the range of receptors that the transmitters can activate.

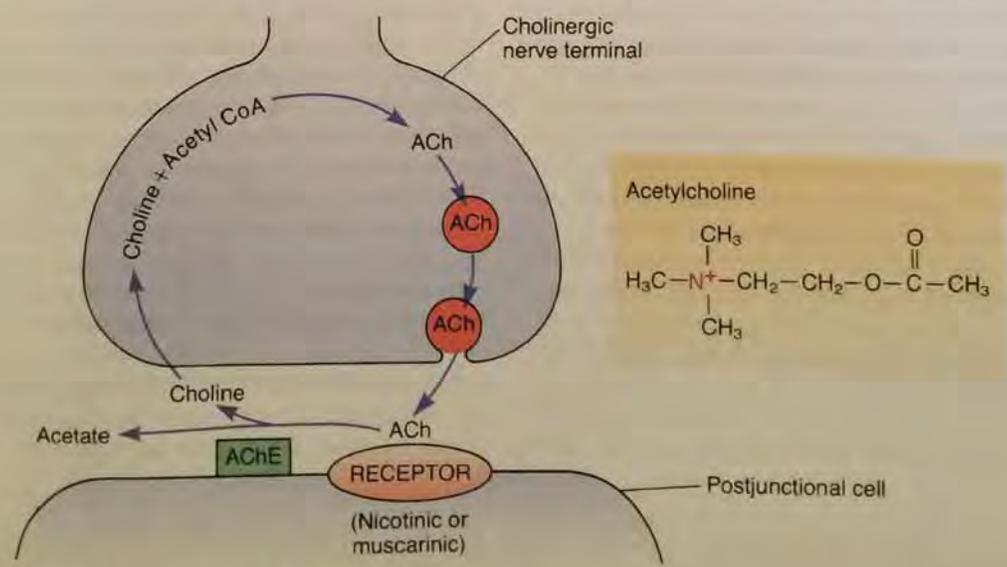


Figure 13-7 • Life cycle of acetylcholine. Note that transmission is terminated by enzymatic degradation of ACh and not by uptake of intact ACh back into the nerve terminal. (Acetyl CoA = acetylcoenzyme A, ACh = acetylcholine, AChE = acetylcholinesterase.)

KEY POINTS

- The peripheral nervous system has two major divisions: the autonomic nervous system and the somatic motor system.
- The autonomic nervous system has two major divisions: the sympathetic nervous system and the parasympathetic nervous system.
- The parasympathetic nervous system has several functions relevant to pharmacology: it slows heart rate, increases gastric secretion, empties the bladder and bowel, focuses the eye for near vision, constricts the pupil, and contracts bronchial smooth muscle.
- Principal functions of the sympathetic nervous system are regulation of the cardiovascular system, regulation of body temperature, and implementation of the fight-or-flight response.
- In some organs (eg, the heart), sympathetic and parasympathetic nerves have opposing effects. In other organs (eg, male sex organs), the sympathetic and parasympathetic systems have complementary effects. And in still other organs (notably blood vessels), function is regulated by only one branch of the autonomic nervous system.
- The baroreceptor reflex helps regulate blood pressure.
- In most organs regulated by the autonomic nervous system, the parasympathetic nervous system provides the dominant tone.
- In blood vessels, the sympathetic nervous system provides the dominant tone.
- Pathways from the spinal cord to organs under sympathetic and parasympathetic control consist of two neurons: a preganglionic neuron and a postganglionic neuron.
- The adrenal medulla is the functional equivalent of a postganglionic sympathetic neuron.
- Somatic motor pathways from the spinal cord to skeletal muscles have only one neuron.
- The peripheral nervous system employs three transmitters: acetylcholine, norepinephrine, and epinephrine.
- Acetylcholine is the transmitter released by all preganglionic neurons of the sympathetic nervous system, all preganglionic neurons of the parasympathetic nervous system, all postganglionic neurons of the sympathetic nervous system that go to sweat glands, and all motor neurons.
- Norepinephrine is the transmitter released by all postganglionic neurons of the sympathetic nervous system, except those that go to sweat glands.
- Epinephrine is the major transmitter released by the adrenal medulla.
- There are three major subtypes of cholinergic receptors: nicotinic, muscarinic, and muscarinic.
- There are four major subtypes of adrenergic receptors: alpha₁, alpha₂, beta₁, and beta₂.
- Although receptor subtypes are of uncertain physiologic significance, they are of great pharmacologic significance.
- Activation of nicotinic receptors promotes transmission at all autonomic ganglia, and promotes release of epinephrine from the adrenal medulla.
- Activation of nicotinic receptors causes contraction of skeletal muscle.
- Activation of muscarinic receptors increases glandular secretion (from pulmonary, gastric, intestinal, and sweat glands); contracts smooth muscle in the bronchi and GI tract; slows heart rate; contracts the iris sphincter; contracts the ciliary muscle (thereby focusing the lens for near vision); dilates blood vessels; and promotes bladder voiding (by contracting the bladder detrusor muscle and relaxing the trigone and sphincter).
- Activation of alpha₁ receptors contracts the radial muscle of the eye (causing mydriasis), constricts veins and arteries, promotes ejaculation, and contracts smooth muscle in the prostatic capsule and bladder (trigone and sphincter).
- Activation of peripheral alpha₂ receptors is of minimal pharmacologic significance.
- Activation of beta₁ receptors increases heart rate, force of myocardial contraction, and conduction velocity through the AV node, and promotes release of renin by the kidney.
- Activation of beta₂ receptors dilates the bronchi, relaxes uterine smooth muscle, increases glycogenolysis, enhances contraction of skeletal muscle, and dilates arterioles (in the heart, lungs, and skeletal muscle).
- Activation of dopamine receptors dilates blood vessels in the kidney.
- Norepinephrine can activate alpha₁, alpha₂, and beta₁ receptors, whereas epinephrine can activate alpha₁, alpha₂, and beta₁ receptors.
- Neurotransmission at cholinergic junctions is terminated by degradation of acetylcholine by acetylcholinesterase.
- Neurotransmission at adrenergic junctions is terminated by reuptake of intact norepinephrine into nerve terminals.
- Following reuptake, norepinephrine may be stored in vesicles for reuse or destroyed by monoamine oxidase.

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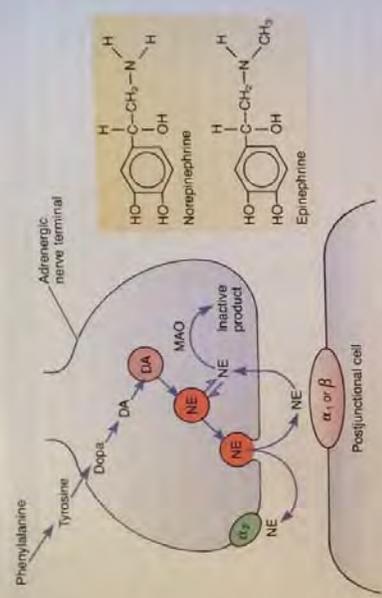


Figure 13-8 • Life cycle of norepinephrine. Note that transmission mediated by NE is terminated by reuptake of NE into the nerve terminal, and not by enzymatic degradation. Be aware that, although postsynaptic cells may have alpha₁, beta₁, and beta₂ receptors, NE can only activate postsynaptic alpha₁ and beta₁ receptors; physiologic activation of beta₂ receptors is done by epinephrine. (DA = dopamine, MAO = monoamine oxidase, NE = norepinephrine.)

Life Cycle of Norepinephrine

The life cycle of norepinephrine is depicted in Figure 13-8. As indicated, the cycle begins with synthesis of norepinephrine from a series of precursors. The final step of synthesis takes place within vesicles, where norepinephrine is then stored prior to release. Following release, norepinephrine binds to adrenergic receptors. As shown in the figure, norepinephrine can interact with *postsynaptic* alpha₁ and beta₁ receptors (but not with beta₂ receptors) and with *presynaptic* alpha₁ receptors. Transmission is terminated by *reuptake* of norepinephrine back into the nerve terminal. (Note that the termination process for norepinephrine differs from that for acetylcholine, whose effects are terminated by enzymatic degradation rather than reuptake.) Following reuptake, norepinephrine can undergo one of two fates: (1) uptake into vesicles for reuse or (2) inactivation by monoamine oxidase (MAO), an enzyme found in the nerve terminal.

Practically every step in the life cycle of norepinephrine can be altered by therapeutic agents. We have drugs that alter the synthesis, storage, and release of norepinephrine; we have drugs that act at adrenergic receptors to mimic or block the effects of norepinephrine; we have drugs, such as cocaine and tricyclic antidepressants, that inhibit the reuptake of norepinephrine (and thereby intensify transmission); and we have drugs that inhibit the breakdown of norepinephrine by MAO, causing an increase in the amount of transmitter available for release.

Life Cycle of Epinephrine

The life cycle of epinephrine is much like that of norepinephrine—although there are significant differences. The cycle begins with synthesis of epinephrine within chromaffin cells of the adrenal medulla. These cells produce epinephrine by first making norepinephrine, which is then converted enzymatically to epinephrine. (Because sympathetic neurons in the adrenal medulla do not produce norepinephrine, the enzyme needed to convert norepinephrine to epinephrine is not produced in sympathetic nerves.) Following synthesis, epinephrine is stored in vesicles to await release. Once released, epinephrine travels via the bloodstream to target organs throughout the body, where it can activate alpha₁, alpha₂, beta₁, and beta₂ receptors. Termination of epinephrine actions is accomplished primarily by hepatic metabolism, and not by uptake into nerves.

I know it's a lot of work, but there's really no way around it. You've got to incorporate this information into your personal database (ie, ya gotta memorize it).

Introduction to Cholinergic Drugs

The cholinergic drugs are agents that influence the activity of cholinergic receptors. Most of these drugs act directly at cholinergic receptors, where they either mimic or block the actions of acetylcholine. Some of these drugs—the cholinesterase inhibitors—influence cholinergic receptors indirectly by preventing the breakdown of acetylcholine.

The cholinergic drugs have both therapeutic and toxicologic significance. Therapeutic applications are limited but valuable. The toxicology of cholinergic drugs is extensive, encompassing such agents as nicotine, insecticides, and compounds designed for chemical warfare.

There are six categories of cholinergic drugs. These categories, along with representative agents, are summarized in Table 1. The *muscarinic agonists*, represented by bethanechol, selectively mimic the effects of acetylcholine at muscarinic receptors. The *muscarinic antagonists*, represented by atropine, selectively block the effects of acetylcholine (and other agonists) at muscarinic receptors. *Ganglionic stimulating agents*, represented by nicotine itself, selectively mimic the effects of acetylcholine at nicotinic_N receptors of autonomic ganglia. *Ganglionic blocking agents*, represented by mecamylamine, selectively block ganglionic nicotinic_N receptors. *Neuromuscular blocking agents*, represented by *d*-tubocurarine and succinylcholine, selectively block the effects of acetylcholine at nicotinic_M receptors at the neuromuscular junction. The *cholinesterase inhibitors*, represented by neostigmine and physostigmine, prevent

the breakdown of acetylcholine by acetylcholinesterase, and thereby increase the activation of all cholinergic receptors.

Table 2 is your master key to understanding the cholinergic drugs. This table lists the three major subtypes of cholinergic receptors (muscarinic, nicotinic_N, and nicotinic_M) and indicates for each receptor type: (1) location, (2) responses to activation, (3) drugs that produce activation (agonists), and (4) drugs that prevent activation (antagonists). This information, along with the detailed information on cholinergic receptor function summarized in Table 13-2, is just about all you need to predict the actions of cholinergic drugs.

An example will demonstrate the combined value of Tables 2 and 13-2. Let's consider *bethanechol*. As indicated in

TABLE 1 ■ Categories of Cholinergic Drugs

Category	Representative Drugs
Muscarinic agonists	Bethanechol
Muscarinic antagonists	Atropine
Ganglionic stimulating agents	Nicotine
Ganglionic blocking agents	Mecamylamine
Neuromuscular blocking agents	<i>d</i> -Tubocurarine, succinylcholine
Cholinesterase inhibitors	Neostigmine, physostigmine

TABLE 2 ■ Summary of Cholinergic Drugs and Their Receptors

	Receptor Subtype		
	Muscarinic	Nicotinic _N	Nicotinic _M
Receptor Location	Sweat glands Blood vessels All organs regulated by the parasympathetic nervous system	All ganglia of the autonomic nervous system	Neuromuscular junctions (NMJs)
Effects of Receptor Activation	Many, including: ↓ Heart rate ↑ Gland secretion Smooth muscle contraction	Promotes ganglionic transmission	Skeletal muscle contraction
Receptor Agonists	Bethanechol	Nicotine	(Nicotine*)
Receptor Antagonists	Atropine	Mecamylamine	<i>d</i> -Tubocurarine, succinylcholine
Indirect-Acting Cholinomimetics	Cholinesterase inhibitors: Physostigmine, neostigmine, and other cholinesterase inhibitors can activate all cholinergic receptors (by causing accumulation of acetylcholine at cholinergic junctions)†		

*The doses of nicotine needed to activate nicotinic_M receptors of the NMJs are much higher than the doses needed to activate nicotinic_N receptors in autonomic ganglia.

†In all prior editions of this book, the cholinesterase inhibitors were grouped together with the receptor agonists, which, by definition, bind directly with receptors to cause activation. Although cholinesterase inhibitors do indeed cause receptor activation, they do so by an indirect mechanism, and hence I should not have grouped them with the true receptor agonists. Rather, they should have been called indirect-acting cholinomimetics. I apologize for any confusion my long-standing oversight may have caused.

Table 2, bethanechol is a selective *agonist* at *muscarinic* cholinergic receptors. Referring to Table 13-2, we see that activation of muscarinic receptors can produce the following: ocular effects (miosis and ciliary muscle contraction), slowing of heart rate, bronchial constriction, urination, glandular secretion, stimulation of the GI tract, penile erection, and vasodilation. Since bethanechol *activates* muscarinic receptors, the drug is capable of eliciting all of these responses. Hence, by knowing which receptors bethanechol activates (from Table 2), and by knowing what those receptors do (from Table 13-2), you can predict the kinds of responses you might expect bethanechol to produce.

In the chapters that follow, we will employ the approach just described. That is, for each cholinergic drug discussed, you will want to know (1) the receptors that the drug affects, (2) the normal responses to activation of those receptors, and (3) whether the drug in question increases or decreases receptor activation. All of this information is contained in Tables 2 and 13-2. Accordingly, if you master the information in these tables now, you will be prepared to follow discussions in succeeding chapters with relative ease—and perhaps even pleasure. In contrast, if you postpone mastery of these tables, you are likely to find it both difficult and dissatisfying to proceed.

Muscarinic Agonists and Antagonists

Muscarinic Agonists

Bethanechol

Other Muscarinic Agonists

Toxicology of Muscarinic Agonists

Muscarinic Antagonists (Anticholinergic Drugs)

Atropine

Muscarinic Antagonists for Overactive Bladder

Other Muscarinic Antagonists

Toxicology of Muscarinic Antagonists

The muscarinic agonists and antagonists produce their effects through *direct* interaction with muscarinic receptors. The muscarinic agonists cause receptor activation; the antagonists produce receptor blockade. Like the muscarinic agonists, another group of drugs—the cholinesterase inhibitors—can also cause receptor activation, but they do so by an *indirect* mechanism. These drugs are discussed separately in Chapter 15.

MUSCARINIC AGONISTS

The muscarinic agonists bind to muscarinic receptors and thereby cause receptor activation. Since nearly all muscarinic receptors are associated with the parasympathetic nervous system, responses to muscarinic agonists closely resemble those produced by stimulation of parasympathetic nerves. Accordingly, muscarinic agonists are also known as *parasympathomimetic agents*.

Bethanechol

Bethanechol [Urecholine, Duvoid ♦] embodies the properties that typify all muscarinic agonists, and hence will serve as our prototype for the group.

Mechanism of Action

Bethanechol is a direct-acting muscarinic agonist. The drug binds reversibly to muscarinic cholinergic receptors to cause activation. At therapeutic doses, bethanechol acts selectively at muscarinic receptors, having little or no effect on nicotinic receptors, either in ganglia or in skeletal muscle.

Pharmacologic Effects

Bethanechol can elicit all of the responses typical of muscarinic receptor activation. Accordingly, we can readily predict the effects of bethanechol by knowing the information on muscarinic responses summarized in Table 13-2.

The principal structures affected by muscarinic activation are the *heart, exocrine glands, smooth muscles, and eye*. Muscarinic agonists act on the heart to cause bradycardia (decreased heart rate) and on exocrine glands to increase sweating, salivation, bronchial secretions, and secretion of gastric acid. In smooth muscles of the lung and GI tract, muscarinic agonists promote contraction. The result is constriction of the bronchi and increased tone and motility of GI smooth muscle. In the bladder, muscarinic activation causes *contraction* of the detrusor muscle and *relaxation* of the trigone and sphincter; the result is bladder emptying. In vascular smooth muscle, these drugs cause relaxation; the resultant vasodilation can produce hypotension. Activation of muscarinic receptors in the eye has two effects: (1) miosis (pupillary constriction), and (2) contraction of the ciliary muscle, resulting in accommodation for near vision. (The ciliary muscle, which is attached to the lens, focuses the eye for near vision by altering lens curvature.)

Pharmacokinetics

Bethanechol is available for oral administration only. (A subQ formulation, available in the past, has been withdrawn.) With oral dosing, effects begin in 30 to 60 minutes and persist about 1 hour. Because bethanechol is a quaternary ammonium compound (Fig. 14-1), the drug crosses membranes poorly. As a result, only a small fraction of each dose is absorbed.

Therapeutic Uses

Although bethanechol can produce a broad spectrum of pharmacologic effects, the drug is approved only for urinary retention.

Urinary Retention. Bethanechol relieves urinary retention by activating muscarinic receptors of the urinary tract. Muscarinic activation relaxes the trigone and sphincter muscles and increases voiding pressure (by contracting the detrusor muscle, which composes the bladder wall). Bethanechol is used to treat urinary retention in postoperative and postpartum patients. The drug should not be used to treat urinary retention caused by physical obstruction of the urinary tract. Why? Because increased pressure in the tract in the presence of blockage could cause injury. When patients are treated with bethanechol, a bedpan or urinal should be readily available.

Investigational GI Uses. Bethanechol has been used on an investigational basis to treat *gastroesophageal reflux*. Benefits may result from increased esophageal motility and increased pressure in the lower esophageal sphincter.

Bethanechol can help treat disorders associated with GI paralysis. Benefits derive from increased tone and motility of GI smooth muscle. Specific applications are *adynamic ileus, gastric atony, and postoperative abdominal distention*. Bethanechol should not be given if physical obstruction of the GI tract is present. Why? Because, in the presence of blockage, increased propulsive contractions might result in damage to the intestinal wall.

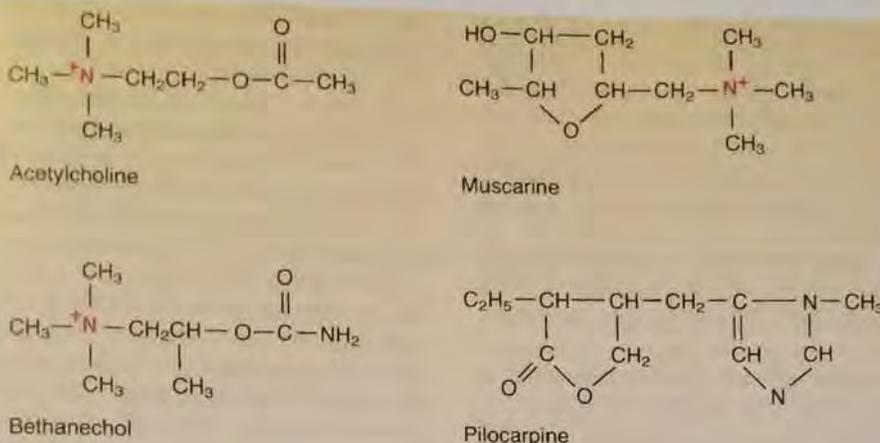


Figure 14-1 • Structures of muscarinic agonists.

Note that, with the exception of pilocarpine, all of these agents are quaternary ammonium compounds, and hence always carry a positive charge. Because of this charge, these compounds cross membranes poorly.

Adverse Effects

In theory, bethanechol can produce the full range of muscarinic responses as side effects. However, with oral dosing, side effects are relatively rare. (When the drug was available for subQ administration, side effects were much more common.)

Cardiovascular System. Bethanechol can cause *hypotension* (secondary to vasodilation) and *bradycardia*. Accordingly, the drug is contraindicated for patients with low blood pressure or low cardiac output.

Alimentary System. At usual therapeutic doses, bethanechol can cause *excessive salivation*, *increased secretion of gastric acid*, *abdominal cramps*, and *diarrhea*. Higher doses can cause involuntary defecation. Bethanechol is contraindicated in patients with gastric ulcers. Why? Because stimulation of acid secretion could intensify gastric erosion, causing bleeding and possibly perforation. The drug is also contraindicated for patients with *intestinal obstruction* and for those recovering from recent *surgery of the bowel*. In both cases, the ability of bethanechol to increase the tone and motility of intestinal smooth muscle could result in rupture of the bowel wall.

Urinary Tract. Because of its ability to contract the bladder detrusor, and thereby *increase pressure within the urinary tract*, bethanechol can be hazardous to patients with urinary tract obstruction or weakness of the bladder wall. In both groups, elevation of pressure within the urinary tract could rupture the bladder. Accordingly, bethanechol is contraindicated for patients with either disorder.

Exacerbation of Asthma. By activating muscarinic receptors in the lungs, bethanechol can cause bronchoconstriction. Accordingly, the drug is contraindicated for patients with latent or active asthma.

Dysrhythmias in Hyperthyroid Patients. Bethanechol can cause dysrhythmias in hyperthyroid patients, and hence is contraindicated for these people. The mechanism of dysrhythmia induction is explained below.

If given to hyperthyroid patients, bethanechol may increase heart rate to the point of initiating a dysrhythmia. (Note that increased heart rate is opposite to the effect that muscarinic agonists have in most patients.) When hyperthyroid patients are given bethanechol, their initial cardiovascular responses are

like those of anyone else: bradycardia and hypotension. In reaction to hypotension, the baroreceptor reflex attempts to return blood pressure to normal. Part of this reflex involves the release of norepinephrine from sympathetic nerves that regulate heart rate. In patients who are *not* hyperthyroid, norepinephrine release serves to increase cardiac output, and thereby helps restore blood pressure. However, in hyperthyroid patients, norepinephrine can induce cardiac dysrhythmias. The reason for this unusual response is that, in hyperthyroid patients, the heart is exquisitely sensitive to the effects of norepinephrine, and hence relatively small amounts can cause stimulation sufficient to elicit a dysrhythmia.

Preparations, Dosage, and Administration

Bethanechol [Urecholine] is available in tablets (5, 10, 25, and 50 mg) for oral therapy. For adults, the oral dosage ranges from 10 to 50 mg given 3 to 4 times a day. Administration with food can cause nausea and vomiting, and hence dosing should be done 1 hour before meals or 2 hours after.

Other Muscarinic Agonists

Cevimeline

Actions and Uses. Cevimeline [Evxac] is a derivative of acetylcholine with actions much like those of bethanechol. The drug is indicated for relief of xerostomia (dry mouth) in patients with *Sjögren's syndrome*, an autoimmune disorder characterized by xerostomia, keratoconjunctivitis sicca (inflammation of the cornea and conjunctiva), and connective tissue disease (typically rheumatoid arthritis). Dry mouth results from extensive damage to salivary glands. Left untreated, dry mouth can lead to multiple complications, including periodontal disease, dental caries, altered taste, oral ulcers and candidiasis, and difficulty eating and speaking. Cevimeline relieves dry mouth by activating muscarinic receptors on residual healthy tissue in salivary glands, thereby promoting salivation. The drug also increases tear production, which can help relieve keratoconjunctivitis. Because it stimulates salivation, cevimeline may also benefit patients with xerostomia induced by radiation therapy for head and neck cancer, although the drug is not approved for this use.

Adverse Effects. Adverse effects result from activating muscarinic receptors, and hence are similar to those of bethanechol. The most common effects are excessive *sweating* (18.9%), *nausea* (13.8%), *rhinitis* (11.2%), and *diarrhea* (10.3%). To compensate for fluid loss caused by sweating and diarrhea, patients should increase fluid intake. Like bethanechol, cevimeline promotes *miosis* (constriction of the pupil) and may also cause *blurred vision*. Both actions can make driving dangerous, especially at night.

Activation of cardiac muscarinic receptors can reduce heart rate and slow cardiac conduction. Accordingly, cevimeline should be used with caution in patients with a history of heart disease.

Because muscarinic activation increases airway resistance, cevimeline is contraindicated for patients with uncontrolled asthma, and should be used with caution in patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease.

Because miosis can exacerbate symptoms of both narrow-angle glaucoma and iritis (inflammation of the iris), cevimeline is contraindicated for people with these disorders.

Drug Interactions. Cevimeline can intensify cardiac depression caused by beta blockers (because both drugs decrease heart rate and cardiac conduction).

Beneficial effects of cevimeline can be antagonized by drugs that block muscarinic receptors. Among these are atropine, tricyclic antidepressants (eg, imipramine), antihistamines (eg, diphenhydramine), and phenothiazine antipsychotics (eg, chlorpromazine).

Preparations, Dosage, and Administration. Cevimeline [Evovac] is supplied in 30-mg capsules. The dosage is 30 mg 3 times a day. The drug may be administered with food to reduce gastric upset.

Pilocarpine

Pilocarpine is a muscarinic agonist used mainly for topical therapy of glaucoma, an ophthalmic disorder characterized by elevated intraocular pressure with subsequent injury to the optic nerve. The basic pharmacology of pilocarpine and its use in glaucoma are discussed in Chapter 104 (Drugs for the Eye).

In addition to its use in glaucoma, pilocarpine is approved for oral therapy of dry mouth resulting from Sjögren's syndrome or from salivary gland damage caused by radiation therapy of head and neck cancer. For these applications, pilocarpine is available in 5-mg tablets under the trade name *Salagen*. The recommended dosage is 5 mg 3 or 4 times a day. At this dosage, the principal adverse effect is sweating, which occurs in 29% of patients. However, if dosage is excessive, pilocarpine can produce the full spectrum of muscarinic effects.

Acetylcholine

Clinical use of acetylcholine [Miochol-E] is limited primarily to producing rapid miosis (pupil constriction) following lens delivery in cataract surgery. Two factors explain the limited utility of this drug. First, acetylcholine lacks selectivity (in addition to activating muscarinic cholinergic receptors, acetylcholine can also activate all nicotinic cholinergic receptors). Second, because of rapid destruction by cholinesterase, acetylcholine has a half-life that is extremely short—too short for most clinical applications.

Muscarine

Although muscarine is not used clinically, this agent has historic and toxicologic significance. Muscarine is of historic interest because of its role in the discovery of cholinergic receptor subtypes. The drug has toxicologic significance because of its presence in certain poisonous mushrooms.

Toxicology of Muscarinic Agonists

Sources of Muscarinic Poisoning. Muscarinic poisoning can result from ingestion of certain mushrooms and from overdose with two kinds of medications: (1) direct-acting muscarinic agonists (eg, bethanechol, pilocarpine), and (2) cholinesterase inhibitors (indirect-acting cholinomimetics).

Of the mushrooms that cause poisoning, only a few do so through muscarinic activation. Mushrooms of the *Inocybe* and *Clitocybe* species have lots of muscarine, hence their ingestion can produce typical signs of muscarinic toxicity. Interestingly, *Amanita muscaria*, the mushroom from which muscarine was originally extracted, actually contains very little muscarine. Poisoning by this mushroom is due to toxins other than muscarinic agonists.

Symptoms. Manifestations of muscarinic poisoning result from excessive activation of muscarinic receptors. Prominent symptoms are profuse salivation, lacrimation (tearing), visual disturbances, bronchospasm, diarrhea, bradycardia, and hypotension. Severe poisoning can produce cardiovascular collapse.

Treatment. Management is direct and specific: administer *atropine* (a selective muscarinic blocking agent) and provide supportive therapy. By blocking access of muscarinic agonists to their receptors, atropine can reverse most signs of toxicity.

MUSCARINIC ANTAGONISTS (ANTICHOLINERGIC DRUGS)

Muscarinic antagonists competitively block the actions of acetylcholine at muscarinic receptors. Because the majority of muscarinic receptors are located on structures innervated by parasympathetic nerves, the muscarinic antagonists are also known as *parasympatholytic drugs*. Additional names for these agents are *antimuscarinic drugs*, *muscarinic blockers*, and *anticholinergic drugs*.

The term *anticholinergic* can be a source of confusion and requires comment. This term is unfortunate in that it implies blockade at *all* cholinergic receptors. However, as normally used, the term *anticholinergic* only denotes blockade of *muscarinic* receptors. Therefore, when a drug is characterized as being anticholinergic, you can take this to mean that it produces selective *muscarinic* blockade—and not blockade of all cholinergic receptors. In this chapter, I use the terms *muscarinic antagonist* and *anticholinergic agent* interchangeably.

Atropine

Atropine [Sal-Tropine, AtroPen, others] is the best-known muscarinic antagonist and will serve as our prototype for the group. The actions of all other muscarinic blockers are much like those of this drug.

Atropine is found naturally in a variety of plants, including *Atropa belladonna* (deadly nightshade) and *Datura stramonium* (aka Jimson weed, stinkweed, and devil's apple). Because of its presence in *Atropa belladonna*, atropine is referred to as a *belladonna alkaloid*.

Mechanism of Action

Atropine produces its effects through competitive blockade at muscarinic receptors. Like all other receptor antagonists, atropine has no direct effects of its own. Rather, all responses to atropine result from *preventing receptor activation* by endogenous acetylcholine (or by drugs that act as muscarinic agonists).

At therapeutic doses, atropine produces selective blockade of muscarinic cholinergic receptors. However, if the dosage is sufficiently high, the drug will produce some blockade of nicotinic receptors too.

Pharmacologic Effects

Since atropine acts by causing muscarinic receptor blockade, its effects are opposite to those caused by muscarinic activation. Accordingly, we can readily predict the effects of atropine by knowing the normal responses to muscarinic receptor activation (see Table 13-2) and by knowing that atropine will reverse those responses. Like the muscarinic agonists, the muscarinic antagonists exert their influence primarily on the *heart*, *exocrine glands*, *smooth muscles*, and *eye*.

Heart. Atropine *increases heart rate*. Because activation of cardiac muscarinic receptors decreases heart rate, blockade of these receptors will cause heart rate to increase.

Exocrine Glands. Atropine *decreases secretion* from salivary glands, bronchial glands, sweat glands, and the acid-secreting cells of the stomach. Note that these effects are opposite to those of muscarinic agonists, which increase secretion from exocrine glands.

Smooth Muscle. By preventing activation of muscarinic receptors on smooth muscle, atropine causes *relaxation* of the

bronchi, decreased tone of the urinary bladder detrusor, and decreased tone and motility of the GI tract. In the absence of an exogenous muscarinic agonist (eg, bethanechol), muscarinic blockade has no effect on vascular smooth muscle tone. Why? Because there is no parasympathetic innervation to muscarinic receptors in blood vessels.

Eye. Blockade of muscarinic receptors on the iris sphincter causes *mydriasis* (dilation of the pupil). Blockade of muscarinic receptors on the ciliary muscle produces *cycloplegia* (relaxation of the ciliary muscle), thereby focusing the lens for far vision.

Central Nervous System (CNS). At therapeutic doses, atropine can cause mild CNS excitation. Toxic doses can cause *hallucinations* and *delirium*, which can resemble psychosis. Extremely high doses can result in coma, respiratory arrest, and death.

Dose Dependency of Muscarinic Blockade. It is important to note that not all muscarinic receptors are equally sensitive to blockade by atropine and most other anticholinergic drugs: At some sites, muscarinic receptors can be blocked with relatively low doses, whereas at other sites much higher doses are needed. Table 14-1 indicates the sequence in which specific muscarinic receptors are blocked as the dose of atropine is increased.

Differences in receptor sensitivity to muscarinic blockers are of clinical significance. As indicated in Table 14-1, the doses needed to block muscarinic receptors in the stomach and bronchial smooth muscle are higher than the doses needed to block muscarinic receptors at all other locations. Accordingly, if we want to use atropine to treat peptic ulcer disease (by suppressing gastric acid secretion) or asthma (by dilating the bronchi), we cannot do so without also affecting the heart, exocrine glands, many smooth muscles, and the eye. Because of these obligatory side effects, atropine and most other muscarinic antagonists are not preferred drugs for treating peptic ulcers or asthma.

Pharmacokinetics

Atropine may be administered orally, topically (to the eye), and by injection (IM, IV, and subQ). The drug is rapidly absorbed following oral administration and distributes to all tissues, including the CNS. Elimination is by a combination of hepatic metabolism and urinary excretion. Atropine has a half-life of approximately 3 hours.

Therapeutic Uses

Preanesthetic Medication. The cardiac effects of atropine can help during surgery. Procedures that stimulate baroreceptors of the carotid body can initiate reflex slowing of the

heart, resulting in profound bradycardia. Since this reflex is mediated by muscarinic receptors on the heart, pretreatment with atropine can prevent a dangerous reduction in heart rate.

Certain anesthetics—especially ether, which is obsolete—irritate the respiratory tract, and thereby stimulate secretion from salivary, nasal, pharyngeal, and bronchial glands. If these secretions are sufficiently profuse, they can interfere with respiration. By blocking muscarinic receptors on secretory glands, atropine can help prevent excessive secretions. Fortunately, modern anesthetics are much less irritating than ether. The availability of these new anesthetics has greatly reduced the use of atropine as an antiseptagogue during anesthesia.

Disorders of the Eye. By blocking muscarinic receptors in the eye, atropine can cause mydriasis and paralysis of the ciliary muscle. Both actions can be of help during eye examinations and ocular surgery. The ophthalmic uses of atropine and other muscarinic antagonists are discussed in Chapter 104.

Bradycardia. Atropine can accelerate heart rate in certain patients with bradycardia. Heart rate is increased because blockade of cardiac muscarinic receptors reverses parasympathetic slowing of the heart.

Intestinal Hypertonicity and Hypermotility. By blocking muscarinic receptors in the intestine, atropine can decrease both the tone and motility of intestinal smooth muscle. This can be beneficial in conditions characterized by excessive intestinal motility, such as mild dysentery and diverticulitis. When taken for these disorders, atropine can reduce both the frequency of bowel movements and associated abdominal cramps.

Muscarinic Agonist Poisoning. Atropine is a specific antidote to poisoning by agents that activate muscarinic receptors. By blocking muscarinic receptors, atropine can reverse all signs of muscarinic poisoning. As discussed above, muscarinic poisoning can result from an overdose with medications that promote muscarinic activation (eg, bethanechol, cholinesterase inhibitors) or from ingestion of certain mushrooms.

Peptic Ulcer Disease. Because it can suppress secretion of gastric acid, atropine has been used to treat peptic ulcer disease. Unfortunately, when administered in doses that are strong enough to block the muscarinic receptors that regulate secretion of gastric acid, atropine also blocks most other muscarinic receptors. Hence, treatment of ulcers is necessarily associated with a broad range of antimuscarinic side effects (dry mouth, blurred vision, urinary retention, constipation, and so on). Because of these side effects, atropine is not a first-choice drug for ulcer therapy. Rather, atropine is reserved for rare cases in which symptoms cannot be relieved with preferred medications (eg, antibiotics, histamine₂ receptor antagonists, proton pump inhibitors).

Asthma. By blocking bronchial muscarinic receptors, atropine can promote bronchial dilation, thereby improving respiration in patients with asthma. Unfortunately, in addition to dilating the bronchi, atropine also causes drying and thickening of bronchial secretions, effects that can be harmful to patients with asthma. Furthermore, when given in the doses needed to dilate the bronchi, atropine causes a variety of antimuscarinic side effects. Because of the potential for harm, and because superior medicines are available, atropine is rarely used for asthma.

Biliary Colic. Biliary colic is characterized by intense abdominal pain brought on by passage of a gallstone through the bile duct. The usual treatment is morphine. In some cases, atropine may be combined with morphine to relax biliary tract smooth muscle, thereby helping alleviate discomfort.

Adverse Effects

Most adverse effects of atropine and other anticholinergic drugs are the direct result of muscarinic receptor blockade. Accordingly, these effects can be predicted from your knowledge of muscarinic receptor function.

Xerostomia (Dry Mouth). Blockade of muscarinic receptors on salivary glands can inhibit salivation, thereby caus-

TABLE 14-1 ■ Relationship Between Dosage and Responses to Atropine

Dosage of Atropine	Response Produced
Low Doses	Salivary glands—decreased secretion Sweat glands—decreased secretion Bronchial glands—decreased secretion Heart—increased rate Eye—mydriasis, blurred vision Urinary tract—interference with voiding Intestine—decreased tone and motility Lung—dilation of bronchi
High Doses	Stomach—decreased acid secretion

Note that doses of atropine that are high enough to decrease gastric acid secretion or dilate the bronchi will also affect all other structures under muscarinic control. As a result, atropine and most other muscarinic antagonists are not very desirable for treating peptic ulcer disease or asthma.

ing dry mouth. Not only is this uncomfortable, it can impede swallowing, and can promote tooth decay, gum problems, and oral infections. Patients should be informed that dryness can be alleviated by sipping fluids, chewing sugar-free gum (eg, Altoids Chewing Gum, Biotene Dry Mouth Gum), treating the mouth with a saliva substitute (eg, Salivart, Biotene Gel), and using an alcohol-free mouthwash (Biotene mouthwash). Owing to increased risk of tooth decay, patients should avoid sugary gum, hard candy, and cough drops.

Blurred Vision and Photophobia. Blockade of muscarinic receptors on the ciliary muscle and the sphincter of the iris can paralyze these muscles. Paralysis of the ciliary muscle focuses the eye for far vision, causing nearby objects to appear blurred. Patients should be forewarned about this effect and advised to avoid hazardous activities if vision is impaired.

Paralysis of the iris sphincter prevents constriction of the pupil, thereby rendering the eye unable to adapt to bright light. Patients should be advised to wear dark glasses if photophobia (intolerance to light) is a problem. Room lighting for hospitalized patients should be kept low.

Elevation of Intraocular Pressure. Paralysis of the iris sphincter can raise intraocular pressure (IOP), by a mechanism discussed in Chapter 104 (Drugs for the Eye). Because they can increase IOP, anticholinergic drugs are contraindicated for patients with glaucoma, a disease characterized by abnormally high IOP. In addition, these drugs should be used with caution in patients who may not have glaucoma per se but for whom a predisposition to glaucoma may be present. Included in this group are all people older than 40.

Urinary Retention. Blockade of muscarinic receptors in the urinary tract reduces pressure within the bladder and increases the tone of the urinary sphincter and trigone. These effects can produce urinary hesitancy or urinary retention. In the event of severe urinary retention, catheterization or treatment with a muscarinic agonist (eg, bethanechol) may be required. Patients should be advised that urinary retention can be minimized by voiding just prior to taking their medication.

Constipation. Muscarinic blockade decreases the tone and motility of intestinal smooth muscle. The resultant delay in transit through the intestine can produce constipation. Patients should be informed that constipation can be minimized by increasing dietary fiber, fluids, and physical activity. A laxative may be needed if constipation is severe. Because of their ability to decrease smooth muscle tone, muscarinic antagonists are contraindicated for patients with intestinal atony, a condition in which intestinal tone is already low.

Anhidrosis. Blockade of muscarinic receptors on sweat glands can produce anhidrosis (a deficiency or absence of sweat). Since sweating is necessary for cooling, people who cannot sweat are at risk of hyperthermia. Patients should be warned of this possibility and advised to avoid activities that might lead to overheating (eg, exercising on a hot day).

Tachycardia. Blockade of cardiac muscarinic receptors eliminates parasympathetic influence on the heart. By removing the "braking" influence of parasympathetic nerves, anticholinergic agents can cause tachycardia (excessive heart rate). Exercise caution in patients with pre-existing tachycardia.

Asthma. In patients with asthma, antimuscarinic drugs can cause thickening and drying of bronchial secretions, and can thereby cause bronchial plugging. Consequently, although muscarinic antagonists can be used to treat asthma, they can also do harm.

Drug Interactions

A number of drugs that are not classified as muscarinic antagonists can nonetheless produce significant muscarinic blockade. Among these are antihistamines, phenothiazine antipsychotics, and tricyclic antidepressants. Because of their prominent anticholinergic actions, these drugs can greatly enhance the antimuscarinic effects of atropine and related agents. Accordingly, it is wise to avoid combined use of atropine with other drugs that can cause muscarinic blockade.

Preparations, Dosage, and Administration

General Systemic Therapy. Atropine sulfate is available in 0.4-mg tablets (sold as Sal-Tropine) for oral administration, and in solution (0.05 to 1 mg/mL) for IM, IV, and subQ administration. The average adult dose is 0.5 mg.

AtroPen for Cholinesterase Inhibitor Poisoning. The AtroPen is a pre-filled auto-injector indicated for IM therapy of poisoning with an organophosphate cholinesterase inhibitor (nerve agent or insecticide). Three strengths are available: 0.5 mg (for children weighing 15 to 40 pounds), 1 mg (for children 40 to 90 pounds), and 2 mg (for adults and children over 90 pounds). Injections are made into the lateral thigh, directly through clothing if necessary.

Ophthalmology. Formulations for ophthalmic use are discussed in Chapter 104.

Muscarinic Antagonists for Overactive Bladder

Overactive Bladder: Characteristics and Overview of Treatment

Overactive bladder (OAB)—also known as urgency incontinence, detrusor instability, and sometimes "can't-hold-it-any-more" incontinence—is a disorder with four major symptoms: urinary urgency (a sudden, compelling desire to urinate), urinary frequency (voiding 8 or more times in 24 hours), nocturia (waking 2 or more times to void), and urge incontinence (involuntary urine leakage associated with a strong urge to void). In almost all cases, urge incontinence results from *involuntary contractions of the bladder detrusor* (the smooth muscle component of the bladder wall). These contractions are often referred to as detrusor instability or detrusor overactivity. Urge incontinence should not be confused with *stress incontinence*, defined as involuntary urine leakage caused by activities (eg, exertion, sneezing, coughing, laughter) that increase pressure within the abdominal cavity.

OAB is a common disorder, affecting up to one-third of Americans. However, relatively few (about 15%) seek medical help. The condition can develop at any age, but is most prevalent in the elderly. Among people ages 40 to 44, symptoms are reported by 3% of men and 9% of women. In comparison, among those 75 and older, symptoms are reported by 42% of men and 31% of women. Because urine leakage, the most disturbing symptom, is both unpredictable and potentially embarrassing, many people with OAB curtail travel, social activities, and even work.

OAB has two primary modes of treatment: *behavioral therapy* and *drug therapy*. Behavioral therapy is at least as effective as drug therapy—and lacks side effects—and hence should be tried first. Behavioral interventions include scheduled voiding, timing fluid intake appropriately, doing Kegel exercises (to strengthen pelvic floor muscles), and avoiding caffeine (it's a diuretic and may also increase detrusor activity). As a rule, drugs should be reserved for patients who don't respond adequately to behavioral measures. Combining behavioral therapy and drug therapy seems to offer little benefit over either modality alone.

If behavioral therapy and drugs are inadequate, *percutaneous tibial nerve stimulation* (PTNS) may be tried. The goal is to reduce urinary urgency by stimulating the posterior tibial nerve, which projects to the sacral plexus, which in turn controls bladder function. Stimulation is accomplished by sending current through a fine needle that has been inserted through the skin into the tibial nerve at a site near the ankle. Treatments are done in the office or clinic for 30 minutes once a week for 12 weeks, and then repeated as needed. PTNS is both safe and effective, with benefits persisting for at least 1 year.

Introduction to Anticholinergic Therapy of OAB

When drug therapy is indicated, *anticholinergic agents* (eg, oxybutynin, tolterodine) are the only option. These drugs block muscarinic receptors on the bladder detrusor, and thereby inhibit bladder contractions and the urge to void.

Unfortunately, drugs that block muscarinic receptors in the bladder can also block muscarinic receptors elsewhere, and hence can cause typical anticholinergic side effects. *Dry mouth* is the primary concern. Other possible effects include constipation, urinary retention, blurred vision, photophobia, and tachycardia. Among the elderly, *cognitive impairment* is a major problem. All of these can be intensified by concurrent use of other drugs that have anticholinergic actions (eg, antihistamines, tricyclic antidepressants, phenothiazine antipsychotic agents).

Anticholinergic side effects can be reduced in at least three ways: (1) using long-acting formulations, (2) using drugs that don't cross the blood-brain barrier, and (3) using drugs that are selective for muscarinic receptors in the bladder. Long-acting formulations (eg, extended-release capsules, transdermal patches) reduce side effects by providing a steady but relatively low level of drug, thereby avoiding the high peak levels that can cause intense side effects. Drugs that can't cross the blood-brain barrier are unable to cause CNS effects.

What about drugs that are selective for muscarinic receptors in the bladder? To answer this question, we must first discuss muscarinic receptor subtypes. As noted in Chapter 13, there are five known muscarinic receptor subtypes. However, only three—designated M_1 , M_2 , and M_3 —have clearly identified functions. Locations of these receptor subtypes, and responses to their activation and blockade, are summarized in Table 14-2. As indicated, M_3 receptors are the most widely distributed, being found in salivary glands, the bladder detrusor, GI smooth muscle, and the eye. M_2 receptors are found only in the heart, and M_1 receptors are found in salivary glands and the CNS. At

each location, responses to receptor activation are the same as we discussed in Chapter 13—although, in that chapter, we didn't identify the receptors by subtype; rather, we simply called all of them *muscarinic*.

With this background, we can consider how receptor selectivity might decrease anticholinergic side effects of drugs for OAB. To be beneficial, an anticholinergic agent must block muscarinic receptors in the bladder *detrusor*. That is, it must block the M_3 receptor subtype. Because M_3 receptors are also found in GI smooth muscle, the eye, and salivary glands, an M_3 -selective blocker will still have some unwanted anticholinergic effects, namely, constipation (from reducing bowel motility), blurred vision and photophobia (from preventing contraction of the ciliary muscle and iris sphincter), dry eyes (from blocking tear production), and *some* degree of dry mouth (from blocking salivary gland M_3 receptors, while sparing salivary M_1 receptors). What an M_3 -selective blocker will *not* do is cause tachycardia (because muscarinic receptors in the heart are the M_2 type) or impairment of CNS function (because muscarinic receptors in the brain are primarily the M_1 type).

Specific Anticholinergic Drugs for OAB

In the United States, we have six anticholinergic drugs approved specifically for OAB (Table 14-3). All six work by M_3 -muscarinic receptor blockade, although most block M_1 and M_2 receptors as well. With all of these drugs, we want sufficient M_3 blockade to reduce symptoms of OAB, but not so much as to cause urinary retention. You should be aware that responses to these agents are relatively modest—about 30% over the response to placebo (which produces about a 30% response by itself). According to a 2009 review, *Treatment of Overactive Bladder in Women*, commissioned by the Agency for Healthcare Research and Quality, none of the anticholinergics used for OAB is clearly superior to the others. However, if one anticholinergic fails to reduce symptoms, a trial with a different one may still help.

Oxybutynin. Oxybutynin [Ditropan XL, Gelnique, Oxytrol] is an anticholinergic agent that acts primarily at M_3 muscarinic receptors. The drug is approved only for OAB. Benefits derive from blocking M_3 -receptors on the bladder detrusor.

Oxybutynin is available in five formulations. Two are short acting (syrup and immediate-release [IR] tablets) and three are long acting (transdermal patch, transdermal gel, and extended-release [ER] tablets). Anticholinergic side effects are less intense with the long-acting products.

Immediate-Release Tablets. Oxybutynin IR tablets (formerly available as Ditropan) can decrease the incidence of urinary urgency, urinary frequency, and urge incontinence. However, benefits are modest—and only somewhat greater than seen with placebo.

TABLE 14-2 • Muscarinic Receptor Subtypes

Muscarinic Subtype	Location	Response to Activation	Impact of Blockade
M_1	Salivary glands	Salivation	Dry mouth
	CNS	Enhanced cognition	Confusion, hallucinations
M_2	Heart	Bradycardia	Tachycardia
M_3	Salivary glands	Salivation	Dry mouth
	Bladder: detrusor	Contraction (increased pressure)	Relaxation (decreased pressure)
	GI smooth muscle	Increased tone and motility	Decreased tone and motility (constipation)
	Eye: Iris sphincter	Contraction (miosis)	Relaxation (mydriasis)
	Eye: Ciliary muscle	Contraction (accommodation)	Relaxation (blurred vision)
Eye: Lacrimal gland	Tearing	Dry eyes	

CNS = central nervous system, GI = gastrointestinal.

TABLE 14-3 ■ Anticholinergic Drugs for Overactive Bladder

Generic and Trade Names	Formulation*	Dosage		Incidence of Dry Mouth
		Initial	Maximum	
Highly M₃ Selective				
Darifenacin				
Enablex	ER tablets	7.5 mg once daily	15 mg once daily	20% with 7.5 mg/day; 35% with 15 mg/day
Primarily M₃ Selective				
Oxybutynin				
(generic only)	Syrup	5 mg 2–3 times/day	5 mg 4 times/day	Dose-related; can exceed 70%
(generic only)	IR tablets	5 mg 2–3 times/day	5 mg 4 times/day	Dose-related; can exceed 70%
Ditropan XL	ER tablets	5 mg once daily	30 mg once daily [†]	Dose-related; can exceed 60%
Oxytrol	Transdermal patch	1 patch twice weekly (delivers 3 mg/day)	1 patch twice weekly	Low: 12% vs. 11% with placebo
Gelnique	Topical gel	100 mg once daily [‡]	100 mg once daily [‡]	Low: 7%
Solifenacin				
VESIcare	Tablets	5 mg once daily	10 mg once daily	11% with 5 mg/day; 28% with 10 mg/day
Nonselective				
Fesoterodine				
Toviaz	ER tablets	4 mg once daily	8 mg once daily	19% with 4 mg once daily
Tolterodine				
Detrol	IR tablets	1–2 mg twice daily	2 mg twice daily	35% with 2 mg twice daily
Detrol LA	ER capsules	2–4 mg once daily	4 mg once daily	Up to 40%
Tropium				
Sanctura, Trosec [◆]	Tablets	20 mg twice daily [§]	20 mg twice daily [§]	20% with 20 mg twice daily
Sanctura XR	ER capsules	60 mg once daily	60 mg once daily [§]	10%

*ER = extended release, IR = immediate release.

[†]Titrate dose upward as needed and tolerated.

[‡]Gelnique is a 10% oxybutynin gel. Therefore, to achieve 100 mg daily, patients must apply 1 gm of gel daily.

[§]Administer at least 1 hour before meals or on an empty stomach.

Oxybutynin is rapidly absorbed from the GI tract, achieving peak plasma levels about 1 hour after dosing. However, despite rapid absorption, absolute bioavailability is low (about 6%). Why? Because oxybutynin undergoes extensive first-pass metabolism—both in the gut wall and liver—primarily by CYP3A4, the 3A4 isozyme of cytochrome P450. One metabolite—*N*-desethyloxybutynin—is highly active, especially against muscarinic receptors in the salivary glands. Oxybutynin is very lipid soluble, and hence can penetrate the blood-brain barrier. The drug has a short half-life (2 to 3 hours), and hence multiple daily doses are required.

Anticholinergic side effects are common. The incidence of dry mouth is very high, in part because of muscarinic blockade by oxybutynin itself, and in part because of blockade by *N*-desethyloxybutynin. Other common side effects include constipation, tachycardia, urinary hesitancy, urinary retention, mydriasis, blurred vision, and dry eyes. In the CNS, cholinergic blockade can result in confusion, hallucinations, insomnia, and nervousness. In postmarketing reports of CNS effects, hallucinations and agitation were prominent among reports involving pediatric patients, while hallucinations, confusion, and sedation were prominent among reports involving elderly patients. Combined use of oxybutynin with other anticholinergic agents (eg, antihistamines, tricyclic antidepressants, phenothiazine antipsychotics) can intensify all anticholinergic side effects.

Drugs that inhibit or induce CYP3A4 may alter oxybutynin blood levels, and may thereby either increase toxicity (inhibitors of CYP3A4) or reduce effectiveness (inducers of CYP3A4).

Immediate-release oxybutynin is available in 5-mg tablets. The usual dosage is 5 mg 2 or 3 times a day. The maximal dosage is 5 mg 4 times a day.

Syrup. The basic and clinical pharmacology of oxybutynin syrup (formerly available as Ditropan) is identical to that of the IR tablets. As with the IR tablets, the incidence of dry mouth and other anticholinergic side effects

is high. The syrup contains 5 mg of oxybutynin/5 mL. The usual dosage is 5 mg 2 or 3 times a day. The maximal dosage is 5 mg 4 times a day.

Extended-Release Tablets. Oxybutynin ER tablets [Ditropan XL] are as effective as the IR tablets and somewhat better tolerated. Although the incidence of dry mouth is reduced using ER tablets, it is nonetheless still high (about 60%). Other adverse effects include constipation (13%), dyspepsia (7%), blurred vision (8%), dry eyes (6%), and CNS effects: somnolence (12%), headache (10%), and dizziness (6%).

The ER tablets are available in three strengths; 5, 10, and 15 mg. The initial dosage is 5 mg once daily. Dosage may be raised weekly in 5-mg increments to a maximum of 30 mg/day. The dosing goal is to achieve a balance between symptom reduction and tolerability of anticholinergic side effects. The ER tablets have an insoluble shell that is eliminated intact in the feces. Patients should be informed of this fact.

Transdermal Patch. The oxybutynin transdermal system [Oxytrol] contains 39 mg of oxybutynin and delivers 3.9 mg/day. Owing to its high lipid solubility, oxybutynin from the patch is readily absorbed directly through the skin. A new patch is applied twice weekly to dry, intact skin of the abdomen, hip, or buttock, rotating the site with each change. Reduction of OAB symptoms is about the same as with the ER tablets.

Pharmacokinetically, the patch is unique in two ways. First, absorption is both slow and steady, and hence the patch produces low but stable blood levels of the drug. Second, transdermal absorption bypasses metabolism in the intestinal wall, and delays metabolism in the liver. As a result, levels of *N*-desethyloxybutynin, the active metabolite, are less than 20% of those achieved with oral therapy.

Transdermal oxybutynin is generally well tolerated. The most common side effect is application-site pruritus (itching), which develops in 15% of patients. The incidence of dry mouth is much lower than with the oral form-

lations (and only slightly higher than with placebo) presumably because (1) formation of *N*-desethyl/oxybutynin is low and (2) high peak levels of oxybutynin itself are avoided. Rates of constipation, blurred vision, and CNS effects are also low.

Topical Gel. Topical oxybutynin gel [Gelnique] is much like the transdermal patch. As with the patch, oxybutynin is absorbed directly through the skin. Stable blood levels are achieved following 10 days of daily application. The most common side effects are application-site reactions (6%) and dry mouth (7%). Other reactions include dizziness (1.5%), headache (1.5%), and constipation (1.3%). Topical oxybutynin is formulated as a 10% gel that contains 100 mg oxybutynin in each 1-gm packet. The recommended dosage is 100 mg oxybutynin (1 gm of gel) applied once daily to dry, intact skin of the abdomen, upper arm/shoulder, or thigh—but not to recently shaved skin—using a different site each day. Advise patients to wash their hands immediately after application, and to avoid showering for at least 1 hour. Applying a sunscreen before or after dosing does not alter efficacy. Topical oxybutynin can be transferred to another person through direct contact. To avoid transfer, patients should cover the application site with clothing.

Darifenacin. Of the anticholinergic agents used for OAB, darifenacin [Enablex] displays the greatest degree of M_3 selectivity. As a result, the drug can reduce OAB symptoms while having no effect on M_1 receptors in the brain or M_2 receptors in the heart. However, darifenacin does block M_3 receptors outside the bladder, and hence still can cause dry mouth, constipation, and other M_3 -related effects.

Clinical benefits are similar to those of oxybutynin and tolterodine. On average, treatment reduces episodes of urge incontinence from 15/week down to 7/week (using 7.5 mg/day) and from 17/week down to 6/week (using 15 mg/day), compared with a decrease from 16/week down to 9/week with placebo. The bottom line? As with other drugs for OAB, responses are relatively modest, and only slightly greater than those seen with placebo.

Darifenacin is administered orally in ER tablets. Absorption is adequate (15% to 19%), and not affected by food. In the blood, darifenacin is 98% protein bound. The drug undergoes extensive hepatic metabolism, primarily by CYP3A4. The resulting inactive metabolites are excreted in the urine (60%) and feces (40%). The drug's half-life is approximately 12 hours.

Darifenacin is relatively well tolerated. The most common side effect is dry mouth, which occurs in 35% of those taking 15 mg/day and 20% of those taking 7.5 mg/day, compared with only 8% of those taking placebo. In experimental animals, inhibition of salivation is less than that caused by oxybutynin, perhaps because darifenacin only blocks M_3 receptors in salivary glands, permitting salivary M_1 receptors to function normally. Constipation is also common, seen in 21% of those taking 15 mg/day and 15% of those taking 7.5 mg/day, compared with only 6% of those taking placebo. Other adverse effects include dyspepsia, gastritis, and headache. Darifenacin has little or no effect on memory, reaction time, word recognition, or cognition. The drug does not increase heart rate.

Levels of darifenacin can be raised significantly by strong inhibitors of CYP3A4. Among these are azole antifungal drugs (eg, ketoconazole, itraconazole), certain protease inhibitors used for HIV/AIDS (eg, ritonavir, nelfinavir), and clarithromycin (a macrolide antibiotic). If darifenacin is combined with any of these, its dosage must be kept low.

Darifenacin is available in 7.5- and 15-mg ER tablets, which should be swallowed whole with liquid. The initial dosage is 7.5 mg once daily. After 2 weeks, dosage may be doubled to 15 mg once daily. In patients with moderate liver impairment, and in those taking powerful inhibitors of CYP3A4, dosage should be kept low (7.5 mg/day or less). In patients with severe liver impairment, darifenacin should be avoided.

Solifenacin. Solifenacin [VESicare] is very similar to darifenacin, although it's not quite as M_3 selective. In clinical trials, the drug reduced episodes of urge incontinence from 18/week down to 8/week (using 5 mg/day) and from 20/week down to 8/week (using 10 mg/day), compared with from 21/week down to 10/week with placebo—indicating that, like other drugs for OAB, solifenacin is only moderately more effective than placebo.

Solifenacin undergoes nearly complete absorption after oral dosing, achieving peak plasma levels in 3 to 6 hours. In the blood, the drug is highly (90%) protein bound. Like darifenacin, solifenacin undergoes extensive metabolism by hepatic CYP3A4. The resulting inactive metabolites are excreted in the urine (62%) and feces (23%). Solifenacin has a long half-life (about 50 hours), and hence can be administered just once a day.

The most common adverse effects are dry mouth (28% at 10 mg/day), constipation (13% at 10 mg/day), and blurred vision (5% at 10 mg/day). Dyspepsia, urinary retention, headache, and nasal dryness occur infrequently. Rarely, solifenacin has caused potentially fatal angioedema of the face, lips, tongue, and/or larynx. At high doses (10 to 30 mg/day), solifenacin can prolong the QT interval, thereby posing a risk of a fatal dysrhythmia. Accord-

ingly, caution is needed in patients with a history of QT prolongation and in those taking other QT-prolonging drugs. As with darifenacin, levels of solifenacin can be increased by strong inhibitors of CYP3A4 (eg, ketoconazole, ritonavir, clarithromycin).

Solifenacin is available in 5- and 10-mg film-coated tablets, which should be swallowed intact with liquid. Dosing may be done with or without food. The initial dosage is 5 mg once daily. If treatment is well tolerated, the dosage can be doubled to 10 mg once daily. For patients with moderate hepatic impairment or severe renal impairment, and for those taking a powerful CYP3A4 inhibitor, dosage should not exceed 5 mg/day. For patients with severe hepatic impairment, solifenacin should be not be used.

Tolterodine. Tolterodine [Detrol, Detrol LA] is a nonselective muscarinic antagonist approved only for OAB. Like oxybutynin, tolterodine is available in short- and long-acting formulations. Anticholinergic side effects are less intense with the long-acting form.

Immediate-Release Tablets. In patients with OAB, tolterodine IR tablets [Detrol] can reduce the incidence of urge incontinence, urinary frequency, and urinary urgency. However, as with other drugs for OAB, benefits are modest.

Tolterodine is rapidly but variably absorbed from the GI tract. Plasma levels peak 1 to 2 hours after dosing. Following absorption, the drug undergoes conversion to 5-hydroxymethyl tolterodine, its active form. The active metabolite is later inactivated by CYP3A4 and CYP2D6 (the 2D6 isozyme of cytochrome P450). Parent drug and metabolites are eliminated in the urine (77%) and feces (17%). Tolterodine has a relatively short half-life, and hence twice-daily dosing is required.

Anticholinergic side effects occur less often than with IR oxybutynin. At a dosage of 2 mg twice daily, the most common side effects are dry mouth (35% vs. 70% with IR oxybutynin), constipation (7%), and dry eyes (3%). Effects on the CNS—somnia, vertigo, dizziness—occur infrequently. The incidence of tachycardia and urinary retention is less than 1%. Anticholinergic effects can be intensified by concurrent use of other drugs with anticholinergic actions (eg, antihistamines, tricyclic antidepressants, phenothiazine antipsychotics). Drugs that inhibit CYP3A4 (eg, erythromycin, ketoconazole) can raise levels of tolterodine, and can thereby intensify beneficial and adverse effects.

In addition to its anticholinergic effects, tolterodine can prolong the QT interval, and can thereby promote serious cardiac dysrhythmias. Because of this risk, dosage should not exceed 4 mg/day.

Tolterodine IR tablets are available in 1- and 2-mg strengths. The initial dosage is 2 mg twice daily, taken with or without food. If this dosage is poorly tolerated, it should be reduced to 1 mg twice daily. A dosage of 1 mg twice daily should also be used by patients with significant hepatic or renal impairment, and for those taking a strong inhibitor of CYP3A4.

Extended-Release Capsules. Tolterodine ER capsules [Detrol LA] are as effective as the IR tablets, and cause less dry mouth (23% vs. 35%). The incidence of other anticholinergic effects is about the same with both formulations. Detrol LA is available in 2- and 4-mg strengths. The recommended dosage is 4 mg once daily. As with the IR tablets, a lower dosage—2 mg once daily—should be used for patients with significant hepatic or renal impairment, and for those taking an inhibitor of CYP3A4.

Fesoterodine. Fesoterodine [Toviaz], approved in 2009, is a nonselective muscarinic antagonist very similar to tolterodine. Both agents are used only for OAB, and, at a dosage of 4 mg/day, both are equally effective. Furthermore, both agents undergo conversion to the same active metabolite—5-hydroxymethyl tolterodine—which is later inactivated by CYP3A4 and CYP2D6. In patients taking a strong inhibitor of CYP3A4 (eg, ketoconazole, clarithromycin), beneficial and adverse effects are increased. Conversely, in patients taking a strong inducer of CYP3A4 (eg, rifampin, carbamazepine), beneficial and adverse effects are reduced. As with tolterodine, the most common side effect is dry mouth (19% at 4 mg/day, 35% at 8 mg/day). The incidence of constipation is 4% to 6%. Less common side effects include dizziness, fatigue, and blurred vision. Unlike tolterodine, fesoterodine has not been associated with QT prolongation, and hence probably does not pose a risk of dysrhythmias.

Fesoterodine is available in 4- and 8-mg ER tablets. Dosing begins at 4 mg once daily, and can be increased to 8 mg once daily. In patients with severe renal impairment, and in those taking a strong inhibitor of CYP3A4, the maximum dosage is 4 mg once daily. In patients taking a strong inducer or inhibitor of CYP2D6, dosage does not need adjustment.

Trospium. Trospium [Sanctura, Sanctura XR, Trosec] is a nonselective muscarinic blocker indicated only for OAB. Like oxybutynin and tolterodine, trospium is available in short- and long-acting formulations. Anticholinergic side effects are less intense with the long-acting form. Compared with other drugs for OAB, trospium is notable for its low bioavailability, lack of CNS effects, and lack of metabolism-related interactions with other drugs.

Immediate-Release Tablets. Trospium IR tablets [Sanctura, Trosec[®]] reduce episodes of urge incontinence from 27/week down to 12/week (compared with 30/week down to 16/week with placebo). Reductions in urinary frequency are minimal.

Trospium is a quaternary ammonium compound (always carries a positive charge), and hence crosses membranes poorly. Following oral dosing, absorption is poor (only 10%) on an empty stomach, and is greatly reduced (70% to 80%) by food. Plasma levels peak 3.5 to 6 hours after dosing, and decline with a half-life of 18 hours. Trospium does not undergo hepatic metabolism, and is eliminated unchanged in the urine.

Trospium IR tablets are generally well tolerated. The most common side effects are dry mouth (20% vs. 6% with placebo) and constipation (10% vs. 5%)—about the same as with long-acting oxybutynin and tolterodine. Rarely, the drug causes dry eyes and urinary retention. Owing to its positive charge, trospium cannot cross the blood-brain barrier, and hence is devoid of CNS effects.

No studies of drug interactions have been done. However, because trospium is eliminated by the kidneys, we can assume it may compete with other drugs that undergo renal tubular excretion. Among these are vancomycin (an antibiotic), metformin (used for diabetes), and digoxin and procainamide (both used for cardiac disorders). Because trospium is not metabolized, the drug is unlikely to influence hepatic metabolism of other agents.

Immediate-release trospium [Sanctura] is available in 20-mg tablets. The usual dosage is 20 mg twice daily, administered at least 1 hour before meals or on an empty stomach. For patients with severe renal impairment, the recommended dosage is 20 mg once daily at bedtime.

Extended-Release Capsules. Trospium ER capsules [Sanctura XR] are as effective as the IR tablets, and cause less dry mouth (10% vs. 20%). The incidence of constipation and other side effects is about the same. Extended-release trospium is available in 60-mg capsules for once-daily dosing.

Other Muscarinic Antagonists

Scopolamine. Scopolamine is an anticholinergic drug with actions much like those of atropine, but with two exceptions. First, whereas therapeutic doses of atropine produce mild CNS *excitation*, therapeutic doses of scopolamine produce *sedation*. And second, scopolamine *suppresses emesis and motion sickness*, whereas atropine does not. Principal uses for scopolamine are motion sickness (see Chapter 80), production of cycloplegia and mydriasis for ophthalmic procedures (see Chapter 104), and production of preanesthetic sedation and obstetric amnesia.

Ipratropium Bromide. Ipratropium [Atrovent] is an anticholinergic drug used to treat asthma, chronic obstructive pulmonary disease, and rhinitis caused by allergies or the common cold. The drug is administered by inhalation, and systemic absorption is minimal. As a result, therapy is not associated with typical antimuscarinic side effects (dry mouth, blurred vision, urinary hesitancy, constipation, and so forth). Ipratropium is discussed fully in Chapter 76.

Antisecretory Anticholinergics. Muscarinic blockers can be used to suppress gastric acid secretion in patients with peptic ulcer disease. However, since superior antiulcer drugs are available, and since anticholinergic agents produce significant side effects (dry mouth, blurred vision, urinary retention, and so forth), most of these drugs have been withdrawn. Today, only four agents—*glycopyrrolate* [Robinul, Cuvposa], *mepenzolate* [Cantil], *methscopolamine* [Pamine], and *propantheline* [Pro-Banthine]—remain on the market. All four are administered orally, and one—glycopyrrolate—may also be given IM and IV. In 2010, glycopyrrolate oral solution [Cuvposa] was approved for reducing severe drooling in children with chronic severe neurologic disorders. The drug is also approved for treating peptic ulcers and for reducing salivation caused by anesthesia.

Dicyclomine. This drug is indicated for irritable bowel syndrome (spastic colon, mucous colitis) and functional bowel disorders (diarrhea, hypermotility). Administration may be oral (40 mg 4 times a day) or by IM injection (20 mg 4 times a day). Trade names include *Bentyl* and *Dibent*.

Pirenzepine and Telenzepine. These drugs produce selective blockade of M₁-muscarinic receptors—the subtype of muscarinic receptor involved in regulating the secretion of gastric acid. Both drugs can effectively suppress acid secretion in patients with peptic ulcer disease, but neither is currently available in the United States. Because these drugs are selective blockers of M₁-muscarinic receptors, the incidence of dry mouth, blurred vision, and other typical antimuscarinic side effects is low.

Mydriatic Cycloplegics. Five muscarinic antagonists—*atropine*, *homatropine*, *scopolamine*, *cyclopentolate*, and *tropicamide*—are employed to produce mydriasis and cycloplegia in ophthalmic procedures. These applications are discussed in Chapter 104.

Centrally Acting Anticholinergics. Several anticholinergic drugs, including *benztropine* [Cogentin] and *trihexyphenidyl* (formerly available as Artane), are used to treat Parkinson's disease and drug-induced parkinsonism. Benefits derive from blockade of muscarinic receptors in the CNS. The centrally acting anticholinergics and their use in Parkinson's disease are discussed in Chapter 21.

Toxicology of Muscarinic Antagonists

Sources of Antimuscarinic Poisoning. Sources of poisoning include natural products (eg, *Atropa belladonna*, *Datura stramonium*), selective antimuscarinic drugs (eg, atropine, scopolamine), and other drugs with pronounced antimuscarinic properties (eg, antihistamines, phenothiazines, tricyclic antidepressants).

Symptoms. Symptoms of antimuscarinic poisoning, which are the direct result of excessive muscarinic blockade, include dry mouth, blurred vision, photophobia, hyperthermia, CNS effects (hallucinations, delirium), and skin that is hot, dry, and flushed. Death results from respiratory depression secondary to blockade of cholinergic receptors in the brain.

Treatment. Treatment consists of (1) minimizing intestinal absorption of the antimuscarinic agent and (2) administering an antidote. Absorption can be reduced by swallowing activated charcoal, which will adsorb the poison within the intestine, thereby preventing its absorption into the blood.

The most effective antidote to antimuscarinic poisoning is *physostigmine*, an inhibitor of acetylcholinesterase. By inhibiting cholinesterase, physostigmine causes acetylcholine to accumulate at all cholinergic junctions. As acetylcholine builds up, it competes with the antimuscarinic agent for receptor binding, thereby reversing excessive muscarinic blockade. The pharmacology of physostigmine is discussed in Chapter 15.

Warning. It is important to differentiate between antimuscarinic poisoning, which often resembles psychosis (hallucinations, delirium), and an actual psychotic episode. We need to make the differential diagnosis because some antipsychotic drugs have antimuscarinic properties of their own, and hence will intensify symptoms if given to a victim of antimuscarinic poisoning. Fortunately, since a true psychotic episode is not ordinarily associated with signs of excessive muscarinic blockade (dry mouth, hyperthermia, dry skin, and so forth), differentiation is not usually difficult.

KEY POINTS

- Muscarinic agonists cause direct activation of muscarinic cholinergic receptors, and can thereby cause bradycardia; increased secretion from sweat, salivary, bronchial, and gastric glands; contraction of intestinal and bronchial smooth muscle; contraction of the bladder detrusor and relaxation of the bladder trigone and sphincter; and, in the eye, miosis and accommodation for near vision.
- Bethanechol, the prototype of the muscarinic agonists, is used primarily to relieve urinary retention.
- Muscarinic agonist poisoning is characterized by profuse salivation, tearing, visual disturbances, bronchospasm, diarrhea, bradycardia, and hypotension.
- Muscarinic agonist poisoning is treated with atropine.
- Atropine, the prototype of the muscarinic antagonists (anticholinergic drugs), blocks the actions of acetylcholine (and all other muscarinic agonists) at muscarinic cholinergic receptors, and thereby (1) increases heart rate; (2) reduces secretion from sweat, salivary, bronchial, and gastric glands; (3) relaxes intestinal and bronchial smooth muscle; (4) causes urinary retention (by relaxing the bladder detrusor and contracting the trigone and sphincter); (5) acts in the eye to cause mydriasis and cycloplegia; and (6) acts in the CNS to produce excitation (at low doses) and delirium and hallucinations (at toxic doses).
- Applications of anticholinergic drugs include preanesthetic medication, ophthalmic examinations, reversal of bradycardia, treatment of overactive bladder (OAB), and management of muscarinic agonist poisoning.
- Anticholinergic drugs that are selective for M₃ muscarinic receptors can still cause many anticholinergic side effects (eg, dry mouth, constipation, impaired vision), but will not slow heart rate (which is mediated by cardiac M₂ receptors) and will be largely devoid of cognitive effects (which are mediated primarily by M₁ receptors).
- Classic adverse effects of anticholinergic drugs are dry mouth, blurred vision, photophobia, tachycardia, urinary retention, constipation, and anhidrosis (suppression of sweating).
- Certain drugs—especially antihistamines, tricyclic antidepressants, and phenothiazine antipsychotics—have prominent antimuscarinic actions. These should be used cautiously, if at all, in patients receiving atropine or other muscarinic antagonists.
- The anticholinergic drugs used for OAB are only moderately effective: Symptom reduction is about 30% greater than with placebo, which itself decreases symptoms by 30%.
- The short-acting anticholinergic drugs used for OAB cause more dry mouth and other anticholinergic side effects than do the long-acting drugs.
- Muscarinic antagonist poisoning is characterized by dry mouth, blurred vision, photophobia, hyperthermia, hallucinations and delirium, and skin that is hot, dry, and flushed.
- The best antidote for muscarinic antagonist poisoning is physostigmine, a cholinesterase inhibitor.

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Summary of Major Nursing Implications*

BETHANECHOL**Preadministration Assessment****Therapeutic Goal**

Treatment of nonobstructive urinary retention.

Baseline Data

Record fluid intake and output.

Identifying High-Risk Patients

Bethanechol is *contraindicated* for patients with peptic ulcer disease, urinary tract obstruction, intestinal obstruction, coronary insufficiency, hypotension, asthma, and hyperthyroidism.

Implementation: Administration**Route**

Oral.

Administration

Advise patients to take bethanechol 1 hour before meals or 2 hours after to reduce gastric upset.

Because effects on the intestine and urinary tract can be rapid and dramatic, ensure that a bedpan or bathroom is readily accessible.

Ongoing Evaluation and Interventions**Evaluating Therapeutic Effects**

Monitor fluid intake and output to evaluate treatment of urinary retention.

Minimizing Adverse Effects

Excessive muscarinic activation can cause salivation, sweating, urinary urgency, bradycardia, and hypotension. Monitor blood pressure and pulse rate. Observe for signs of muscarinic excess and report these to the prescriber. **Inform**

*Patient education information is highlighted as blue text.

Continued

Summary of Major Nursing Implications—cont'd

patients about manifestations of muscarinic excess and advise them to notify the prescriber if they occur.

Management of Acute Toxicity

Overdose produces manifestations of excessive muscarinic stimulation (salivation, sweating, involuntary urination and defecation, bradycardia, severe hypotension). Treat with parenteral atropine and supportive measures.

ATROPINE AND OTHER MUSCARINIC ANTAGONISTS (ANTICHOLINERGIC DRUGS)

Preadministration Assessment

Therapeutic Goal

Atropine has many applications, including preanesthetic medication and treatment of bradycardia, biliary colic, intestinal hypertonicity and hypermotility, and muscarinic agonist poisoning.

Identifying High-Risk Patients

Atropine and other muscarinic antagonists are *contraindicated* for patients with glaucoma, intestinal atony, urinary tract obstruction, and tachycardia. Use with *caution* in patients with asthma.

Implementation: Administration

Routes

Atropine is administered PO, IV, IM, and subQ.

Administration

Dry mouth from muscarinic blockade may interfere with swallowing. Advise patients to moisten the mouth by sipping water prior to oral administration.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Xerostomia (Dry Mouth). Decreased salivation can dry the mouth. Teach patients that xerostomia can be relieved by sipping fluids, chewing sugar-free gum (eg, Altoids Chewing Gum, Biotene Dry Mouth Gum), treating the mouth with a saliva substitute (eg, Salivart, Entertainer's Secret), and using an alcohol-free mouthwash (eg, Biotene Mouth-

wash). Owing to increased risk of tooth decay, advise patients to avoid sugary gum, hard candy, and cough drops.

Blurred Vision. Paralysis of the ciliary muscle may reduce visual acuity. Warn patients to avoid hazardous activities if vision is impaired.

Photophobia. Muscarinic blockade prevents the pupil from constricting in response to bright light. Keep hospital room lighting low to reduce visual discomfort. Advise patients to wear sunglasses outdoors.

Urinary Retention. Muscarinic blockade in the urinary tract can cause urinary hesitancy or retention. Advise patients that urinary retention can be minimized by voiding just prior to taking anticholinergic medication. If urinary retention is severe, catheterization or treatment with bethanechol (a muscarinic agonist) may be required.

Constipation. Reduced tone and motility of the gut may cause constipation. Advise patients that constipation can be reduced by increasing dietary fiber and fluids, and treated with a laxative if severe.

Hyperthermia. Suppression of sweating may result in hyperthermia. Advise patients to avoid vigorous exercise in warm environments.

Tachycardia. Blockade of cardiac muscarinic receptors can accelerate heart rate. Monitor pulse and report significant increases.

Minimizing Adverse Interactions

Antihistamines, *tricyclic antidepressants*, and *phenothiazines* have prominent antimuscarinic actions. Combining these agents with atropine and other anticholinergic drugs can cause excessive muscarinic blockade.

Management of Acute Toxicity

Symptoms. Overdose produces dry mouth, blurred vision, photophobia, hyperthermia, hallucinations, and delirium; the skin becomes hot, dry, and flushed. Differentiate muscarinic antagonist poisoning from psychosis!

Treatment. Treatment centers on limiting absorption of ingested poison (eg, by giving activated charcoal to adsorb the drug) and administering physostigmine, an inhibitor of acetylcholinesterase.

Cholinesterase Inhibitors and Their Use in Myasthenia Gravis

Reversible Cholinesterase Inhibitors

Neostigmine

Other Reversible Cholinesterase Inhibitors

"Irreversible" Cholinesterase Inhibitors

Basic Pharmacology

Toxicology

Myasthenia Gravis

Pathophysiology

Treatment with Cholinesterase Inhibitors

Cholinesterase inhibitors are drugs that prevent the degradation of acetylcholine (ACh) by acetylcholinesterase (also known simply as cholinesterase [ChE]). By preventing the inactivation of ACh, cholinesterase inhibitors enhance the actions of ACh released from cholinergic neurons. Hence, the cholinesterase inhibitors can be viewed as indirect-acting cholinergic agonists. Since cholinesterase inhibitors can intensify transmission at all cholinergic junctions (muscarinic, ganglionic, and neuromuscular), these drugs can elicit a broad spectrum of responses. Because they lack selectivity, cholinesterase inhibitors have limited therapeutic applications. Cholinesterase inhibitors are also known as *anticholinesterase agents*.

There are two basic categories of cholinesterase inhibitors: (1) *reversible inhibitors* and (2) *"irreversible" inhibitors*. The reversible inhibitors produce effects of moderate duration, and the irreversible inhibitors produce effects of long duration.

REVERSIBLE CHOLINESTERASE INHIBITORS

Neostigmine

Neostigmine [Prostigmin] typifies the reversible cholinesterase inhibitors and will serve as our prototype for the group. The drug's principal indication is *myasthenia gravis*.

Chemistry

As indicated in Figure 15-1, neostigmine contains a quaternary nitrogen atom, and hence always carries a positive charge. Because of this charge, neostigmine cannot readily cross membranes, including those of the GI tract, blood-brain barrier, and placenta. Consequently, neostigmine is absorbed poorly following oral administration and has minimal effects on the brain and fetus.

Mechanism of Action

Neostigmine and the other reversible cholinesterase inhibitors can be envisioned as poor substrates for ChE. As indicated in Figure 15-2, the normal function of ChE is to break down

acetylcholine into choline and acetic acid. This process is termed a *hydrolysis* reaction because of the water molecule involved. As depicted in Figure 15-3A, hydrolysis of ACh takes place in two steps: (1) binding of ACh to the active center of ChE, followed by (2) splitting of ACh, which regenerates free ChE. The overall reaction between ACh and ChE is extremely fast. As a result, one molecule of ChE can break down a huge amount of ACh in a very short time.

As depicted in Figure 15-3B, the reaction between neostigmine and ChE is much like the reaction between ACh and ChE. The only difference is that ChE splits neostigmine more slowly than it splits ACh. Hence, once neostigmine becomes bound to the active center of ChE, the drug remains in place for a relatively long time, thereby preventing ChE from catalyzing the breakdown of ACh. ChE remains inhibited until it finally succeeds in splitting neostigmine off.

Pharmacologic Effects

By preventing inactivation of ACh, neostigmine and the other cholinesterase inhibitors can intensify transmission at virtually all junctions where ACh is the transmitter. In sufficient doses, cholinesterase inhibitors can produce skeletal muscle

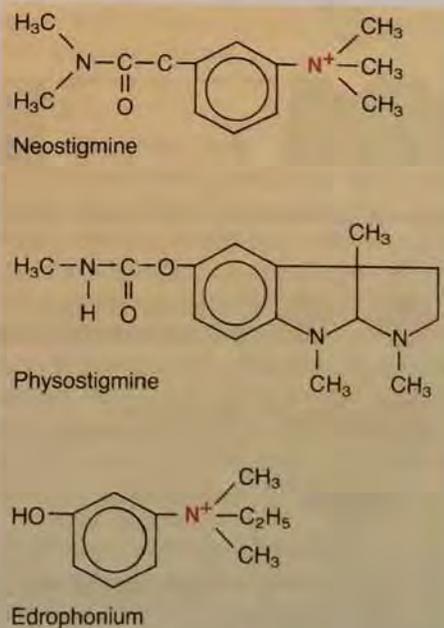


Figure 15-1 • Structural formulas of reversible cholinesterase inhibitors.

Note that neostigmine and edrophonium are quaternary ammonium compounds, but physostigmine is not. What does this difference imply about the relative abilities of these drugs to cross membranes, including the blood-brain barrier?

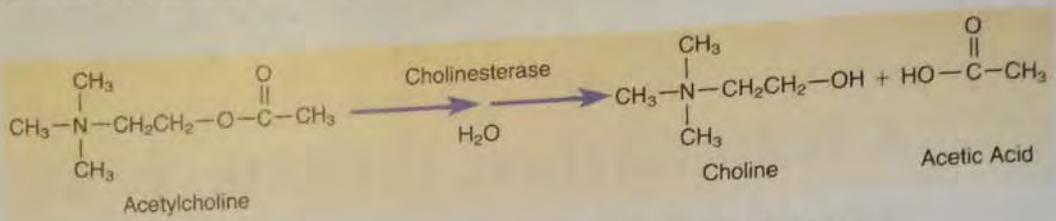


Figure 15-2 • Hydrolysis of acetylcholine by cholinesterase.

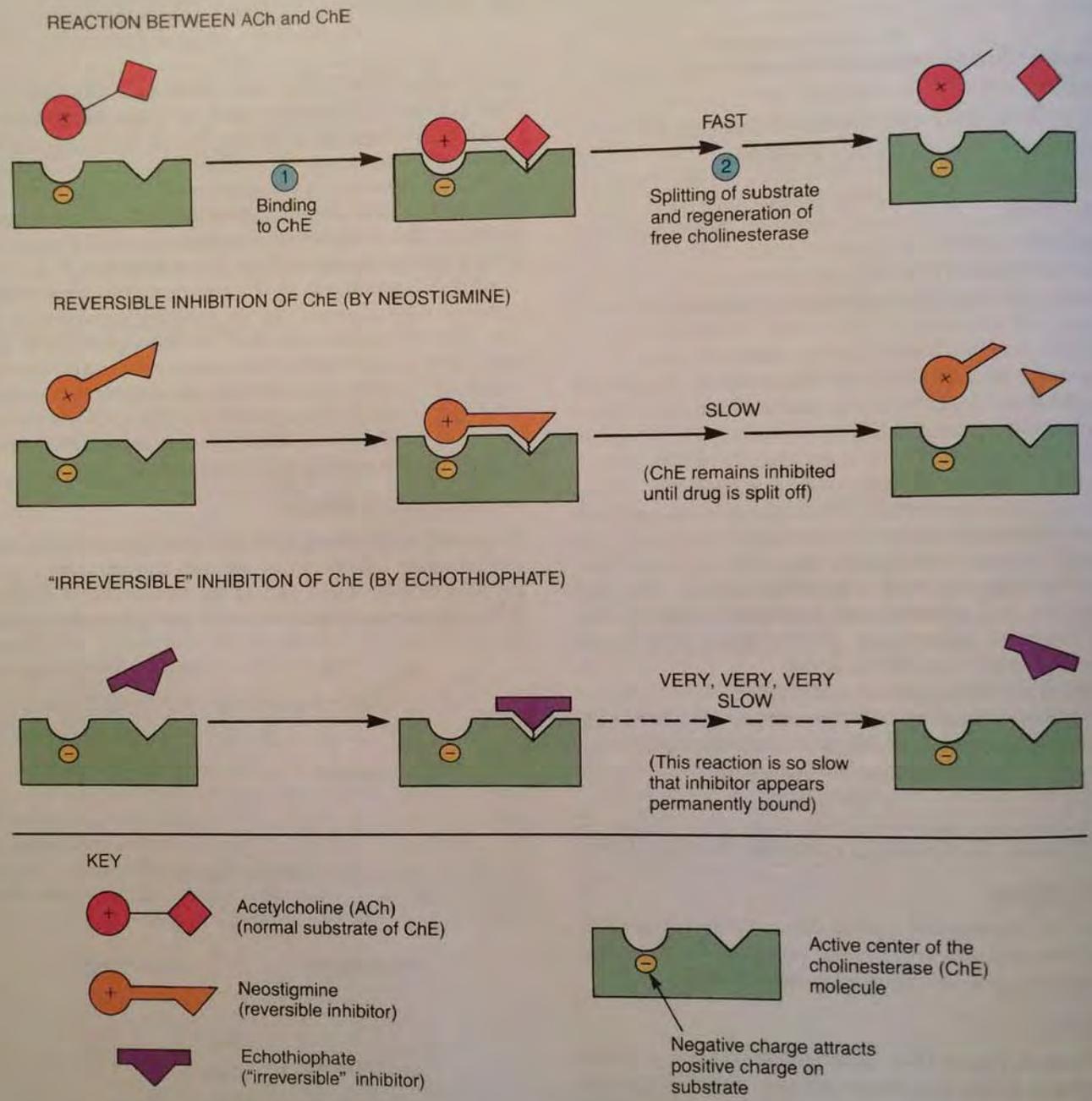


Figure 15-3 • Inhibition of cholinesterase by reversible and "irreversible" inhibitors. (See text for details.)

stimulation, ganglionic stimulation, activation of peripheral muscarinic receptors, and activation of cholinergic receptors in the central nervous system (CNS). However, when used *therapeutically*, cholinesterase inhibitors usually affect only muscarinic receptors on organs and nicotinic receptors of the

neuromuscular junction (NMJ). Ganglionic transmission and CNS function are usually unaltered.

Muscarinic Responses. Muscarinic effects of the cholinesterase inhibitors are identical to those of the direct-acting muscarinic agonists. By preventing breakdown of ACh, cho-

linesterase inhibitors can cause bradycardia, bronchial constriction, urinary urgency, increased glandular secretions, increased tone and motility of GI smooth muscle, miosis, and focusing of the lens for near vision.

Neuromuscular Effects. The effects of cholinesterase inhibitors on skeletal muscle are dose dependent. At *therapeutic* doses, these drugs *increase* force of contraction. In contrast, *toxic* doses *reduce* force of contraction. Contractile force is reduced because excessive amounts of ACh at the NMJ keep the motor end-plate in a state of constant depolarization, thereby causing depolarizing neuromuscular blockade (see Chapter 16).

Central Nervous System. Effects on the CNS vary with drug concentration. *Therapeutic* levels can produce mild *stimulation*, whereas *toxic* levels *depress* the CNS, including the areas that regulate respiration. However, keep in mind that, for CNS effects to occur, the inhibitor must first penetrate the blood-brain barrier, which some cholinesterase inhibitors can do only when present in very high concentrations.

Pharmacokinetics

Neostigmine may be administered orally or by injection (IM, IV, subQ). Because neostigmine carries a positive charge, the drug is poorly absorbed following oral administration. Once absorbed, neostigmine can reach sites of action at the NMJ and peripheral muscarinic receptors, but cannot cross the blood-brain barrier to affect the CNS. Duration of action is 2 to 4 hours. Neostigmine is eliminated by enzymatic degradation: Cholinesterase, the enzyme that neostigmine inhibits, eventually converts neostigmine itself to an inactive product.

Therapeutic Uses

Myasthenia Gravis. Myasthenia gravis is a major indication for neostigmine and several other reversible cholinesterase inhibitors. Treatment of myasthenia gravis is discussed separately later.

Reversal of Competitive (Nondepolarizing) Neuromuscular Blockade. By causing accumulation of ACh at the NMJ, cholinesterase inhibitors can reverse the effects of competitive neuromuscular blocking agents (eg, pancuronium). This ability has two clinical applications: (1) reversal of neuromuscular blockade in postoperative patients and (2) treatment of overdose with a competitive neuromuscular blocker. When neostigmine is used to treat neuromuscular blocker overdose, artificial respiration must be maintained until muscle function has fully recovered. At the doses employed to reverse neuromuscular blockade, neostigmine is likely to elicit substantial muscarinic responses. If necessary, these can be reduced with atropine. It is important to note that cholinesterase inhibitors cannot be employed to counteract the effects of succinylcholine, a *depolarizing* neuromuscular blocker.

Adverse Effects

Excessive Muscarinic Stimulation. Accumulation of ACh at muscarinic receptors can result in excessive salivation, increased gastric secretions, increased tone and motility of the GI tract, urinary urgency, bradycardia, sweating, miosis, and spasm of accommodation (focusing of the lens for near vision). If necessary, these responses can be suppressed with atropine.

Neuromuscular Blockade. If administered in toxic doses, cholinesterase inhibitors can cause accumulation of ACh in amounts sufficient to produce depolarizing neuromuscular blockade. Paralysis of the respiratory muscles can be fatal.

Precautions and Contraindications

Most of the precautions and contraindications regarding the cholinesterase inhibitors are the same as those for the direct-acting muscarinic agonists. These include (1) obstruction of the GI tract, (2) obstruction of the urinary tract, (3) peptic ulcer disease, (4) asthma, (5) coronary insufficiency, and (6) hyperthyroidism. The rationales underlying these precautions are discussed in Chapter 14. In addition to precautions related to muscarinic stimulation, cholinesterase inhibitors are contraindicated for patients receiving succinylcholine.

Drug Interactions

Muscarinic Antagonists. The effects of cholinesterase inhibitors at muscarinic receptors are opposite to those of atropine (and all other muscarinic antagonists). Consequently, cholinesterase inhibitors can be used to overcome excessive muscarinic blockade caused by atropine. Conversely, atropine can be used to reduce excessive muscarinic stimulation caused by cholinesterase inhibitors.

Competitive Neuromuscular Blockers. By causing accumulation of ACh at the NMJ, cholinesterase inhibitors can reverse muscle relaxation induced with pancuronium and other competitive neuromuscular blocking agents.

Depolarizing Neuromuscular Blockers. Cholinesterase inhibitors do not reverse the muscle-relaxant effects of succinylcholine, a depolarizing neuromuscular blocker. In fact, because cholinesterase inhibitors will decrease the breakdown of succinylcholine by cholinesterase, cholinesterase inhibitors will actually *intensify* neuromuscular blockade caused by succinylcholine.

Acute Toxicity

Symptoms. Overdose with cholinesterase inhibitors causes *excessive muscarinic stimulation* and *respiratory depression*. (Respiratory depression results from a combination of depolarizing neuromuscular blockade and CNS depression.) The state produced by cholinesterase inhibitor poisoning is sometimes referred to as *cholinergic crisis*.

Treatment. Intravenous *atropine* can alleviate the muscarinic effects of cholinesterase inhibition. Respiratory depression from cholinesterase inhibitors cannot be managed with drugs. Rather, treatment consists of mechanical ventilation with oxygen. Suctioning may be necessary if atropine fails to suppress bronchial secretions.

Preparations, Dosage, and Administration

Preparations. Neostigmine [Prostigmin] is available as two salts: *neostigmine bromide* (for oral use) and *neostigmine methylsulfate* (for IM, IV, and subQ use). Neostigmine bromide is available in 15-mg tablets. Neostigmine methylsulfate is available in solution (0.25, 0.5, and 1 mg/mL).

Dosage and Administration. Dosages for *myasthenia gravis* are highly individualized, ranging from 15 to 375 mg/day administered PO in divided doses every 3 to 4 hours. You should note that oral doses are *much* higher than parenteral doses.

To treat *poisoning by competitive neuromuscular blockers*, the initial dose is 0.5 to 2 mg administered by slow IV injection. Additional doses totaling a maximum of 5 mg may be given as required.

Other Reversible Cholinesterase Inhibitors

Physostigmine

The basic pharmacology of physostigmine is identical to that of neostigmine—except that physostigmine readily crosses membranes whereas neostigmine does not. Why? Because, in contrast to neostigmine, physostigmine is *not* a quaternary ammonium compound and hence does *not* carry a charge. Because physostigmine is uncharged, the drug crosses membranes with ease.

Physostigmine is the drug of choice for treating *poisoning by atropine and other drugs that cause muscarinic blockade*, including antihistamines and phenothiazine antipsychotics—but *not* tricyclic antidepressants, owing to a risk of causing seizures and cardiotoxicity. Physostigmine counteracts antimuscarinic poisoning by causing ACh to build up at muscarinic junctions. The accumulated ACh competes with the muscarinic blocker for receptor binding, and thereby reverses receptor blockade. Physostigmine is preferred to neostigmine because, lacking a charge, physostigmine is able to cross the blood-brain barrier to reverse muscarinic blockade in the CNS. The usual dose to treat antimuscarinic poisoning is 2 mg given by IM or slow IV injection.

Ambenonium, Edrophonium, and Pyridostigmine

Ambenonium [Mytelase], edrophonium [Enlon, Reversol], and pyridostigmine [Mestinon] have pharmacologic effects much like those of neostigmine. One of these drugs—edrophonium—is noteworthy for its very brief duration of action. All three drugs are used for *myasthenia gravis*. Routes of administration and indications are summarized in Table 15-1.

Drugs for Alzheimer's Disease

Four cholinesterase inhibitors—*donepezil* [Aricept], *galantamine* [Razadyne], *rivastigmine* [Exelon], and *tacrine* [Cognex]—are approved for Alzheimer's disease, and two of them—donepezil and rivastigmine—are also

approved for dementia of Parkinson's disease. With all four, benefits derive from inhibiting cholinesterase in the CNS. The pharmacology of these drugs is discussed in Chapter 22.

"IRREVERSIBLE" CHOLINESTERASE INHIBITORS

The "irreversible" cholinesterase inhibitors are highly toxic. These agents are employed primarily as *insecticides*. During World War II, huge quantities of irreversible cholinesterase inhibitors were produced for possible use as *nerve agents*, but were never deployed. Today, there is concern that these agents might be employed as weapons of terrorism. The only clinical indication for the irreversible inhibitors is *glaucoma*.

Basic Pharmacology

Chemistry

All irreversible cholinesterase inhibitors contain an atom of *phosphorus* (Fig. 15-4). Because of this phosphorus atom, the irreversible inhibitors are known as *organophosphate* cholinesterase inhibitors.

Almost all irreversible cholinesterase inhibitors are *highly lipid soluble*. As a result, these drugs are readily absorbed from all routes of administration. They can even be absorbed directly through the skin. Easy absorption, coupled with high toxicity, is what makes these drugs good insecticides—and gives them potential as agents of chemical warfare. Once absorbed, the organophosphate inhibitors have ready access to all tissues and organs, including the CNS.

TABLE 15-1 ■ Clinical Applications of Cholinesterase Inhibitors

Generic Name [Trade Name]	Routes	Myasthenia Gravis		Glaucoma	Reversal of Competitive Neuromuscular Blockade	Antidote to Poisoning by Muscarinic Antagonists	Alzheimer's Disease
		Diagnosis	Treatment				
Reversible Inhibitors							
Neostigmine [Prostigmin]	PO, IM, IV, subQ		✓		✓		
Ambenonium [Mytelase]	PO		✓				
Pyridostigmine [Mestinon]	PO		✓				
Edrophonium [Enlon, Reversol]	IM, IV	✓			✓		
Physostigmine [Antilirium]	IM, IV					✓	
Donepezil [Aricept]*	PO						✓
Galantamine [Razadyne]	PO						✓
Rivastigmine [Exelon]*	PO, Transdermal						✓
Tacrine [Cognex]	PO						✓
Irreversible Inhibitor							
Echothiophate [Phospholine Iodide]	Topical			✓			

*Also used for Parkinson's disease dementia.

eyelids), difficulty swallowing, and weakness of skeletal muscles. Patients with severe MG may have difficulty breathing owing to weakness of the muscles of respiration.

Symptoms of MG result from an autoimmune process in which the patient's immune system produces antibodies that attack nicotinic_M receptors on skeletal muscle. As a result, the number of functional receptors at the NMJ is reduced by 70% to 90%, thereby causing muscle weakness.

Treatment with Cholinesterase Inhibitors

Beneficial Effects. Reversible cholinesterase inhibitors (eg, neostigmine) are the mainstay of therapy. By preventing ACh inactivation, anticholinesterase agents can intensify the effects of ACh released from motor neurons, and can thereby increase muscle strength. Cholinesterase inhibitors do not cure MG. Rather, they only produce symptomatic relief, and hence patients usually need therapy lifelong.

When working with a hospitalized patient, keep in mind that muscle strength may be insufficient to permit swallowing. Accordingly, you should assess the ability to swallow before giving oral medications. Assessment is accomplished by giving the patient a few sips of water. If the patient is unable to swallow the water, parenteral medication must be substituted for oral medication.

Side Effects. Because cholinesterase inhibitors can inhibit acetylcholinesterase at any location, these drugs will cause ACh to accumulate at muscarinic junctions as well as at NMJs. If muscarinic responses are excessive, atropine may be given to suppress them. However, atropine should not be employed *routinely*. Why? Because the drug can mask the early signs (eg, excessive salivation) of overdose with anticholinesterase agents.

Dosage Adjustment. In the treatment of MG, establishing an optimal dosage for cholinesterase inhibitors can be a challenge. Dosage determination is accomplished by administering a small initial dose followed by additional small doses until an optimal level of muscle function has been achieved. Important signs of improvement include increased ease of swallowing and increased ability to raise the eyelids. You can help establish a correct dosage by keeping records of (1) times of drug administration, (2) times at which fatigue occurs, (3) the state of muscle strength before and after drug administration, and (4) signs of excessive muscarinic stimulation.

To maintain optimal responses, patients must occasionally modify dosage themselves. To do this, they must be taught to recognize signs of undermedication (ptosis, difficulty in swal-

lowing) and signs of overmedication (excessive salivation and other muscarinic responses). Patients may also need to modify dosage in anticipation of exertion. For example, they may find it necessary to take supplementary medication 30 to 60 minutes prior to such activities as eating and shopping.

Usual adult dosages for the three agents used to treat myasthenia gravis are

- *Ambenonium*—15 to 100 mg/day in divided doses
- *Neostigmine*—15 to 375 mg/day in divided doses
- *Pyridostigmine*—60 to 1500 mg/day in divided doses

Myasthenic Crisis and Cholinergic Crisis. *Myasthenic Crisis.* Patients who are inadequately medicated may experience myasthenic crisis, a state characterized by extreme muscle weakness (caused by insufficient ACh at the NMJ). Left untreated, myasthenic crisis can result in death from paralysis of the muscles of respiration. A cholinesterase inhibitor (eg, neostigmine) is used to relieve the crisis.

Cholinergic Crisis. As noted, overdose with a cholinesterase inhibitor can produce cholinergic crisis. Like myasthenic crisis, cholinergic crisis is characterized by extreme muscle weakness or frank paralysis. In addition, cholinergic crisis is accompanied by signs of excessive muscarinic stimulation. Treatment consists of respiratory support plus atropine. The offending cholinesterase inhibitor should be withheld until muscle strength has returned.

Distinguishing Myasthenic Crisis from Cholinergic Crisis. Because myasthenic crisis and cholinergic crisis share similar symptoms (muscle weakness or paralysis), but are treated very differently, it is essential to distinguish between them. A history of medication use or signs of excessive muscarinic stimulation are usually sufficient to permit a differential diagnosis. If these clues are inadequate, the differential diagnosis can be made by administering a challenging dose of *edrophonium*, an ultrashort-acting cholinesterase inhibitor. If edrophonium-induced elevation of ACh levels alleviates symptoms, the crisis is myasthenic. Conversely, if edrophonium intensifies symptoms, the crisis is cholinergic. Since the symptoms of cholinergic crisis will be made even worse by edrophonium, atropine and oxygen should be immediately available whenever edrophonium is used for this test.

Use of Identification by the Patient. Because of the possibility of experiencing either myasthenic crisis or cholinergic crisis, and because both crises can be fatal, patients with MG should be encouraged to wear a Medic Alert bracelet or some other form of identification to inform emergency medical personnel of their condition.

KEY POINTS

- Cholinesterase inhibitors prevent breakdown of ACh by acetylcholinesterase, causing ACh to accumulate in synapses, which in turn causes activation of muscarinic receptors, nicotinic receptors in ganglia and the NMJ, and cholinergic receptors in the CNS.
- The major use of reversible cholinesterase inhibitors is treatment of myasthenia gravis. Benefits derive from accumulation of ACh at the NMJ.
- Secondary uses for reversible cholinesterase inhibitors are reversal of competitive (nondepolarizing) neuromuscular blockade and treatment of glaucoma, Alzheimer's disease, Parkinson's disease dementia, and poisoning by muscarinic antagonists.
- Because physostigmine crosses membranes easily, this drug is the preferred cholinesterase inhibitor for treating poisoning by muscarinic antagonists.
- Irreversible cholinesterase inhibitors, also known as organophosphate cholinesterase inhibitors, are used primarily as insecticides. The only indication for these potentially toxic drugs is glaucoma.
- Most organophosphate cholinesterase inhibitors are highly lipid soluble. As a result, they can be absorbed directly through the skin and distribute easily to all tissues and organs.
- Overdose with cholinesterase inhibitors produces cholinergic crisis, characterized by depolarizing neuromuscular blockade plus signs of excessive muscarinic stimulation (hypersalivation, tearing, sweating, bradycardia, involuntary urination and defecation, miosis, and spasm of accommodation). Death results from respiratory depression.
- Poisoning by reversible cholinesterase inhibitors is treated with atropine (to reverse muscarinic stimulation) plus mechanical ventilation.
- Poisoning by organophosphate cholinesterase inhibitors is treated with atropine, mechanical ventilation, pralidoxime (to reverse inhibition of cholinesterase, primarily at the NMJ), and diazepam (to suppress seizures).

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Summary of Major Nursing Implications*

REVERSIBLE CHOLINESTERASE INHIBITORS

- Ambenonium
- Donepezil
- Edrophonium
- Galantamine
- Neostigmine
- Physostigmine
- Pyridostigmine
- Rivastigmine
- Tacrine

Preadministration Assessment

Therapeutic Goal

Cholinesterase inhibitors are used to treat myasthenia gravis, glaucoma, Alzheimer's disease, Parkinson's disease dementia, and poisoning by muscarinic antagonists, and to reverse competitive (nondepolarizing) neuromuscular blockade. Applications of individual agents are indicated in Table 15-1.

Baseline Data

Myasthenia Gravis: Determine the extent of neuromuscular dysfunction by assessing muscle strength, fatigue, ptosis, and ability to swallow.

Identifying High-Risk Patients

Cholinesterase inhibitors are **contraindicated** for patients with mechanical obstruction of the intestine or urinary tract.

*Exact calculation information is highlighted as blue text.

Summary of Major Nursing Implications—cont'd

Implementation: Measures to Enhance Therapeutic Effects

Myasthenia Gravis

Promoting Compliance. Inform patients that MG is not usually curable, and hence treatment is lifelong. Encourage patients to take their medication as prescribed and to play an active role in dosage adjustment.

Using Identification. Because patients with MG are at risk of fatal complications (cholinergic crisis, myasthenic crisis), encourage them to wear a Medic Alert bracelet or similar identification to inform emergency medical personnel of their condition.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Myasthenia Gravis. Monitor and record (1) times of drug administration; (2) times at which fatigue occurs; (3) state of muscle strength, ptosis, and ability to swallow; and (4) signs of excessive muscarinic stimulation. Dosage is increased or decreased based on these observations.

Monitor for **myasthenic crisis** (extreme muscle weakness, paralysis of respiratory muscles), which can occur when cholinesterase inhibitor dosage is insufficient. Manage with respiratory support and increased dosage.

Be certain to distinguish myasthenic crisis from cholinergic crisis. How? By observing for signs of excessive muscarinic stimulation, which will accompany cholinergic crisis but not myasthenic crisis. If necessary, these crises can be differentiated by giving **edrophonium**, which reduces symptoms of myasthenic crisis and intensifies symptoms of cholinergic crisis.

Minimizing Adverse Effects

Excessive Muscarinic Stimulation. Accumulation of ACh at muscarinic receptors can cause profuse salivation, increased tone and motility of the gut, urinary urgency, sweating, miosis, spasm of accommodation, bronchospasm, and bradycardia. **Inform patients about signs of excessive muscarinic stimulation and advise them to notify the prescriber if these occur.** Excessive muscarinic response can be managed with **atropine**.

Cholinergic Crisis. This condition results from cholinesterase inhibitor overdose. Manifestations are skeletal muscle paralysis (from depolarizing neuromuscular blockade) and signs of excessive muscarinic stimulation (eg, salivation, sweating, miosis, bradycardia).

Manage with mechanical ventilation and atropine. Cholinergic crisis must be distinguished from myasthenic crisis

Drugs That Block Nicotinic Cholinergic Transmission: Neuromuscular Blocking Agents and Ganglionic Blocking Agents

NEUROMUSCULAR BLOCKING AGENTS

Control of Muscle Contraction

Competitive (Nondepolarizing) Neuromuscular Blockers

Group Properties

Properties of Individual Agents

Depolarizing Neuromuscular Blockers: Succinylcholine

Therapeutic Uses of Neuromuscular Blockers

GANGLIONIC BLOCKING AGENTS

The drugs discussed in this chapter block nicotinic cholinergic receptors. The *neuromuscular* blocking agents block nicotinic_M receptors at the neuromuscular junction. The *ganglionic* blocking agents block nicotinic_N receptors in autonomic ganglia. The neuromuscular blockers have important clinical applications. In contrast, the ganglionic blockers, once used widely for hypertension, have been replaced by newer drugs.

NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents prevent acetylcholine from activating nicotinic_M receptors on skeletal muscles, and thereby cause muscle relaxation. These drugs are given to produce muscle relaxation during surgery, endotracheal intubation, mechanical ventilation, and other procedures. Based on mechanism of action, the neuromuscular blockers fall into two major groups: *competitive (nondepolarizing)* agents and *depolarizing* agents.

CONTROL OF MUSCLE CONTRACTION

Before we discuss the neuromuscular blockers, we need to review physiologic control of muscle contraction. In particular, we need to understand *excitation-contraction coupling*, the process by which an action potential in a motor neuron leads to contraction of a muscle.

Basic Concepts: Polarization, Depolarization, and Repolarization

The concepts of *polarization*, *depolarization*, and *repolarization* are important to understanding both muscle contraction and the neuromuscular blocking drugs. In *resting* muscle

there is uneven distribution of electrical charge across the inner and outer surfaces of the cell membrane. As shown in Figure 16-1, positive charges cover the outer surface of the membrane and negative charges cover the inner surface. Because of this uneven charge distribution, the resting membrane is said to be *polarized*.

When the membrane *depolarizes*, positive charges move from outside to inside. So many positive charges move inward that the inside of the membrane becomes more positive than the outside (see Fig. 16-1).

Under physiologic conditions, depolarization of the muscle membrane is followed almost instantaneously by *repolarization*. Repolarization is accomplished by pumping positively charged ions out of the cell. Repolarization restores the original resting membrane state, with positive charges on the outer surface and negative charges on the inner surface.

Steps in Muscle Contraction

The steps leading to muscle contraction are summarized in Figure 16-2. The process begins with the arrival of an action potential at the terminal of a motor neuron, causing release of acetylcholine (ACh) into the subneural space. Acetylcholine then binds reversibly to nicotinic_M receptors on the motor end-plate (a specialized region of the muscle membrane that contains the receptors for ACh) and causes the end-plate to *depolarize*. This depolarization initiates a muscle action potential (ie, a wave of depolarization that spreads rapidly over the entire muscle membrane), which in turn triggers the release of calcium from the sarcoplasmic reticulum (SR) of the muscle. This calcium permits the interaction of actin and myosin, thereby causing contraction. Very rapidly, ACh dissociates from the motor end-plate, the motor end-plate repolarizes, the muscle membrane repolarizes, and calcium is taken back up into the SR. Because there is no longer any calcium available to support the interaction of actin and myosin, the muscle relaxes.

Sustained muscle contraction requires a continuous series of motor neuron action potentials. These action potentials cause repeated release of ACh, which causes repeated activation of nicotinic receptors on the motor end-plate. As a result, the end-plate goes through repeating cycles of depolarization and repolarization, which results in sufficient release of calcium to sustain contraction. If for some reason the motor end-plate fails to repolarize—that is, if the end-plate remains in a *depolarized* state—the signal for calcium release will stop,

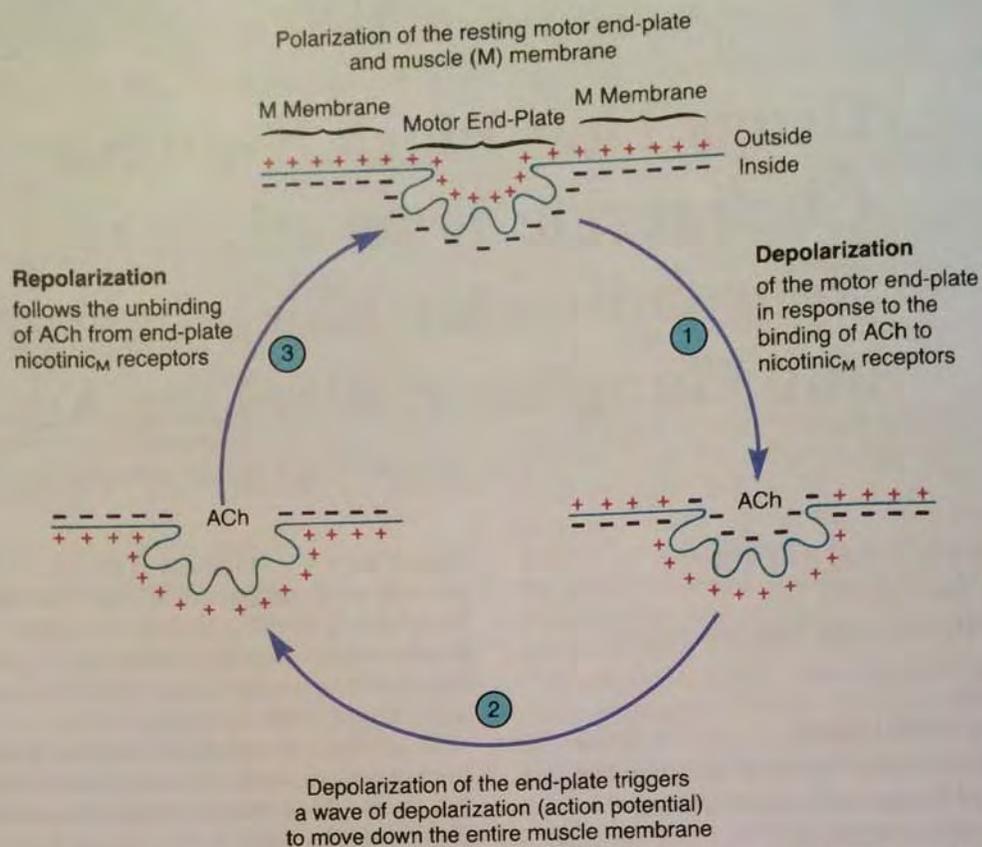


Figure 16-1 = The depolarization-repolarization cycle of the motor end-plate and muscle membrane. (ACh = acetylcholine.)

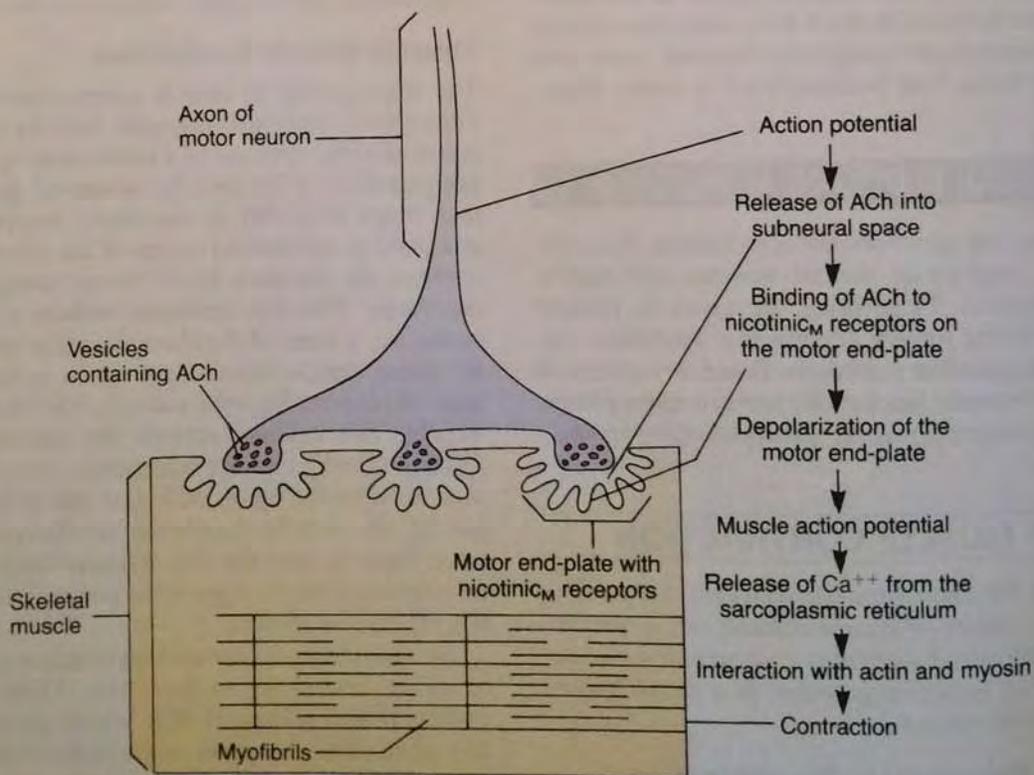


Figure 16-2 = Steps in excitation-contraction coupling. (ACh = acetylcholine.)

calcium will undergo immediate reuptake into the SR, and contraction will cease.

COMPETITIVE (NONDEPOLARIZING) NEUROMUSCULAR BLOCKERS

In this section, we discuss the competitive neuromuscular blocking agents, drugs that compete with ACh for binding to nicotinic_M receptors. These drugs are also known as *nondepolarizing* neuromuscular blockers, because, unlike the depolarizing neuromuscular blockers (see below), they do not depolarize the motor end-plate.

The powers of *tubocurarine*, the oldest competitive neuromuscular blocker, were known to primitive hunters long before coming to the attention of modern scientists. Tubocurarine is one of several active principles found in *curare*, an arrow poison used for hunting by South American Indians. When shot into a small animal, curare-tipped arrows cause relaxation (paralysis) of skeletal muscles. Death results from paralyzing the muscles of respiration.

The clinical utility of the neuromuscular blockers is based on the same action that is useful in hunting: production of skeletal muscle relaxation. Relaxation of skeletal muscles is helpful in patients undergoing surgery, endotracheal intubation, mechanical ventilation, and other procedures.

Group Properties

In all prior editions of this book, we have used tubocurarine as the prototype of the competitive neuromuscular blockers. However, since tubocurarine is no longer used, and since the similarities among the competitive agents are more striking than the differences, we will discuss the properties of these agents as a group, rather than picking one of them to be a prototype.

Chemistry

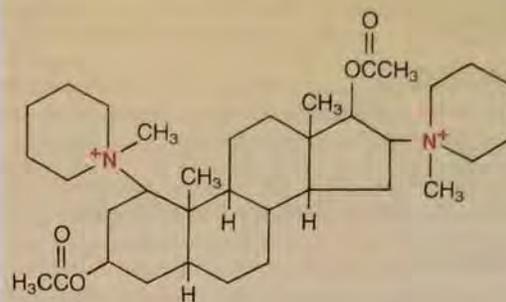
All of the neuromuscular blocking agents contain at least one *quaternary nitrogen* atom (Fig. 16-3). As a result, these drugs always carry a positive charge, and therefore cannot readily cross membranes.

The inability to cross membranes has three clinical consequences. First, neuromuscular blockers cannot be administered orally. Instead, they must all be administered parenterally (almost always IV). Second, these drugs cannot cross the blood-brain barrier, and hence have no effect on the central nervous system (CNS). Third, neuromuscular blockers cannot readily cross the placenta, and hence have little or no effect on the fetus.

Mechanism of Action

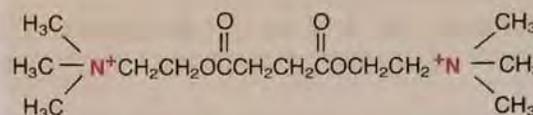
As their name implies, the competitive neuromuscular blockers compete with ACh for binding to nicotinic_M receptors on the motor end-plate (Fig. 16-4). However, unlike ACh, these drugs do not cause receptor activation. When they bind to nicotinic_M receptors, they block receptor activation by acetylcholine, causing the muscle to relax. Muscle relaxation persists as long as the amount of competitive neuromuscular blocker at the neuromuscular junction (NMJ) is sufficient to prevent receptor occupation by ACh. Muscle function can be restored by eliminating the drug from the body or by increasing the amount of ACh at the NMJ.

COMPETITIVE BLOCKER



Pancuronium

DEPOLARIZING BLOCKER



Succinylcholine

Figure 16-3 • Structural formulas of representative neuromuscular blocking agents.

Note that both agents contain a quaternary nitrogen atom and therefore cross membranes poorly. Consequently, they must be administered parenterally and have little effect on the central nervous system or the developing fetus.

Pharmacologic Effects

Muscle Relaxation. The primary effect of neuromuscular blockers is relaxation of skeletal muscle, causing a state known as *flaccid paralysis*. Although these drugs can paralyze all skeletal muscles, not all muscles are affected at once. The first to become paralyzed are the levator muscle of the eyelid and the muscles of mastication. Paralysis occurs next in muscles of the limbs, abdomen, and glottis. The last muscles affected are the muscles of respiration—the intercostals and diaphragm.

Hypotension. Some neuromuscular blockers can lower blood pressure. Two mechanisms may be involved: (1) release of histamine from mast cells and (2) partial blockade of nicotinic_N receptors in autonomic ganglia. Histamine lowers blood pressure by causing vasodilation. Partial ganglionic blockade lowers blood pressure by decreasing sympathetic tone to arterioles and veins.

Central Nervous System. As noted, the neuromuscular blockers cannot cross the blood-brain barrier. Consequently, these drugs have no effect on the CNS. Please note: *Neuromuscular blockers do not diminish consciousness or perception of pain—even when administered in doses that produce complete paralysis.*

Pharmacokinetics

With the competitive neuromuscular blockers in use today, paralysis develops within minutes of IV injection. Peak effects persist 20 to 45 minutes and then decline. Complete recovery takes about 1 hour. As shown in Table 16-1, the mode of elimi-

nation—spontaneous degradation, degradation by plasma cholinesterase, renal excretion, or hepatic metabolism—depends on the agent involved.

Therapeutic Uses

The competitive neuromuscular blockers are used to provide muscle relaxation during surgery, mechanical ventilation, and endotracheal intubation. These applications are discussed later under *Therapeutic Uses of Neuromuscular Blockers*.

Adverse Effects

Respiratory Arrest. Paralysis of respiratory muscles can produce respiratory arrest. Because of this risk, facilities for artificial ventilation must be immediately available. Patients must be monitored closely and continuously. When neuromuscular blockers are withdrawn, vital signs must be monitored until muscle function fully recovers.

Hypotension. One competitive agent—atracurium—can release significant amounts of histamine. Hypotension can result.

Precautions and Contraindications

Myasthenia Gravis. Neuromuscular blocking agents must be used with special care in patients with myasthenia gravis, a condition characterized by skeletal muscle weakness. The cause of weakness is a reduction in the number of nicotinic_M receptors on the motor end-plate. Because receptor number is reduced, neuromuscular blockade occurs readily. Also, doses that would have a minimal effect on others can produce complete paralysis in patients with myasthenia. Accordingly, dosing must be done with great care. Myasthenia gravis and its treatment are discussed in Chapter 15.

Electrolyte Disturbances. Responses to neuromuscular blockers can be altered by electrolyte abnormalities. For example, low potassium levels can enhance paralysis, whereas high potassium levels can reduce paralysis. Because electrolyte status can influence the depth of neuromuscular blockade, it is important to maintain normal electrolyte balance.

Drug Interactions

Neuromuscular blockers can interact with many other drugs. Interactions of primary interest are discussed below.

General Anesthetics. All inhalation anesthetics produce some degree of skeletal muscle relaxation, and can thereby enhance the actions of neuromuscular blockers. Consequently, when general anesthetics and neuromuscular blockers are combined (as they often are), the dosage of the neuromuscular blocker should be reduced to avoid excessive neuromuscular blockade.

Antibiotics. Several antibiotics can intensify responses to neuromuscular blockers. Among them are aminoglycosides (eg, gentamicin), tetracyclines, and certain other nonpenicillin antibiotics.

Cholinesterase Inhibitors. Cholinesterase inhibitors can decrease the effects of competitive neuromuscular blockers. How? By reducing the degradation of ACh, cholinesterase inhibitors increase the amount of ACh available to compete with the blocker. As more ACh (and less of the blocker) occupies nicotinic_M receptors on the motor end-plate, the degree of neuromuscular blockade declines.

The ability of cholinesterase inhibitors to decrease responses to competitive neuromuscular blockers has two clinical applications: (1) management of overdose with a competitive neuromuscular blocker and (2) reversal of neuromuscular blockade following surgery and other procedures.

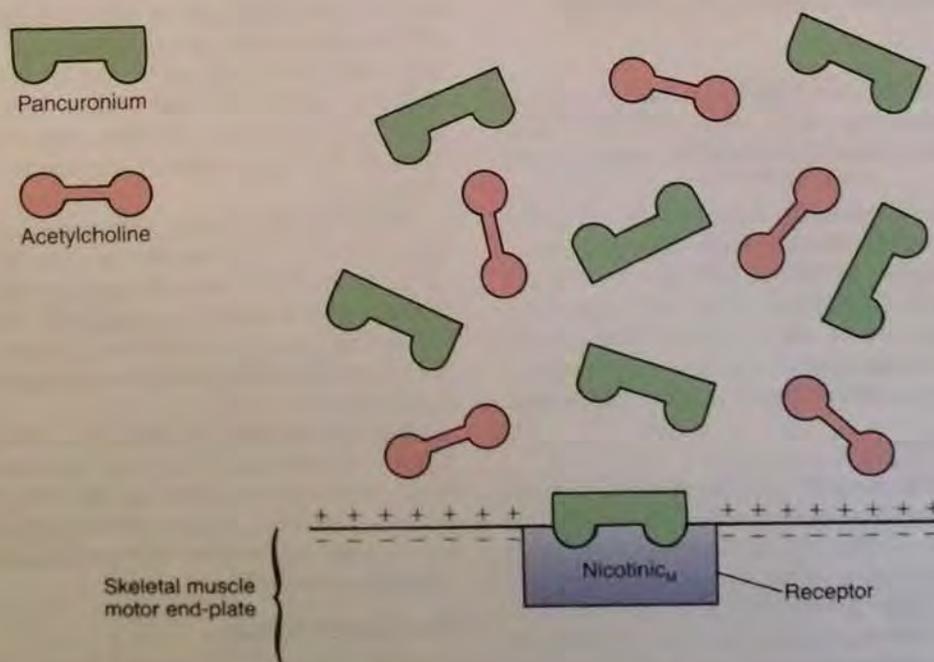


Figure 16-4 • Mechanism of competitive neuromuscular blockade.

Pancuronium, a competitive blocker, competes with acetylcholine (ACh) for binding to nicotinic_M receptors on the motor end-plate. Binding of pancuronium does not depolarize the end-plate, and therefore does not cause contraction. At the same time, the presence of pancuronium prevents ACh from binding to the receptor, and hence contraction is prevented.

As discussed later in the chapter, cholinesterase inhibitors increase responses to succinylcholine, a *depolarizing* neuromuscular blocker. Note that this is opposite to the effect that cholinesterase inhibitors have on competitive neuromuscular blockade.

Toxicity

When dosage is too high, all competitive neuromuscular blockers can produce *prolonged apnea*. Management consists of providing respiratory support plus a cholinesterase inhibitor (eg, neostigmine) to reverse neuromuscular blockade. One competitive agent—*atracurium*—can cause hypotension secondary to release of histamine. Antihistamines can be given to counteract this effect.

Properties of Individual Agents

All competitive neuromuscular blockers share the same mechanism of action (blockade of ACh binding to nicotinic_M receptors), and they all have the same indications: production of muscle relaxation during intubation, general anesthesia, and mechanical ventilation. Differences among the drugs relate primarily to histamine release and mode of elimination (see Table 16-1). With all of these agents, respiratory depression secondary to neuromuscular blockade is the major concern. Respiratory depression can be reversed with a cholinesterase inhibitor.

Atracurium. Atracurium [Tracrium] is approved for muscle relaxation during surgery, intubation, and mechanical ventilation. The drug can cause hypotension secondary to histamine release. Like succinylcholine (see below), atracurium is eliminated primarily by *plasma cholinesterase*, not by the liver or kidneys. Hence, atracurium may be desirable for patients with renal or hepatic dysfunction, since these disorders will not prolong the drug's effects.

Cisatracurium. Cisatracurium [Nimbex], a close relative of atracurium, is approved for muscle relaxation during surgery, intubation, and mechanical ventilation. Elimination is by spontaneous degradation, not by hepatic metabolism or renal excretion. Hence, like atracurium, cisatracurium would seem desirable for patients with kidney or liver dysfunction. Histamine release is minimal.

Pancuronium. Pancuronium, formerly available as *Pavulon*, is approved for muscle relaxation during general anesthesia, intubation, and mechanical ventilation. The drug does not cause histamine release, ganglionic blockade, or hypotension. Vagolytic effects may produce tachycardia. Elimination is primarily renal.

Rocuronium. Rocuronium [Zemuron] is approved for muscle relaxation during intubation, surgery, and mechanical ventilation. Muscle relaxation begins in 1 to 3 minutes, faster than with any other competitive agent. The only neuromuscular blocker with a faster onset is succinylcholine, a depolarizing agent. In contrast to succinylcholine, whose effects fade relatively quickly, effects of rocuronium persist for 20 to 40 minutes before starting to decline. Rocuronium does not cause histamine release. Elimination is by hepatic metabolism.

Vecuronium. Vecuronium [Norcuron], an analog of pancuronium, is used for muscle relaxation during intubation, general anesthesia, and mechanical ventilation. The drug does not produce ganglionic or vagal block and does not release histamine. Consequently, cardiovascular effects are minimal. Vecuronium is excreted primarily in the bile, and hence paralysis may be prolonged in patients with liver dysfunction. Paralysis may also be prolonged in obese patients.

DEPOLARIZING NEUROMUSCULAR BLOCKERS: SUCCINYLCHOLINE

Succinylcholine [Anectine, Quelicin], an ultrashort-acting drug, is the only depolarizing neuromuscular blocker in clinical use. This drug differs from the competitive blockers with regard to time course, mechanism of action, mode of elimination, interaction with cholinesterase inhibitors, and management of toxicity.

Mechanism of Action

Succinylcholine produces a state known as *depolarizing neuromuscular blockade*. Like acetylcholine, succinylcholine binds to nicotinic_M receptors on the motor end-plate and thereby causes depolarization. This depolarization produces transient muscle contractions (fasciculations). Then, instead of dissociating rapidly from the receptor, succinylcholine remains bound, and thereby prevents the end-plate from repolarizing. That is, succinylcholine maintains the end-plate in a state of *constant depolarization*. Because the end-plate must repeatedly depolarize and repolarize to maintain muscle contraction, succinylcholine's

TABLE 16-1 • Properties of Competitive and Depolarizing Neuromuscular Blockers

Generic Name	Route	Time Course of Action*			Promotes Histamine Release	Mode of Elimination
		Time to Maximum Paralysis (min)	Duration of Effective Paralysis (min)	Time to Nearly Full Spontaneous Recovery [†]		
Competitive Agents						
Atracurium [Tracrium]	IV	2-5	20-35	60-70 min	Yes	Plasma cholinesterase
Cisatracurium [Nimbex]	IV	2-5	20-35	—	Minimal	Spontaneous degradation
Pancuronium	IV	3-4	35-45	60-70 min	No	Renal
Rocuronium [Zemuron]	IV	1-3	20-40	—	No	Hepatic
Vecuronium [Norcuron]	IV	3-5	25-30	45-60 min	No	Hepatic/biliary
Depolarizing Agent						
Succinylcholine [Anectine, Quelicin]	IV, IM [‡]	1	4-6	—	Yes	Plasma cholinesterase

*Time course of action can vary widely with dosage and route of administration. The values presented are for an average adult dose administered as a single IV injection.

[†]Because spontaneous recovery can take a long time, recovery from the *competitive* agents (all of the drugs listed except succinylcholine, which is a depolarizing agent) is often accelerated by giving a cholinesterase inhibitor.

[‡]Intramuscular administration is rare.

ability to keep the end-plate depolarized causes paralysis (following the brief initial period of contraction). Paralysis persists until plasma levels of succinylcholine decline, thereby allowing the drug to dissociate from its receptors.

Pharmacologic Effects

Muscle Relaxation. The muscle-relaxant effects of succinylcholine are much like those of the competitive blockers, in that both produce a state of flaccid paralysis. However, despite this similarity, there are two important differences: (1) paralysis from succinylcholine is preceded by transient contractions and (2) paralysis from succinylcholine abates much more rapidly.

Central Nervous System. Like the depolarizing blockers, succinylcholine has no effect on the CNS. The drug can produce complete paralysis without decreasing consciousness or the ability to feel pain.

Pharmacokinetics

Succinylcholine has an extremely short duration of action. Paralysis peaks about 1 minute after IV injection and fades completely 4 to 10 minutes later.

Paralysis is brief because succinylcholine is rapidly degraded by *pseudocholinesterase*, an enzyme present in plasma. (This enzyme is called pseudocholinesterase to distinguish it from "true" cholinesterase, the enzyme found at synapses where ACh is the transmitter.) Because of its presence in plasma, pseudocholinesterase is also known as *plasma cholinesterase*. In most individuals, pseudocholinesterase is highly active and can eliminate succinylcholine in minutes.

Therapeutic Uses

Succinylcholine is used primarily for muscle relaxation during endotracheal intubation, electroconvulsive therapy, endoscopy, and other short procedures. Because of its brief duration, succinylcholine is poorly suited for use in prolonged procedures, such as surgery or mechanical ventilation, although it is approved for use in these situations.

Adverse Effects

Prolonged Apnea in Patients with Low Pseudocholinesterase Activity. A few people, because of their genetic makeup, produce a form of pseudocholinesterase that has extremely low activity. As a result, they are unable to degrade succinylcholine rapidly. If succinylcholine is given to these people, paralysis can persist for hours, rather than just a few minutes. Not surprisingly, succinylcholine is contraindicated for these individuals.

Patients suspected of having low pseudocholinesterase activity should be tested for this possibility before receiving a full succinylcholine dose. Pseudocholinesterase activity can be assessed by direct measurement of a blood sample or by administering a tiny test dose of succinylcholine. If the test dose produces muscle relaxation that is unexpectedly intense and prolonged, pseudocholinesterase activity is probably low.

Malignant Hyperthermia. Malignant hyperthermia is a rare and potentially fatal condition that can be triggered by succinylcholine, and by all inhalation anesthetics as well. The condition is characterized by muscle rigidity associated with a profound elevation of body temperature—sometimes to as high as 43°C. Temperature becomes elevated owing to excessive and uncontrolled metabolic activity in muscle, secondary

to increased release of calcium from the SR. Left untreated, the condition can rapidly prove fatal. Malignant hyperthermia is a genetically determined reaction that has an incidence of about 1 in 25,000. Individuals with a family history of the reaction should not receive succinylcholine.

Treatment of malignant hyperthermia includes (1) immediate discontinuation of succinylcholine and the accompanying anesthetic (and switching to nontrigger anesthesia), (2) cooling the patient with external ice packs and IV infusion of cold saline, and (3) administering intravenous *dantrolene*, a drug that stops heat generation by acting directly on skeletal muscle to reduce its metabolic activity. The pharmacology of dantrolene is discussed in Chapter 25 (Drugs for Muscle Spasm and Spasticity).

Postoperative Muscle Pain. Between 10% and 70% of patients receiving succinylcholine experience postoperative muscle pain, most commonly in the neck, shoulders, and back. Pain develops 12 to 24 hours after surgery and may persist several hours or even days. The cause may be the muscle contractions that occur during the initial phase of succinylcholine action.

Hyperkalemia. Succinylcholine promotes release of potassium from tissues. Rarely, potassium release is sufficient to cause severe hyperkalemia. Death from cardiac arrest has resulted. Significant hyperkalemia is most likely in patients with major burns, multiple trauma, denervation of skeletal muscle, or upper motor neuron injury. Accordingly, the drug is contraindicated for these patients.

Drug Interactions

Cholinesterase Inhibitors. These drugs *potentiate* (intensify) the effects of succinylcholine. How? Cholinesterase inhibitors decrease the activity of pseudocholinesterase, the enzyme that inactivates succinylcholine. Note that the effect of cholinesterase inhibitors on succinylcholine is opposite to their effect on *competitive* neuromuscular blockers.

Antibiotics. The effects of succinylcholine can be intensified by certain antibiotics. Among these are aminoglycosides, tetracyclines, and certain other nonpenicillin antibiotics.

Toxicology

Overdose can produce prolonged apnea. Since there is no specific antidote to succinylcholine poisoning, management is purely supportive. Recall that paralysis from overdose with a competitive agent can be reversed with a cholinesterase inhibitor. Since cholinesterase inhibitors *delay* the degradation of succinylcholine, use of these agents would prolong—not reverse—succinylcholine toxicity.

Preparations, Dosage, and Administration

Succinylcholine chloride [Anectine, Quelicin] is available in solution and as a powder for reconstitution. The drug is usually administered IV but can also be given IM. Solutions of succinylcholine are unstable and should be used within 24 hours. Multidose vials are stable for up to 2 weeks.

Dosage must be individualized and depends on the specific application. A typical adult dose for a brief procedure is 0.6 mg/kg, administered as a single IV injection. For prolonged procedures, succinylcholine may be administered by infusion at a rate of 2.5 to 4.3 mg/min.

THERAPEUTIC USES OF NEUROMUSCULAR BLOCKERS

The primary applications of the neuromuscular blocking agents are discussed below. All of the *competitive* agents in current use are indicated for muscle relaxation during general

anesthesia, mechanical ventilation, and intubation. Succinylcholine is used primarily for muscle relaxation during intubation, electroconvulsive therapy, and other short procedures.

Muscle Relaxation During Surgery

Production of muscle relaxation during surgery offers two benefits. First, relaxation of skeletal muscles, especially those of the abdominal wall, makes the surgeon's work easier. Second, muscle relaxants allow us to decrease the dosage of the general anesthetic, thereby decreasing the risks associated with anesthesia. Before neuromuscular blockers became available, surgical muscle relaxation had to be achieved with the general anesthetic alone, often requiring high levels of anesthetic. (As noted earlier, inhalation anesthetics have muscle relaxant properties of their own.) By combining a neuromuscular blocker with the general anesthetic, we can achieve adequate surgical muscle relaxation with less anesthetic than was possible when paralysis had to be achieved with an anesthetic by itself. By allowing a reduction in anesthetic levels, neuromuscular blockers have decreased the risk of respiratory depression from anesthesia. In addition, because less anesthetic is administered, recovery from anesthesia occurs faster.

Whenever neuromuscular blockers are employed during surgery, it is very, very important that anesthesia be maintained at a level sufficient to produce unconsciousness. Recall that neuromuscular blockers do not enter the CNS, and therefore have no effect on hearing, thinking, or the ability to feel pain; all these drugs do is produce paralysis. Neuromuscular blockers are obviously and definitely not a substitute for anesthesia. It does not require much imagination to appreciate the horror of the surgical patient who is completely paralyzed from neuromuscular blockade yet fully awake because of inadequate anesthesia. Does this really happen? Yes. In fact, it happens in between 0.1% and 0.2% of surgeries in which neuromuscular blockers are used. Clearly, full anesthesia must be provided whenever surgery is performed on a patient who is under neuromuscular blockade.

With the agents in current use, full recovery from surgical neuromuscular blockade takes about an hour. (With long-acting agents, which are no longer used, recovery could take several hours.) During the recovery period, patients must be monitored closely to ensure adequate ventilation. A patent airway should be maintained until the patient can swallow or speak. Recovery from the effects of *competitive* neuromuscular blockers (eg, pancuronium) can be accelerated with a cholinesterase inhibitor.

Facilitation of Mechanical Ventilation

Some patients who require mechanical ventilation still have some spontaneous respiratory movements, which can fight the rhythm of the respirator. By suppressing these movements, neuromuscular blocking agents can reduce resistance to ventilation.

When neuromuscular blockers are used to facilitate mechanical ventilation, patients should be treated as if they were awake—even though they appear to be asleep. (Remember that the patient is paralyzed, and hence there is no way to assess state of consciousness.) Because the patient may be fully awake, steps should be taken to ensure comfort at all times. Furthermore, because neuromuscular blockade does not affect hearing, nothing should be said in the patient's presence that might be inappropriate for him or her to hear.

Being fully awake but completely paralyzed can be a stressful and generally horrific experience. Think about it. Accordingly, many clinicians do not recommend routine use of

neuromuscular blockers during prolonged mechanical ventilation in intensive care units.

Endotracheal Intubation

An endotracheal tube is a large catheter that is inserted past the glottis and into the trachea to facilitate ventilation. Gag reflexes can fight tube insertion. By suppressing these reflexes, neuromuscular blockers can make intubation easier. Because of its short duration of action, succinylcholine is the preferred agent for this use, although all of the competitive agents are also approved for this use.

Adjunct to Electroconvulsive Therapy

Electroconvulsive therapy is an effective treatment for severe depression (see Chapter 32). Benefits derive strictly from the effects of electroshock on the brain; the convulsive movements that can accompany electroshock don't help relieve depression. Since convulsions per se serve no useful purpose, and since electroshock-induced convulsions can be harmful, a neuromuscular blocker is now used to prevent convulsive movements during electroshock therapy. Because of its short duration of action, succinylcholine is the preferred neuromuscular blocker for this application.

Diagnosis of Myasthenia Gravis

An intermediate-acting neuromuscular blocker can be used to diagnose myasthenia gravis (MG) when safer diagnostic procedures have been inconclusive. To diagnose MG, a small test dose of the blocker is administered. Because the dose is too small to affect individuals who do not have MG, a significant reduction in muscle strength would be diagnostic. If the test dose *does* decrease strength, neostigmine (a cholinesterase inhibitor) should be administered immediately; the resultant elevation in ACh at the NMJ will reverse neuromuscular blockade. It must be stressed that use of a neuromuscular blocker to diagnose myasthenia gravis is not without risk: If the patient does have MG, the challenging dose may be sufficient to cause pronounced respiratory depression. Consequently, facilities for artificial ventilation must be immediately available.

GANGLIONIC BLOCKING AGENTS

Ganglionic blocking agents produce a broad spectrum of pharmacologic effects. Because they lack selectivity, ganglionic blockers have limited applications. In fact, use of these drugs is so limited that the last one available—mecamylamine [Inversine]—was voluntarily withdrawn in 2009. Prior to being withdrawn, mecamylamine had only one use: reduction of blood pressure in patients who could not be managed with any other drugs.

Although ganglionic blockers are no longer used, they remain worthy of our consideration. Why? Recall that selectivity of action is highly desirable in a drug, and that the opposite—lack of selectivity—is highly undesirable. The ganglionic blockers, which lacked selectivity, are a great example of why selectivity is so important.

Mechanism of Action

Ganglionic blockers interrupt impulse transmission through ganglia of the autonomic nervous system. How? By competing with ACh for binding to nicotinic_N receptors in autonomic ganglia. Because the nicotinic_N receptors of sympathetic and parasympathetic ganglia are the same, ganglionic blockers stop transmission at *all* autonomic ganglia. By doing so, these drugs can, in effect, shut down the entire autonomic nervous system, thereby depriving organs of autonomic regulation.

Pharmacologic Effects

Because ganglionic blockers act by depriving organs of autonomic regulation, to predict their effects, we need to know how the autonomic nervous system is affecting specific organs when these drugs are given. That is, we need to know which branch of the autonomic nervous system is providing the predominant tone to specific organs. By knowing the source of predominant tone to an organ, and by knowing that ganglionic blockade will remove that tone, we can predict the effects that ganglionic blockade will produce.

Table 16-2 indicates (1) the major structures innervated by autonomic nerves, (2) the branch of the autonomic nervous system that provides the

TABLE 16-2 • Predominant Autonomic Tone and Responses to Ganglionic Blockade

Location	Predominant Tone	Response to Ganglionic Blockade
Salivary glands	Parasympathetic	Dry mouth
GI tract muscle	Parasympathetic	Blurred vision
Iris sphincter	Parasympathetic	Phonophobia (from mydriasis)
Urinary bladder	Parasympathetic	Urinary retention
Gastrointestinal tract	Parasympathetic	Constipation
Heart	Parasympathetic	Tachycardia
Sweat glands	Sympathetic*	Anhidrosis
Arterioles	Sympathetic	Hypotension (from vasodilation)
Veins	Sympathetic	Orthostatic hypotension (from pooling of blood in veins secondary to venous dilation)

*Sympathetic nerves to sweat glands release acetylcholine as their transmitter, which acts at muscarinic receptors on the sweat glands.

predominant tone to those structures, and (3) the responses to ganglionic blockade. As indicated, the predominant autonomic tone to most organs is provided by the parasympathetic nervous system. The sympathetic branch provides the predominant tone only to sweat glands, arterioles, and veins.

Since the parasympathetic nervous system provides the predominant tone to most organs, and since the parasympathetic nervous system works through muscarinic receptors to influence organ function, most responses to ganglionic blockade resemble those produced by muscarinic antagonists. These responses include dry mouth, blurred vision, photophobia, urinary retention, constipation, tachycardia, and anhidrosis.

In addition to their parasympatholytic effects, ganglionic blockers produce hypotension. The mechanism is blockade of sympathetic nerve traffic to arterioles and veins, which results in vasodilation.

Therapeutic Use
 Prior to their withdrawal, ganglionic blockers were used for essential hypertension in selected patients. Specifically, these drugs were reserved for those rare cases in which blood pressure could not be reduced with more desirable medications.

Adverse Effects
 Ganglionic blockers can produce a broad spectrum of undesired effects, all of which are predictable consequences of generalized inhibition of the autonomic nervous system. Adverse effects fall into two major groups: (1) anti-

KEY POINTS

- All of these key points apply to the neuromuscular blocking agents—not to ganglionic blocking agents.
- Sustained contraction of skeletal muscle results from repetitive activation of nicotinic receptors on the motor end-plate, causing the end-plate to go through repeating cycles of depolarization and repolarization.
- Neuromuscular blockers interfere with nicotinic receptors, and thereby cause muscle relaxation.
- Competitive neuromuscular blockers act by competing with ACh for binding to nicotinic receptors.
- Succinylcholine, the only depolarizing neuromuscular blocker in use, binds to nicotinic receptors, causing the end-plate to depolarize; the drug then remains bound, which keeps the end-plate from repolarizing.
- Neuromuscular blockers are used to produce muscle relaxation during surgery, endotracheal intubation, mechanical ventilation, and electroshock therapy.
- Neuromuscular blockers do not reduce consciousness or pain.

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Summary of Major Nursing Implications*

NEUROMUSCULAR-BLOCKING AGENTS

- Atracurium
- Cisatracurium
- Pancuronium
- Rocuronium
- Succinylcholine
- Vacoronium

Except where noted, the implications summarized below apply to all neuromuscular blocking agents.

Preadministration Assessment

Provision of muscle relaxation during surgery, endotracheal intubation, mechanical ventilation, electroconvulsive therapy, and other procedures.

Identifying High-Risk Patients

Use all neuromuscular blockers with caution in patients with myasthenia gravis.
 Succinylcholine is contraindicated for patients with low pseudocholinesterase activity, a personal or familial history of malignant hyperthermia, or conditions that predispose to hyperkalemia (major burns, multiple trauma, denervation of skeletal muscle, upper motor neuron injury).

Implementation: Administration

Routes
 Intravenous. All neuromuscular blockers, including succinylcholine.
 Intramuscular. Only succinylcholine, and only rarely.

Administration

Neuromuscular blockers are dangerous drugs that should be administered by clinicians skilled in their use.

Implementation: Measures to Enhance Therapeutic Effects

Neuromuscular blockers do not affect consciousness or perception of pain. When used during surgery, these drugs must be accompanied by adequate anesthesia. When neuromuscular blockers are used for prolonged paralysis during mechanical ventilation, care should be taken to ensure comfort (eg, patient education information is highlighted in blue text).

positioning the patient comfortably, moistening the mouth periodically). Because patients may be awake (but won't appear to be), conversations held in their presence should convey only information appropriate for them to hear.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects
Apnea. All neuromuscular blockers can cause respiratory arrest. Facilities for intubation and mechanical ventilation should be immediately available.
 Monitor respiration constantly during the period of peak drug action. When drug administration is discontinued, take vital signs at least every 17 minutes until recovery is complete.

A cholinesterase inhibitor can be used to reverse respiratory depression caused by competitive neuromuscular blockers, but not by succinylcholine, a depolarizing blocker.
Hypotension. Atracurium may cause hypotension by releasing histamine. Ambihistamines can help counteract this effect.

Malignant Hyperthermia. Succinylcholine can trigger malignant hyperthermia. Predisposition to this reaction is genetic. Assess for a family history of the reaction. Management consists of stopping succinylcholine and the offending anesthetic (and substituting a safer anesthetic), cooling with ice packs, and cold IV saline, and giving IV dantrolene.

Hyperkalemia with Cardiac Arrest. Succinylcholine can cause severe hyperkalemia resulting in cardiac arrest if given to patients with major burns, multiple trauma, denervation of skeletal muscle, or upper motor neuron injury.

Muscle Pain. Succinylcholine may cause muscle pain. Reassure the patient that this response, although unpleasant, is not unusual.

Minimizing Adverse Interactions

Antibiotics. Certain antibiotics, including aminoglycosides and tetracyclines, can intensify neuromuscular blockade. Use them with caution.

Cholinesterase Inhibitors. These drugs delay inactivation of succinylcholine, thereby greatly prolonging paralysis. Accordingly, cholinesterase inhibitors are contraindicated for patients receiving succinylcholine.

Adrenergic Agonists

Mechanisms of Adrenergic Receptor Activation

Overview of the Adrenergic Agonists

Chemical Classification: Catecholamines Versus Noncatecholamines

Receptor Specificity

Therapeutic Applications and Adverse Effects of Adrenergic Receptor Activation

Clinical Consequences of Alpha₁ Activation

Clinical Consequences of Alpha₂ Activation

Clinical Consequences of Beta₁ Activation

Clinical Consequences of Beta₂ Activation

Clinical Consequences of Dopamine Receptor Activation

Multiple Receptor Activation: Treatment of Anaphylactic Shock

Properties of Representative Adrenergic Agonists

Epinephrine

Norepinephrine

Isoproterenol

Dopamine

Dobutamine

Phenylephrine

Albuterol

Ephedrine

Discussion of Adrenergic Agonists in Other Chapters

Si Box 17-1. The EpiPen: Don't Leave Home Without It!

By definition, adrenergic agonists produce their effects by activating adrenergic receptors. Since the sympathetic nervous system acts through these same receptors, responses to adrenergic agonists and responses to stimulation of the sympathetic nervous system are very similar. Because of this similarity, adrenergic agonists are often referred to as *sympathomimetics*. Adrenergic agonists have a broad spectrum of indications, ranging from heart failure to asthma to preterm labor.

Learning about adrenergic agonists can be a challenge. To facilitate the process, our approach to these drugs has four stages. We begin with the general mechanisms by which drugs can activate adrenergic receptors. Next we establish an overview of the major adrenergic agonists, focusing on their receptor specificity and chemical classification. After that, we address the adrenergic receptors themselves; for each receptor type—alpha₁, alpha₂, beta₁, beta₂, and dopamine—we discuss the beneficial and harmful effects that can result from receptor activation. Finally, we integrate all of this information by

discussing the characteristic properties of representative sympathomimetic drugs.

Please note that this chapter is intended only as an *introduction* to the adrenergic agonists. Our objective here is to discuss the basic properties of the sympathomimetic drugs and establish an overview of their applications and adverse effects. In later chapters, we will discuss the clinical applications of these agents in greater depth.

MECHANISMS OF ADRENERGIC RECEPTOR ACTIVATION

Drugs can activate adrenergic receptors by four basic mechanisms: (1) direct receptor binding, (2) promotion of norepinephrine (NE) release, (3) blockade of NE reuptake, and (4) inhibition of NE inactivation. Note that only the first mechanism is *direct*. With the other three, receptor activation occurs by an *indirect* process. Examples of drugs that act by these four mechanisms are presented in Table 17-1.

Direct Receptor Binding. Direct interaction with receptors is the most common mechanism by which drugs activate peripheral adrenergic receptors. The direct-acting receptor stimulants produce their effects by binding to adrenergic receptors and mimicking the actions of natural transmitters (NE, epinephrine, dopamine). In this chapter, all of the drugs discussed activate receptors directly.

Promotion of NE Release. By acting on terminals of sympathetic nerves to cause NE release, drugs can bring about activation of adrenergic receptors. Agents that act by this mechanism include amphetamines and ephedrine. (Ephedrine can also activate adrenergic receptors directly.)

TABLE 17-1 ■ Mechanisms of Adrenergic Receptor Activation

Mechanism of Stimulation	Examples
Direct Mechanism	
Receptor activation through direct binding	Dopamine Epinephrine Isoproterenol Ephedrine*
Indirect Mechanisms	
Promotion of NE release	Amphetamine Ephedrine*
Inhibition of NE reuptake	Cocaine Tricyclic antidepressants
Inhibition of MAO	MAO inhibitors

MAO = monoamine oxidase, NE = norepinephrine.

*Ephedrine is a mixed-acting drug that activates receptors directly and by promoting release of norepinephrine.

Inhibition of NE Reuptake. Recall that reuptake of NE into terminals of sympathetic nerves is the major mechanism for terminating adrenergic transmission. By blocking NE reuptake, drugs can cause NE to accumulate within the synaptic gap, and can thereby increase receptor activation. Agents that act by this mechanism include cocaine and the tricyclic antidepressants (eg, imipramine).

Inhibition of NE Inactivation. As discussed in Chapter 13, some of the NE in terminals of adrenergic neurons is subject to inactivation by monoamine oxidase (MAO). Hence, drugs that inhibit MAO can increase the amount of NE available for release, and can thereby enhance receptor activation. (It should be noted that, in addition to being present in sympathetic nerves, MAO is present in the liver and the intestinal wall. The significance of MAO at these other sites is considered later in the chapter.)

In this chapter, which is dedicated to *peripherally* acting sympathomimetics, nearly all of the drugs discussed act exclusively by *direct* receptor activation. The only exception is *ephedrine*, a drug that works by a combination of direct receptor activation and promotion of NE release.

Most of the indirect-acting adrenergic agonists are used for their ability to activate adrenergic receptors in the central nervous system (CNS)—not for their effects in the periphery. The indirect-acting sympathomimetics (eg, amphetamine, cocaine) are mentioned here to emphasize that, although these agents are employed for effects on the brain, they can and will cause activation of adrenergic receptors in the periphery. Peripheral activation is responsible for certain toxicities of these drugs (eg, cardiac dysrhythmias, hypertension).

OVERVIEW OF THE ADRENERGIC AGONISTS

Chemical Classification: Catecholamines Versus Noncatecholamines

The adrenergic agonists fall into two major chemical classes: catecholamines and noncatecholamines. As discussed below, the catecholamines and noncatecholamines differ in three important respects: (1) oral usability, (2) duration of action, and (3) the ability to act in the CNS. Accordingly, if we know to which category a particular adrenergic agonist belongs, we will know three of its prominent features.

Catecholamines

The catecholamines are so named because they contain a *catechol* group and an *amine* group. A catechol group is simply a benzene ring that has hydroxyl groups on two adjacent carbons (Fig. 17-1). The amine component of the catecholamines is *ethylamine*. Structural formulas for each of the major catecholamines—epinephrine, norepinephrine, isoproterenol, dopamine, and dobutamine—are presented in Figure 17-1. Because of their chemistry, all catecholamines have three properties in common: (1) they cannot be used orally, (2) they have a brief duration of action, and (3) they cannot cross the blood-brain barrier.

The actions of two enzymes—*monoamine oxidase* and *catechol-O-methyltransferase* (COMT)—explain why the catecholamines have short half-lives and cannot be used orally. MAO and COMT are located in the liver and in the intestinal

wall. Both enzymes are very active and quickly destroy catecholamines administered by any route. Because these enzymes are located in the liver and intestinal wall, catecholamines that are administered orally become inactivated before they can reach the systemic circulation. Hence, catecholamines are ineffective if given by mouth. Because of rapid inactivation by MAO and COMT, three catecholamines—norepinephrine, dopamine, and dobutamine—are effective only if administered by continuous infusion. Administration by other parenteral routes (eg, subQ, IM) will not yield adequate blood levels, owing to rapid hepatic inactivation.

Catecholamines are polar molecules, and hence cannot cross the blood-brain barrier. (Recall from Chapter 4 that polar compounds penetrate membranes poorly.) The polar nature of the catecholamines is due to the hydroxyl groups on the catechol portion of the molecule. Because they cannot cross the blood-brain barrier, catecholamines have minimal effects on the CNS.

Be aware that catecholamine-containing solutions, which are colorless when first prepared, turn pink or brown over time. This pigmentation is caused by oxidation of the catecholamine molecule. As a rule, *catecholamine solutions should be discarded as soon as discoloration develops*. The only exception is dobutamine, which can be used up to 24 hours after the solution was made, even if discoloration appears.

Noncatecholamines

The noncatecholamines have ethylamine in their structure (see Fig. 17-1), but do not contain the catechol moiety that characterizes the catecholamines. In this chapter, we discuss three noncatecholamines: ephedrine, albuterol, and phenylephrine.

The noncatecholamines differ from the catecholamines in three important respects. First, because they lack a catechol group, noncatecholamines are not substrates for COMT and are metabolized slowly by MAO. As a result, the half-lives of noncatecholamines are much longer than those of catecholamines. Second, because they do not undergo rapid degradation by MAO and COMT, noncatecholamines can be given orally, whereas catecholamines cannot. Third, noncatecholamines are considerably less polar than catecholamines, and hence are more able to cross the blood-brain barrier.

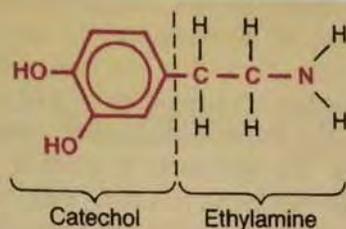
Receptor Specificity

To understand the actions of individual adrenergic agonists, we need to know their receptor specificity. Since the sympathomimetic drugs differ widely with respect to the receptors they can activate, learning the receptor specificity of these drugs will take some effort.

Variability in receptor specificity among the adrenergic agonists can be illustrated with three drugs: albuterol, isoproterenol, and epinephrine. Albuterol is highly selective, acting at β_2 receptors only. Isoproterenol is less selective, acting at β_1 receptors and β_2 receptors. Epinephrine is less selective yet, acting at all four adrenergic receptor subtypes: α_1 , α_2 , β_1 , and β_2 .

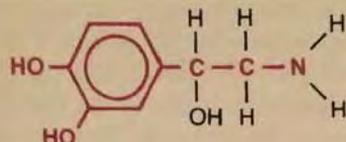
The receptor specificities of the major adrenergic agonists are summarized in Table 17-2. In the upper part of the table, receptor specificity is presented in tabular form. In the lower part, the same information is presented schematically. By learning (memorizing) the content of Table 17-2, you will be well on your way toward understanding the pharmacology of the sympathomimetic drugs.

Basic structure of the catecholamines

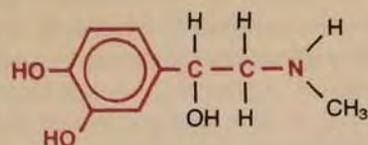


Catecholamines

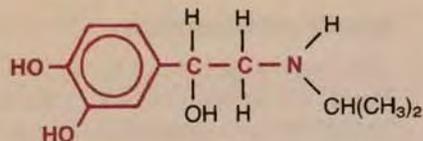
Norepinephrine



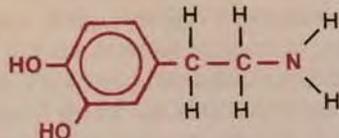
Epinephrine



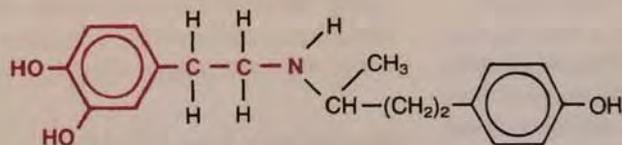
Isoproterenol



Dopamine

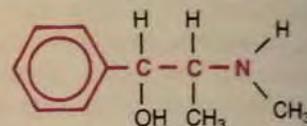


Dobutamine

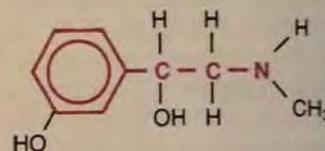


Noncatecholamines

Ephedrine



Phenylephrine



Albuterol

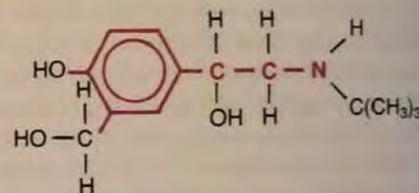


Figure 17-1 ■ Structures of representative catecholamines and noncatecholamines.

Catecholamines: Note that all of the catecholamines share the same basic chemical formula. Because of their biochemical properties, the catecholamines cannot be used orally, cannot cross the blood-brain barrier, and have short half-lives (owing to rapid inactivation by MAO and COMT).

Noncatecholamines: Although structurally similar to catecholamines, noncatecholamines differ from catecholamines in three important ways: they can be used orally; they can cross the blood-brain barrier; and, because they are not rapidly metabolized by MAO or COMT, they have much longer half-lives.

Please note that the concept of receptor specificity is relative, not absolute. The ability of a drug to selectively activate certain receptors to the exclusion of others depends on the dosage: at low doses, selectivity is maximal; as dosage increases, selectivity declines. For example, when albuterol is administered in low to moderate doses, the drug is highly selective for beta₂-adrenergic receptors. However, if the dosage is high, albuterol will activate beta₁ receptors as well. The information on receptor specificity in Table 17-2 refers to usual therapeutic doses. So-called selective agents will activate additional adrenergic receptors if the dosage is abnormally high.

THERAPEUTIC APPLICATIONS AND ADVERSE EFFECTS OF ADRENERGIC RECEPTOR ACTIVATION

In this section we discuss the responses—both therapeutic and adverse—that can be elicited with sympathomimetic drugs. Since many adrenergic agonists activate more than one type of receptor (see Table 17-2), it could be quite confusing if we were to talk about the effects of the sympathomimetics while employing specific drugs as examples. Consequently, rather than attempting to structure this presentation around

TABLE 17-2 • Receptor Specificity of Representative Adrenergic Agonists

Catecholamines		Noncatecholamines		
Drug	Receptors Activated	Drug	Receptors Activated	
Epinephrine	$\alpha_1, \alpha_2, \beta_1, \beta_2$	Ephedrine*	$\alpha_1, \alpha_2, \beta_1, \beta_2$	
Norepinephrine	$\alpha_1, \alpha_2, \beta_1$	Phenylephrine	α_1	
Isoproterenol	β_1, β_2	Albuterol	β_2	
Dobutamine	β_1			
Dopamine [†]	$\alpha_1, \beta_1, \text{dopamine}$			

Receptors Activated [†]				
Alpha ₁	Alpha ₂	Beta ₁	Beta ₂	Dopamine
		Epinephrine		
		Ephedrine*		
	Norepinephrine			
Phenylephrine			Isoproterenol	
		Dobutamine	Albuterol	
Dopamine [†]		Dopamine [†]		Dopamine [†]

α = alpha, β = beta.

*Ephedrine is a mixed-acting agent that causes NE release and also activates alpha and beta receptors directly.

[†]Receptor activation by dopamine is dose dependent.

[‡]This chart represents in graphic form the same information on receptor specificity given above. Arrows indicate the range of receptors that the drugs can activate (at usual therapeutic doses).

representative drugs, we discuss the actions of the adrenergic agonists one receptor at a time. Our discussion begins with alpha₁ receptors, and then moves to alpha₂ receptors, beta₁ receptors, beta₂ receptors, and finally dopamine receptors. For each receptor type, we discuss both the therapeutic and adverse responses that can result from receptor activation.

To understand the effects of any specific adrenergic agonist, all you need is two types of information: (1) the identity of the receptors at which the drug acts and (2) the effects produced by activating those receptors. Combining these two types of information will reveal a profile of drug action. This is the same approach to understanding neuropharmacologic agents that we discussed in Chapter 12.

Before you go deeper into this chapter, I encourage you (strongly advise you) to review Table 13-3. Since we are about to discuss the clinical consequences of adrenergic receptor activation, and since Table 13-3 summarizes the responses to activation of those receptors, the benefits of being familiar with Table 13-3 are obvious. If you choose not to memorize Table 13-3 now, at least be prepared to refer back to it as we discuss the consequences of receptor activation.

Clinical Consequences of Alpha₁ Activation

In this section we discuss the therapeutic and adverse effects that can result from activation of alpha₁-adrenergic receptors. As shown in Table 17-2, drugs capable of activating alpha₁ receptors include epinephrine, NE, phenylephrine, ephedrine, and dopamine.

Therapeutic Applications of Alpha₁ Activation

Activation of alpha₁ receptors elicits two responses that can be of therapeutic use: (1) *vasoconstriction* (in blood vessels of the skin, viscera, and mucous membranes); and (2) *mydriasis*. Of the two, vasoconstriction is the one for which

alpha₁ agonists are used most often. Using these drugs for mydriasis is rare.

Hemostasis. Hemostasis is defined as the arrest of bleeding, which alpha₁ agonists accomplish through vasoconstriction. Alpha₁ stimulants are given to stop bleeding primarily in the skin and mucous membranes. Epinephrine, applied topically, is the alpha₁ agonist used most for this purpose.

Nasal Decongestion. Nasal congestion results from dilation and engorgement of blood vessels in the nasal mucosa. Drugs can relieve congestion by causing alpha₁-mediated vasoconstriction. Specific alpha₁-activating agents employed as nasal decongestants include phenylephrine (applied topically) and pseudoephedrine (taken orally).

Adjunct to Local Anesthesia. Alpha₁ agonists are frequently combined with local anesthetics to delay anesthetic absorption. The mechanism is alpha₁-mediated vasoconstriction, which reduces blood flow to the site of anesthetic administration. Why delay anesthetic absorption? Because doing so prolongs anesthesia, allows a reduction in anesthetic dosage, and reduces the systemic effects that a local anesthetic might produce. The drug used most frequently to delay anesthetic absorption is epinephrine.

Elevation of Blood Pressure. Because of their ability to cause vasoconstriction, alpha₁ agonists can elevate blood pressure in hypotensive patients. Please note, however, that alpha₁ agonists are not the primary therapy for hypotension. Rather, they are reserved for situations in which fluid replacement and other measures have failed to restore blood pressure to a satisfactory level.

Mydriasis. Activation of alpha₁ receptors on the radial muscle of the iris causes mydriasis (dilation of the pupil), which can facilitate eye examinations and ocular surgery. Note that producing mydriasis is the only clinical use of alpha₁ activation that is not based on vasoconstriction.

Adverse Effects of Alpha₁ Activation

All of the adverse effects caused by alpha₁ activation result directly or indirectly from vasoconstriction.

Hypertension. Alpha₁ agonists can produce hypertension by causing widespread vasoconstriction. Severe hypertension is most likely with parenteral dosing. Accordingly, when alpha₁ agonists are given parenterally, cardiovascular status must be monitored continuously. Never leave the patient unattended.

Necrosis. If the IV line employed to administer an alpha₁ agonist becomes extravasated, local seepage of the drug may result in necrosis (tissue death). The cause is lack of blood flow secondary to intense local vasoconstriction. If extravasation occurs, the area should be infiltrated with an alpha₁-blocking agent (eg, phentolamine), which will counteract alpha₁-mediated vasoconstriction, and thereby help minimize injury.

Bradycardia. Alpha₁ agonists can cause reflex slowing of the heart. The mechanism is this: Alpha₁-mediated vasoconstriction elevates blood pressure, which triggers the baroreceptor reflex, causing heart rate to decline. In patients with marginal cardiac reserve, the decrease in cardiac output may compromise tissue perfusion.

Clinical Consequences of Alpha₂ Activation

As discussed in Chapter 13, alpha₂ receptors in the periphery are located *presynaptically*, and their activation inhibits NE release. Several adrenergic agonists (eg, epinephrine, NE) are capable of causing alpha₂ activation. However, their ability to activate alpha₂ receptors in the periphery has little clinical significance. There are no therapeutic applications related to activation of peripheral alpha₂ receptors. Furthermore, activation of these receptors rarely causes significant adverse effects.

In contrast to alpha₂ receptors in the *periphery*, alpha₂ receptors in the *CNS* are of great clinical significance. By activating central alpha₂ receptors, we can produce two useful effects: (1) *reduction* of sympathetic outflow to the heart and blood vessels and (2) relief of severe pain. The central alpha₂ agonists used for effects on the heart and blood vessels, and the agents used to relieve pain, are discussed in Chapters 19 and 28, respectively.

Clinical Consequences of Beta₁ Activation

All of the clinically relevant responses to activation of beta₁ receptors result from activating beta₁ receptors in the *heart*; activation of renal beta₁ receptors is not associated with either beneficial or adverse effects. As indicated in Table 17-2, beta₁ receptors can be activated by epinephrine, NE, isoproterenol, dopamine, dobutamine, and ephedrine.

Therapeutic Applications of Beta₁ Activation

Heart Failure. Heart failure is characterized by a reduction in the force of myocardial contraction, resulting in insufficient cardiac output. Because activation of beta₁ receptors in the heart has a positive inotropic effect (ie, increases the force of contraction), drugs that activate these receptors can improve cardiac performance.

Shock. This condition is characterized by profound hypotension and greatly reduced tissue perfusion. The primary goal of treatment is to maintain blood flow to vital organs. By increasing heart rate and force of contraction, beta₁

stimulants can increase cardiac output and can thereby improve tissue perfusion.

Atrioventricular Heart Block. Atrioventricular (AV) heart block is a condition in which impulse conduction from the atria to the ventricles is either impeded or blocked entirely. As a consequence, the ventricles are no longer driven at an appropriate rate. Since activation of cardiac beta₁ receptors can enhance impulse conduction through the AV node, beta₁ stimulants can help overcome AV block. It should be noted, however, that these drugs are only a temporary form of treatment. For long-term management, a pacemaker is implanted.

Cardiac Arrest Caused by Asystole. By activating cardiac beta₁ receptors, drugs can initiate contraction in a heart that has stopped beating. It should be noted, however, that these drugs are not the preferred treatment. Initial management focuses on cardiopulmonary resuscitation (CPR), external pacing (if available), and identification and treatment of the underlying cause (eg, hypoxia, severe acidosis, drug overdose). When a beta₁ agonist is indicated, epinephrine, administered IV, is the preferred drug. If IV access is not possible, epinephrine can be injected directly into the heart.

Adverse Effects of Beta₁ Activation

All of the adverse effects of beta₁ activation result from activating beta₁ receptors in the heart. Activating renal beta₁ receptors is not associated with untoward effects.

Altered Heart Rate or Rhythm. Overstimulation of cardiac beta₁ receptors can produce *tachycardia* (excessive heart rate) and *dysrhythmias* (irregular heartbeat).

Angina Pectoris. In some patients, drugs that activate beta₁ receptors can precipitate an attack of angina pectoris, a condition characterized by substernal pain in the region of the heart. Anginal pain occurs when cardiac oxygen supply (blood flow) is insufficient to meet cardiac oxygen needs. The most common cause of angina is coronary atherosclerosis (accumulation of lipids and other substances in coronary arteries). Since beta₁ agonists increase cardiac oxygen demand (by increasing heart rate and force of contraction), patients with compromised coronary circulation are at risk of an anginal attack.

Clinical Consequences of Beta₂ Activation

Therapeutic Applications of Beta₂ Activation

Therapeutic applications of beta₂ activation are limited to the *lungs* and the *uterus*. Drugs used for their beta₂-activating ability include epinephrine, isoproterenol, and albuterol.

Asthma. Asthma is a chronic condition characterized by inflammation and bronchoconstriction occurring in response to a variety of stimuli. During a severe attack, the airflow reduction can be life threatening. Since drugs that activate beta₂ receptors in the lung promote bronchodilation, these drugs can help relieve or prevent asthma attacks.

For therapy of asthma, adrenergic agonists that are *selective for beta₂ receptors* (eg, albuterol) are preferred to less selective agents (eg, isoproterenol). This is especially true for patients who also suffer from *angina pectoris* or *tachycardia*. Why? Because drugs that can activate beta₁ receptors would aggravate these cardiac disorders.

Most beta₂ agonists used to treat asthma are administered by *inhalation*. This route is desirable in that it helps minimize adverse systemic effects. It should be noted, however, that inhalation does not guarantee safety: Serious systemic toxic

ity can result from overdosing with inhaled sympathomimetics. Accordingly, patients must be warned against inhaling too much drug.

Delay of Preterm Labor. Activation of beta₂ receptors in the uterus relaxes uterine smooth muscle. This action can be exploited to delay preterm labor.

Adverse Effects of Beta₂ Activation

Hyperglycemia. The most important adverse response to beta₂ activation is hyperglycemia (elevation of blood glucose). The mechanism is activation of beta₂ receptors in the liver and skeletal muscles, which promotes breakdown of glycogen into glucose. As a rule, beta₂ agonists cause hyperglycemia only in patients with *diabetes*; in patients with normal pancreatic function, insulin release will maintain blood glucose at an appropriate level. If hyperglycemia develops in the diabetic patient, insulin dosage should be increased.

Tremor. Tremor is the most common side effect of beta₂ agonists. It occurs because activation of beta₂ receptors in skeletal muscle enhances contraction. Tremor generally fades over time and can be minimized by initiating therapy at low doses.

Clinical Consequences of Dopamine Receptor Activation

Activation of peripheral dopamine receptors causes dilation of the renal vasculature. This effect is exploited in the treatment of *shock*: by dilating renal blood vessels, we can improve renal perfusion and can thereby reduce the risk of renal failure. *Dopamine* itself is the only drug available that can activate dopamine receptors. It should be noted that, when dopamine is given to treat shock, the drug also enhances cardiac performance (because it activates beta₁ receptors in the heart).

Multiple Receptor Activation: Treatment of Anaphylactic Shock

Pathophysiology of Anaphylaxis. Anaphylactic shock is a manifestation of severe allergy. The reaction is characterized by *hypotension* (from widespread vasodilation), *bronchoconstriction*, and *edema of the glottis*. Although histamine contributes to these responses, symptoms are due largely to release of other mediators (eg, leukotrienes). Anaphylaxis can be triggered by a variety of substances, including bee venom, wasp venom, latex rubber, certain foods (eg, peanuts, shellfish), and certain drugs (eg, penicillins).

Treatment. *Epinephrine*, injected IM, is the treatment of choice for anaphylactic shock. Benefits derive from activating three types of adrenergic receptors: alpha₁, beta₁, and beta₂. By activating these receptors, epinephrine can reverse the most severe manifestations of the anaphylactic reaction. Activation of beta₁ receptors increases cardiac output, thereby helping elevate blood pressure. Blood pressure is also increased because epinephrine promotes alpha₁-mediated vasoconstriction. In addition to increasing blood pressure, vasoconstriction helps suppress glottal edema. By activating beta₂ receptors, epinephrine can counteract bronchoconstriction. Individuals who are prone to severe allergic responses should carry an epinephrine auto-injector (eg, EpiPen) at all times (Box 17-1). Antihistamines are not especially useful against anaphylaxis because histamine is only a minor contributor to the reaction.

PROPERTIES OF REPRESENTATIVE ADRENERGIC AGONISTS

Our aim in this section is to establish an overview of the adrenergic agonists. The information is presented in the form of “drug digests” that highlight characteristic features of representative sympathomimetic agents.

As noted, there are two keys to understanding individual adrenergic agonists: (1) knowledge of the receptors that the drug can activate and (2) knowledge of the therapeutic and adverse effects that receptor activation can elicit. By integrating these two types of information, you can easily predict the spectrum of effects that a particular drug can produce.

Unfortunately, knowing the effects that a drug is *capable* of producing does not always indicate how that drug is *actually used* in a clinical setting. Why? Because some adrenergic agonists are not used for all the effects they can produce. Norepinephrine, for example, can activate alpha₁ receptors and can therefore produce mydriasis. However, although NE can produce mydriasis, the drug is not actually used for this purpose. Similarly, although isoproterenol is capable of producing uterine relaxation (through beta₂ activation), isoproterenol is not employed clinically for this effect. Because receptor specificity is not always a predictor of the therapeutic applications of a particular adrenergic agonist, for each of the drugs discussed below, approved clinical applications are indicated.

Epinephrine

- **Receptor specificity:** alpha₁, alpha₂, beta₁, beta₂
- **Chemical classification:** catecholamine

Epinephrine [Adrenalin, others] was among the first adrenergic agonists employed clinically and can be considered the prototype of the sympathomimetic drugs. Because of its prototypic status, epinephrine is discussed in detail.

Therapeutic Uses

Epinephrine can activate all four subtypes of adrenergic receptors. As a consequence, the drug can produce a broad spectrum of beneficial sympathomimetic effects:

- Because it can cause alpha₁-mediated vasoconstriction, epinephrine is used to (1) delay absorption of local anesthetics, (2) control superficial bleeding, and (3) elevate blood pressure. In the past, epinephrine-induced vasoconstriction was also used for nasal decongestion.
- Activation of alpha₁ receptors on the iris can be used to produce mydriasis during ophthalmologic procedures.*
- Because it can activate beta₁ receptors, epinephrine is used to (1) overcome AV heart block and (2) restore cardiac function in patients experiencing cardiac arrest caused by asystole.
- Activation of beta₂ receptors in the lung promotes bronchodilation, which can be useful in patients with asthma (although other drugs are preferred).
- Because it can activate a combination of alpha and beta receptors, epinephrine is the treatment of choice for anaphylactic shock.

*Epinephrine for ophthalmic use is no longer available in the United States.

BOX 17-1 ■ SPECIAL INTEREST TOPIC

THE EPIPEN: DON'T LEAVE HOME WITHOUT IT!

The EpiPen is an epinephrine auto-injector, one of three brands available in the United States.* The device is indicated for emergency treatment of anaphylaxis, a life-threatening allergic reaction caused by severe hypersensitivity to insect venoms (eg, from bees, wasps, fire ants), certain foods (eg, peanuts, walnuts, shellfish), and certain drugs (especially penicillins). Every year, anaphylaxis kills about 6000 Americans: 125 who have food allergies, between 40 and 400 who have venom allergies, and over 5400 who have penicillin allergy. Could most of these deaths be avoided? Yes—through immediate injection of epinephrine. Unfortunately, many of the people at risk don't carry an epinephrine injector, and many of those who do aren't sure how to use it. So listen up: By encouraging highly allergic clients to carry an EpiPen, and by teaching them when and how to use it, you could well save someone's life.

EpiPen Description and Dosage

The EpiPen auto-injector is a single-use delivery device, featuring a spring-activated needle, designed for IM injection of epinephrine. Two strengths are available. The larger one, sold as EpiPen, delivers a 0.3-mg dose (for individuals weighing 66 pounds or more). The smaller one, sold as EpiPen Jr, delivers a 0.15-mg dose (for individuals between 33 and 66 pounds). If one injection fails to completely reverse symptoms, a second injection (using a second EpiPen) may be given. The EpiPen is available only by prescription.

EpiPen Storage and Replacement

Epinephrine is sensitive to extreme heat and light, and hence the EpiPen should be stored at room temperature in a dark place. The factory-issue storage tube provides additional protection from UV light. Refrigeration can compromise the injection mechanism, and should be avoided. If the epinephrine solution turns brown, if a precipitate forms, or if the expiration date has passed, the unit should be replaced. (The distributor offers a free service to remind patients when their EpiPen is about to expire.)

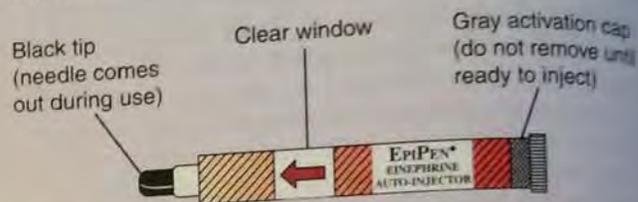
Who Should Carry an EpiPen and When Should They Use It?

Anyone who has experienced a severe, systemic allergic reaction should *always* carry at least one epinephrine auto-injector! Anaphylaxis can develop within minutes after allergen exposure. To prevent a full-blown reaction, epinephrine should be injected as soon as early symptoms appear (eg, swelling, shortness of breath). People who do not carry an EpiPen, and hence must wait for an emergency response team, greatly increase their risk of death.

What's the Self-Injection Procedure?

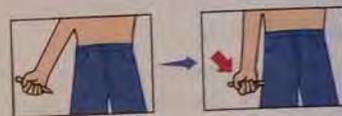
The EpiPen auto-injector is a tubular device with three prominent external features: a black tip (the needle comes out through this end), a clear window (for examining the epineph-

rine solution), and a gray cap (which prevents activation until being removed).



Injections are made into the outer thigh as follows:

1. Form a fist around the unit with the black tip pointing down.
2. With the free hand, pull off the gray activation cap.
3. Jab the device firmly into the outer thigh, at an angle perpendicular to the thigh, and hold it there for 10 seconds. (The injection may be made directly through clothing.)



4. Remove the unit and massage the area for 10 seconds to facilitate absorption.

To ensure the injection was made, examine the used EpiPen: If the needle is projecting through the black tip, the procedure was a success; if the needle is not projecting, jab the device in again. *Note:* The EpiPen contains 2 mL of epinephrine solution, but only 0.3 mL is actually injected. Hence, even after a successful injection, the device will not be empty.

What Should Be Done After the Injection?

Following epinephrine injection, it is important to get immediate medical attention. Why? Because (1) the effects of epinephrine begin to fade in 10 to 20 minutes and (2) anaphylactic reactions can be biphasic and prolonged. Accordingly, to ensure a good outcome, hospitalization (up to 6 hours) is recommended. Hospital staff should be informed that epinephrine has been injected, and should be shown the used EpiPen (to confirm the dosage). Prednisone may be given to manage delayed or persistent symptoms.

Does IM Epinephrine Have Side Effects?

Of course. The injection itself may cause discomfort, and the epinephrine may cause tachycardia, palpitations, and a feeling of nervousness. The drug may also cause sweating, dizziness, headache, nausea, and vomiting.

*In addition to the EpiPen, two other epinephrine auto-injectors—Adrenaclick and Twinject—are now available. The Adrenaclick injector is nearly identical to the EpiPen. Twinject differs from the other two products in that it can deliver two separate doses. The first dose is injected automatically just as with EpiPen and Adrenaclick. The second dose, if needed, is injected manually.

Pharmacokinetics

Absorption. Epinephrine may be administered topically or by injection. The drug cannot be given orally because, as discussed, epinephrine and other catecholamines undergo destruction by MAO and COMT before reaching the systemic circulation. Following subQ injection, absorption is slow owing to epinephrine-induced local vasoconstriction. Absorption is more rapid following IM injection.

Inactivation. Epinephrine has a short half-life because of two processes: enzymatic inactivation and uptake into adrenergic nerves. The enzymes that inactivate epinephrine and other catecholamines are MAO and COMT.

Adverse Effects

Because it can activate the four major adrenergic receptor subtypes, epinephrine can produce multiple adverse effects.

Hypertensive Crisis. Vasoconstriction secondary to excessive α_1 activation can produce a dramatic increase in blood pressure. Cerebral hemorrhage can occur. Because of the potential for severe hypertension, patients receiving *parenteral* epinephrine must undergo continuous cardiovascular monitoring.

Dysrhythmias. Excessive activation of β_1 receptors in the heart can produce dysrhythmias. Because of their sensitivity to catecholamines, hyperthyroid patients are at high risk for epinephrine-induced dysrhythmias.

Angina Pectoris. By activating β_1 receptors in the heart, epinephrine can increase cardiac work and oxygen demand. If the increase in oxygen demand is big enough, an anginal attack may ensue. Causing angina is especially likely in patients with coronary atherosclerosis.

Necrosis Following Extravasation. If an IV line containing epinephrine becomes extravasated, the resultant localized vasoconstriction may result in necrosis. Because of this possibility, patients receiving IV epinephrine should be monitored closely. If extravasation occurs, injury can be minimized by local injection of phentolamine, an alpha-adrenergic antagonist.

Hyperglycemia. In diabetic patients, epinephrine can cause hyperglycemia. How? By causing breakdown of glycogen secondary to activation of β_2 receptors in liver and skeletal muscle. If hyperglycemia develops, insulin dosage should be increased.

Drug Interactions

MAO Inhibitors. As their name implies, MAO inhibitors suppress the activity of MAO. These drugs are used primarily to treat depression (see Chapter 32). Because MAO is one of the enzymes that inactivate epinephrine and other catecholamines, inhibition of MAO will prolong and intensify epinephrine's effects. As a rule, patients receiving an MAO inhibitor should not receive epinephrine.

Tricyclic Antidepressants. Tricyclic antidepressants block the uptake of catecholamines into adrenergic neurons. Since neuronal uptake is one mechanism by which the actions of norepinephrine and other catecholamines are terminated, blocking uptake can intensify and prolong epinephrine's effects. Accordingly, patients receiving a tricyclic antidepressant may require a reduction in epinephrine dosage.

General Anesthetics. Several inhalation anesthetics render the myocardium hypersensitive to activation by β_1 agonists. When the heart is in this hypersensitive state, exposure to epinephrine and other β_1 agonists can cause tachydysrhythmias.

Alpha-Adrenergic Blocking Agents. Drugs that block alpha-adrenergic receptors can prevent receptor activation by epinephrine. Alpha blockers (eg, phentolamine) can be used to treat toxicity (eg, hypertension, local vasoconstriction) caused by excessive epinephrine-induced alpha activation.

Beta-Adrenergic Blocking Agents. Drugs that block beta-adrenergic receptors can prevent receptor activation by epinephrine. Beta-blocking agents (eg, propranolol) can reduce adverse effects (eg, dysrhythmias, anginal pain) caused by epinephrine and other β_1 agonists.

Preparations, Dosage, and Administration

Epinephrine [Adrenalin, EpiPen, Primatene Mist, others] is supplied in solution for administration by several routes: IV, IM, subQ, intracardiac, intraspinal, inhalation, and topical. As indicated in Table 17-3, the strength of the epinephrine solution employed depends on the route of administration. Note that solutions intended for *intravenous* administration are *less concentrated* than solutions intended for administration by most other routes. Why? Because *intravenous administration of a concentrated epinephrine solution can produce potentially fatal reactions* (severe dysrhythmias and hypertension). Therefore, *before you give epinephrine IV, check to ensure that the concentration is appropriate!* Aspirate prior to IM or subQ injection to avoid inadvertent injection into a vein.

Patients receiving IV epinephrine should be monitored constantly. They should be observed for signs of excessive cardiovascular activation (eg, tachydysrhythmias, hypertension) and for possible extravasation of the IV line. If systemic toxicity develops, epinephrine should be discontinued; if indicated, an alpha-adrenergic blocker, a beta-adrenergic blocker, or both should be given to suppress symptoms. If an epinephrine-containing IV line becomes extravasated, administration should be discontinued and the region of extravasation infiltrated with an alpha-adrenergic blocker.

Treatment of anaphylaxis using an epinephrine auto-injector [EpiPen, Twinject, Adrenaclick] is discussed in Box 17-1.

Norepinephrine

- *Receptor specificity:* α_1 , α_2 , β_1
- *Chemical classification:* catecholamine

Norepinephrine [Levophed] is similar to epinephrine in several respects. With regard to receptor specificity, NE differs from epinephrine only in that NE does not activate β_2 receptors. Accordingly, NE can elicit all of the responses that epinephrine can, except those that are β_2 mediated. Because NE is a catecholamine, the drug is subject to rapid inactivation by MAO and

TABLE 17-3 ■ Epinephrine Solutions: Concentrations for Different Routes of Administration

Concentration of Epinephrine Solution	Route of Administration
1% (1:100)	Oral inhalation
0.1% (1:1000)	Subcutaneous Intramuscular Intraspinal
0.01% (1:10,000)	Intravenous Intracardiac
0.001% (1:100,000)	In combination with local anesthetics

COMT, and hence cannot be given orally. Adverse effects are nearly identical to those of epinephrine: tachydysrhythmias, angina, hypertension, and local necrosis upon extravasation. In contrast to epinephrine, NE does not promote hyperglycemia, a response that is β_2 mediated. As with epinephrine, responses to NE can be modified by MAO inhibitors, tricyclic antidepressants, general anesthetics, and adrenergic blocking agents.

Despite its similarity to epinephrine, NE has limited clinical applications. The only recognized indications are *hypotensive states* and *cardiac arrest*.

Norepinephrine is supplied in solution (1 mg/mL) for administration by IV infusion only. Never leave the patient unattended. Monitor cardiovascular status continuously. Take care to avoid extravasation.

Isoproterenol

- *Receptor specificity:* β_1 and β_2
- *Chemical classification:* catecholamine

Isoproterenol (formerly available as *Isuprel*) differs significantly from NE and epinephrine in that isoproterenol acts only at beta-adrenergic receptors. Isoproterenol was the first beta-selective agent employed clinically and will serve as our prototype of the beta-selective adrenergic agonists.

Therapeutic Uses

Cardiovascular. By activating β_1 receptors in the heart, isoproterenol can benefit patients with cardiovascular disorders. Specifically, it can help overcome AV heart block, restart the heart following cardiac arrest, and increase cardiac output during shock.

Bronchospasm. Although isoproterenol is no longer used for asthma, it is used to treat bronchospasm during anesthesia. Benefits derive from activating β_2 receptors in the lung.

Asthma. By activating β_2 receptors in the lung, isoproterenol can cause bronchodilation, thereby decreasing airway resistance. Following its introduction, isoproterenol became a mainstay of asthma therapy. However, because we now have even more selective beta-adrenergic agonists (ie, drugs that activate β_2 receptors only), use of isoproterenol for asthma has been abandoned.

Adverse Effects

Because isoproterenol does not activate alpha-adrenergic receptors, it produces fewer adverse effects than NE or epinephrine. The major undesired responses, caused by activating β_1 receptors in the heart, are *tachydysrhythmias* and *angina pectoris*. In diabetic patients, isoproterenol can cause *hyperglycemia* (by promoting β_2 -mediated glycogenolysis).

Drug Interactions

The major drug interactions of isoproterenol are nearly identical to those of epinephrine. Effects are enhanced by MAO inhibitors and tricyclic antidepressants and reduced by beta-adrenergic blocking agents. Like epinephrine, isoproterenol can cause dysrhythmias in patients receiving certain inhalation anesthetics.

Preparations and Administration

Isoproterenol hydrochloride is available in solution (0.2 and 0.02 mg/mL) for parenteral administration.

When used to *stimulate the heart*, isoproterenol can be administered IV and IM and by intracardiac injection. The dosage for IM administration is about 10 times greater than the dosage employed for the other two routes.

When used to relieve *bronchospasm*, isoproterenol is administered IV.

Dopamine

- *Receptor specificity:* dopamine, β_1 , and, at high doses, α_1
- *Chemical classification:* catecholamine

Receptor Specificity

Dopamine has *dose-dependent* receptor specificity. When administered in low therapeutic doses, dopamine acts on dopamine receptors only. At moderate therapeutic doses, dopamine activates β_1 receptors in addition to dopamine receptors. And at very high doses, dopamine activates alpha receptors along with β_1 and dopamine receptors.

Therapeutic Uses

Shock. The major indication for dopamine is shock. Benefits derive from effects on the heart and renal blood vessels. By activating β_1 receptors in the heart, dopamine can increase cardiac output, thereby improving tissue perfusion. By activating dopamine receptors in the kidney, dopamine can dilate renal blood vessels, thereby improving renal perfusion. Success can be evaluated by monitoring output of urine.

Heart Failure. Heart failure is characterized by reduced tissue perfusion secondary to reduced cardiac output. Dopamine can help alleviate symptoms by activating β_1 receptors on the heart, which increases myocardial contractility, and thereby increases cardiac output.

Acute Renal Failure. Because of its ability to increase renal blood flow and urine output, low-dose dopamine has long been used in efforts to preserve renal function in patients with evolving acute renal failure (ARF). However, we now have evidence that the drug is not effective: In patients with early ARF, dopamine failed to protect renal function, shorten hospital stays, or reduce the number of patients needing a kidney transplant. Accordingly, it would appear that it is time to abandon low-dose dopamine as a treatment for ARF.

Adverse Effects

The most common adverse effects of dopamine—*tachycardia*, *dysrhythmias*, and *anginal pain*—result from activation of β_1 receptors in the heart. Because of its cardiac actions, dopamine is contraindicated for patients with tachydysrhythmias or ventricular fibrillation. Since high concentrations of dopamine cause α_1 activation, extravasation may result in *necrosis* from localized vasoconstriction. Tissue injury can be minimized by local infiltration of phentolamine, an alpha-adrenergic antagonist.

Drug Interactions

MAO inhibitors can intensify the effects of dopamine on the heart and blood vessels. If a patient is receiving an MAO inhibitor, the dosage of dopamine must be reduced by at least 90%. Tricyclic antidepressants can also intensify dopamine's actions, but not to the extent seen with MAO inhibitors. Certain general anesthetics can sensitize the myocardium to stimulation by dopamine and other catecholamines, thereby increasing the risk of dysrhythmias. Diuretics can complement the beneficial effects of dopamine on the kidney.

Preparations, Dosage, and Administration

Preparations. Dopamine hydrochloride is supplied in aqueous solutions that range in concentration from 0.8 to 160 mg/mL.

Dosage. Concentrated solutions must be diluted prior to infusion. For treatment of shock, a concentration of 400 mcg/mL can be used. The recommended initial rate of infusion is 2 to 5 mcg/kg/min. If needed, the infusion rate can be gradually increased to a maximum of 20 to 50 mcg/kg/min.

Administration. Dopamine is administered IV. Because of extremely rapid inactivation by MAO and COMT, the drug must be given by *continuous infusion*. A metering device is needed to control flow rate. Cardiovascular

status must be closely monitored. If extravasation occurs, the infusion should be stopped and the affected area infiltrated with an alpha-adrenergic antagonist (eg, phentolamine).

Dobutamine

- *Receptor specificity:* beta₁
- *Chemical classification:* catecholamine

Actions and Uses. At therapeutic doses, dobutamine causes selective activation of beta₁-adrenergic receptors. The only indication for the drug is heart failure.

Adverse Effects. The major adverse effect is tachycardia. Blood pressure and the electrocardiogram (ECG) should be monitored closely.

Drug Interactions. Effects of dobutamine on the heart and blood vessels are intensified greatly by MAO inhibitors. Accordingly, in patients receiving an MAO inhibitor, dobutamine dosage must be reduced at least 90%. Concurrent use of tricyclic antidepressants may cause a moderate increase in the cardiovascular effects. Certain general anesthetics can sensitize the myocardium to stimulation by dobutamine, thereby increasing the risk of dysrhythmias.

Preparations, Dosage, and Administration. Dobutamine hydrochloride is supplied in concentrated and dilute solutions. The concentrated solution (12.5 mg/mL in 20- and 40-mL vials) must be diluted prior to use. The dilute solutions (1, 2, and 4 mg/mL in 250-mL single-use containers) can be used as is. Because of rapid inactivation by MAO and COMT, dobutamine is administered by continuous IV infusion. The usual rate is 2.5 to 10 mcg/kg/min.

Phenylephrine

- *Receptor specificity:* alpha₁
- *Chemical classification:* noncatecholamine

Phenylephrine [Neo-Synephrine, others] is a selective alpha₁ agonist. The drug can be administered locally to reduce nasal congestion and parenterally to elevate blood pressure. In addition, phenylephrine eye drops can be used to dilate the pupil. Also, phenylephrine can be coadministered with local anesthetics to retard anesthetic absorption.

Albuterol

- *Receptor specificity:* beta₂
- *Chemical classification:* noncatecholamine

Therapeutic Uses

Asthma. Albuterol [Ventolin, VoSpire, others] can reduce airway resistance in asthma by causing beta₂-mediated bronchodilation. Because albuterol is “selective” for beta₂ receptors, it produces much less activation of cardiac beta₁ receptors than does isoproterenol. As a result, albuterol and other beta₂-selective agents have replaced isoproterenol for therapy of asthma. Remember, however, that receptor selectivity is only relative: If administered in large doses, albuterol will lose selectivity and activate beta₁ receptors as well as beta₂ receptors. Accordingly, patients should be warned not to exceed recommended doses, since doing so may cause undesired cardiac stimulation. Preparations and dosages for asthma are presented in Chapter 76.

Adverse Effects

Adverse effects are minimal at therapeutic doses. *Tremor* is most common. If dosage is excessive, albuterol can cause *tachycardia* by activating beta₁ receptors in the heart.

Ephedrine

- *Receptor specificity:* alpha₁, alpha₂, beta₁, beta₂
- *Chemical classification:* noncatecholamine

Ephedrine is referred to as a *mixed-acting drug*, because it activates adrenergic receptors by direct and indirect mechanisms. *Direct* activation results from binding of the drug to alpha and beta receptors. *Indirect* activation results from release of NE from adrenergic neurons.

Owing to the development of more selective adrenergic agonists, uses for ephedrine are limited. By promoting beta₂-mediated bronchodilation, ephedrine can benefit patients with *asthma*. By activating a combination of alpha and beta receptors, ephedrine can improve hemodynamic status in patients with *shock*. In the past, the drug was used for nasal decongestion.

Because ephedrine activates the same receptors as epinephrine, both drugs share the same adverse effects: hypertension, dysrhythmias, angina, and hyperglycemia. In addition, because ephedrine can cross the blood-brain barrier, it can act in the CNS to cause insomnia.

DISCUSSION OF ADRENERGIC AGONISTS IN OTHER CHAPTERS

All of the drugs presented in this chapter are discussed again in chapters that address specific applications. For example, the use of alpha₁ agonists to relieve nasal congestion is discussed in Chapter 77. Table 17-4 summarizes the chapters in which adrenergic agonists are discussed again.

TABLE 17-4 ■ Discussion of Adrenergic Agonists in Other Chapters

Drug Class	Discussion Topic	Chapter
Alpha ₁ Agonists	Nasal congestion	77
	Ophthalmology	104
Alpha ₂ Agonists	Cardiovascular effects	19
	Pain relief	28
	Hypertension	47
	Ophthalmology	104
Beta ₁ Agonists	Heart failure	48
Beta ₂ Agonists	Asthma	76
	Preterm labor	64
Amphetamines	Basic pharmacology	36
	Attention-deficit/hyperactivity disorder	36
	Drug abuse	40
	Appetite suppression	82

KEY POINTS

- Adrenergic agonists are also known as *sympathomimetics*. Why? Because their effects mimic those caused by the sympathetic nervous system.
- Most adrenergic agonists act by direct activation of adrenergic receptors. A few act by indirect mechanisms: promotion of norepinephrine release, blockade of norepinephrine uptake, and inhibition of norepinephrine breakdown.
- Adrenergic agonists fall into two chemical classes: catecholamines and noncatecholamines.
- Agents in the catecholamine family cannot be taken orally (because of destruction by MAO and COMT), have a brief duration of action (because of destruction by MAO and COMT), and cannot cross the blood-brain barrier (because they are polar molecules).
- Adrenergic agonists that are noncatecholamines can be taken orally, have a longer duration than the catecholamines, and can cross the blood-brain barrier.
- Activation of α_1 receptors causes vasoconstriction and mydriasis.
- α_1 agonists are used for hemostasis, nasal decongestion, and elevation of blood pressure, and as adjuncts to local anesthetics.
- Major adverse effects that can result from α_1 activation are hypertension and local necrosis (if extravasation occurs).
- Activation of α_2 receptors in the periphery is of minimal clinical significance. In contrast, drugs that activate α_2 receptors in the CNS produce useful effects (see Chapters 19 and 28).
- All of the clinically relevant responses to activation of β_1 receptors result from activating β_1 receptors in the heart.
- Activation of cardiac β_1 receptors increases heart rate, force of contraction, and conduction through the AV node.
- Drugs that activate β_1 receptors can be used to treat heart failure, AV block, and cardiac arrest caused by asystole.
- Potential adverse effects from β_1 activation are tachycardia, dysrhythmias, and angina.
- Drugs that activate β_2 receptors are used primarily for asthma.
- Principal adverse effects from β_2 activation are hyperglycemia (mainly in diabetic patients) and tremor.
- Activation of dopamine receptors dilates renal blood vessels, which helps maintain renal perfusion in shock.
- Epinephrine is a catecholamine that activates α_1 , α_2 , β_1 , and β_2 receptors.
- Epinephrine is the drug of choice for treating anaphylactic shock: By activating α_1 , β_1 , and β_2 receptors, epinephrine can elevate blood pressure, suppress glottal edema, and counteract bronchoconstriction.
- Epinephrine can also be used to control superficial bleeding, restart the heart after cardiac arrest, and delay absorption of local anesthetics.
- Epinephrine should not be combined with MAO inhibitors, and should be used cautiously in patients taking tricyclic antidepressants.
- Isoproterenol is a catecholamine that activates β_1 and β_2 receptors.
- Isoproterenol can be used to enhance cardiac performance (by activating β_1 receptors) and to treat bronchospasm (by activating β_2 receptors).
- Dopamine is a catecholamine whose receptor specificity is highly dose dependent: at low therapeutic doses, dopamine acts on dopamine receptors only; at moderate doses, dopamine activates β_1 receptors in addition to dopamine receptors; and at high doses, dopamine activates α_1 receptors along with β_1 receptors and dopamine receptors.
- Albuterol is a noncatecholamine that produces selective activation of β_2 receptors.
- Albuterol is used to treat asthma.
- Because albuterol is “selective” for β_2 receptors, it produces much less stimulation of the heart than does isoproterenol. Accordingly, albuterol and related drugs have replaced isoproterenol for therapy of asthma.

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Summary of Major Nursing Implications

EPINEPHRINE

Preadministration Assessment

Therapeutic Goal

Epinephrine has multiple indications. The major use is treatment of *anaphylaxis*. Other uses include *control of superficial bleeding*, *delay of local anesthetic absorption*, and *management of cardiac arrest*.

Identifying High-Risk Patients

Epinephrine must be used with *great caution* in patients with hyperthyroidism, cardiac dysrhythmias, organic heart disease, or hypertension. *Caution* is also needed in patients with angina pectoris or diabetes and in those receiving MAO inhibitors, tricyclic antidepressants, or general anesthetics.

Summary of Major Nursing Implications—cont'd

Implementation: Administration

Routes

Topical, inhalation, and parenteral (IV, IM, subQ, intracardiac, intraspinal). Rapid inactivation by MAO and COMT prohibits oral use.

Administration

The concentration of epinephrine solutions varies according to the route of administration (see Table 17-3). To avoid serious injury, check solution strength to ensure that the concentration is appropriate for the intended route. Aspirate prior to IM and subQ administration to avoid inadvertent injection into a vein.

Epinephrine solutions oxidize over time, causing them to turn pink or brown. Discard discolored solutions.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

In patients receiving IV epinephrine, monitor cardiovascular status continuously.

Minimizing Adverse Effects

Cardiovascular Effects. By stimulating the heart, epinephrine can cause *anginal pain*, *tachycardia*, and *dysrhythmias*. These responses can be reduced with a beta-adrenergic blocking agent (eg, propranolol).

By activating alpha₁ receptors on blood vessels, epinephrine can cause intense vasoconstriction, which can result in *severe hypertension*. Blood pressure can be lowered with an alpha-adrenergic blocking agent (eg, phentolamine).

Necrosis. If an IV line delivering epinephrine becomes extravasated, necrosis may result. Exercise care to avoid extravasation. If extravasation occurs, infiltrate the region with phentolamine to minimize injury.

Hyperglycemia. Epinephrine may cause hyperglycemia in diabetic patients. If hyperglycemia develops, insulin dosage should be increased.

Minimizing Adverse Interactions

MAO Inhibitors and Tricyclic Antidepressants. These drugs prolong and intensify the actions of epinephrine. Patients taking these antidepressants require a reduction in epinephrine dosage.

General Anesthetics. When combined with certain general anesthetics, epinephrine can induce cardiac dysrhythmias. Dysrhythmias may respond to a beta₁-adrenergic blocker.

DOBUTAMINE

Preadministration Assessment

Therapeutic Goal

Dobutamine is used to improve hemodynamic status in patients with *shock* or *heart failure*. Benefits derive from enhanced cardiac performance and increased renal perfusion.

Summary of Major Nursing Implications—cont'd

DOBUTAMINE

Preadministration Assessment

Improvement of hemodynamic status in patients with heart failure.

Baseline Data

Full assessment of cardiac, renal, and hemodynamic status is needed.

Identifying High-Risk Patients

Use with *great caution* in patients with organic heart disease, hyperthyroidism, tachydysrhythmias, or hypertension and in those taking an MAO inhibitor. *Caution* is also needed in patients with angina pectoris and in those receiving tricyclic antidepressants or general anesthetics.

Implementation: Administration

Route

Intravenous.

Administration

Administer by continuous IV infusion. Dilute concentrated solutions prior to use. Infusion rates usually range from 2.5 to 10 mcg/kg/min. Adjust the infusion rate on the basis of the cardiovascular response.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor cardiac function (heart rate, ECG), blood pressure, and urine output. When possible, monitor central venous pressure and pulmonary wedge pressure.

Minimizing Adverse Effects

Major adverse effects are *tachycardia* and *dysrhythmias*. Monitor the ECG and blood pressure closely. Adverse cardiac effects can be reduced with a beta-adrenergic antagonist.

Minimizing Adverse Interactions

MAO Inhibitors. Concurrent use of an MAO inhibitor with dobutamine can cause severe cardiovascular toxicity. If a patient is taking an MAO inhibitor, dobutamine dosage must be reduced by at least 90%.

Tricyclic Antidepressants. These drugs can prolong and intensify the actions of dobutamine. Patients receiving them may require a reduction in dobutamine dosage.

General Anesthetics. When combined with certain general anesthetics, dobutamine can cause cardiac dysrhythmias. These may respond to a beta₁-adrenergic antagonist.

ALPHA-ADRENERGIC ANTAGONISTS

Therapeutic and Adverse Responses to Alpha Blockade

Therapeutic Applications of Alpha Blockade

Adverse Effects of Alpha Blockade

Properties of Individual Alpha Blockers

Prazosin

Terazosin

Doxazosin

Tamsulosin

Alfuzosin

Silodosin

Phentolamine

Phenoxybenzamine

BETA-ADRENERGIC ANTAGONISTS

Therapeutic and Adverse Responses to Beta Blockade

Therapeutic Applications of Beta Blockade

Adverse Effects of Beta Blockade

Properties of Individual Beta Blockers

Propranolol

Metoprolol

Other Beta-Adrenergic Blockers

The adrenergic antagonists cause direct blockade of adrenergic receptors. With one exception, all of the adrenergic antagonists produce *reversible* (competitive) blockade.

Unlike many adrenergic agonists, which act at alpha- and beta-adrenergic receptors, most adrenergic antagonists are more selective. As a result, the adrenergic antagonists can be neatly divided into two major groups: (1) *alpha-adrenergic blocking agents* (drugs that produce selective blockade of alpha-adrenergic receptors); and (2) *beta-adrenergic blocking agents* (drugs that produce selective blockade of beta receptors).^{*} Members of these two groups are listed in Table 18-1.

Our approach to the adrenergic antagonists mirrors the approach we took with the adrenergic agonists. That is, we begin by discussing the therapeutic and adverse effects that can result from alpha- and beta-adrenergic blockade, after which we discuss the individual drugs that produce receptor blockade.

Remember that it is much easier to understand responses to the adrenergic drugs if you first understand the responses to activation of adrenergic receptors. Accordingly, if you have not yet mastered (memorized) Table 13-3, you should do so now (or at least be prepared to consult the table as we proceed).

^{*}Only two adrenergic antagonists—carvedilol and labetalol—act at alpha and beta receptors.

TABLE 18-1 ■ Receptor Specificity of Adrenergic Antagonists

Category	Drugs	Receptors Blocked
Alpha-Adrenergic Blocking Agents		
Nonselective Agents	Phenoxybenzamine	alpha ₁ , alpha ₂
	Phentolamine	alpha ₁ , alpha ₂
Alpha ₁ -Selective Agents	Alfuzosin	alpha ₁
	Doxazosin	alpha ₁
	Prazosin	alpha ₁
	Silodosin	alpha ₁
	Tamsulosin	alpha ₁
Terazosin	alpha ₁	
Beta-Adrenergic Blocking Agents		
Nonselective Agents	Carteolol	beta ₁ , beta ₂
	Nadolol	beta ₁ , beta ₂
	Penbutolol	beta ₁ , beta ₂
	Pindolol	beta ₁ , beta ₂
	Propranolol	beta ₁ , beta ₂
	Sotalol	beta ₁ , beta ₂
	Timolol	beta ₁ , beta ₂
	Carvedilol	beta ₁ , beta ₂ , alpha ₁
	Labetalol	beta ₁ , beta ₂ , alpha ₁
Beta ₁ -Selective Agents	Acebutolol	beta ₁
	Atenolol	beta ₁
	Betaxolol	beta ₁
	Bisoprolol	beta ₁
	Esmolol	beta ₁
	Metoprolol	beta ₁
	Nebivolol	beta ₁

ALPHA-ADRENERGIC ANTAGONISTS**THERAPEUTIC AND ADVERSE RESPONSES TO ALPHA BLOCKADE**

In this section we discuss the beneficial and adverse responses that can result from blockade of alpha-adrenergic receptors. Properties of individual alpha-blocking agents are discussed after that.

Therapeutic Applications of Alpha Blockade

Most of the clinically useful responses to alpha-adrenergic antagonists result from blockade of alpha₁ receptors on blood vessels. Blockade of alpha₁ receptors in the bladder and prostate can help men with benign prostatic hyperplasia (BPH). Blockade of alpha₁ receptors in the eye and blockade of alpha₂ receptors have no recognized therapeutic applications.

Essential Hypertension. Hypertension (high blood pressure) can be treated with a variety of drugs, including the al-

pha-adrenergic antagonists. Alpha antagonists lower blood pressure by blocking alpha₁ receptors on arterioles and veins, causing vasodilation. Dilation of arterioles reduces arterial pressure directly. Dilation of veins lowers arterial pressure by an indirect process: In response to venous dilation, return of blood to the heart decreases, thereby decreasing cardiac output, which in turn reduces arterial pressure. The role of alpha-adrenergic blockers in essential hypertension is discussed further in Chapter 47 (Drugs for Hypertension).

Reversal of Toxicity from Alpha₁ Agonists. Overdose with an alpha-adrenergic agonist (eg, epinephrine) can produce *hypertension* secondary to excessive activation of alpha₁ receptors on blood vessels. When this occurs, blood pressure can be lowered by reversing the vasoconstriction with an alpha-blocking agent.

If an IV line containing an alpha agonist becomes extravasated, necrosis can occur secondary to intense local vasoconstriction. By infiltrating the region with phentolamine (an alpha-adrenergic antagonist), we can block the vasoconstriction and thereby prevent injury.

Benign Prostatic Hyperplasia. BPH results from proliferation of cells in the prostate gland. Symptoms include dysuria, increased frequency of daytime urination, nocturia, urinary hesitance and intermittence, urinary urgency, a sensation of incomplete voiding, and a reduction in the size and force of the urinary stream. All of these symptoms can be improved with drugs that block alpha₁ receptors. Benefits derive from reduced contraction of smooth muscle in the prostatic capsule and the bladder neck (trigone and sphincter). BPH is discussed at length in Chapter 66.

Pheochromocytoma. A pheochromocytoma is a catecholamine-secreting tumor derived from cells of the sympathetic nervous system. These tumors are usually located in the adrenal medulla. If secretion of catecholamines (epinephrine, norepinephrine) is sufficiently great, persistent hypertension can result. The principal cause of hypertension is activation of alpha₁ receptors on blood vessels, although activation of beta₁ receptors on the heart can also contribute. The preferred treatment is surgical removal of the tumor, but alpha-adrenergic blockers may also be employed.

Alpha-blocking agents have two roles in managing pheochromocytoma. First, in patients with inoperable tumors, alpha blockers are given chronically to suppress hypertension. Second, when surgery is indicated, alpha blockers are administered preoperatively to reduce the risk of acute hypertension during the procedure. (The surgical patient is at risk because manipulation of the tumor can cause massive catecholamine release.)

Raynaud's Disease. Raynaud's disease is a peripheral vascular disorder characterized by vasospasm in the toes and fingers. Prominent symptoms are local sensations of pain and cold. Alpha blockers can suppress symptoms by preventing alpha-mediated vasoconstriction. It should be noted, however, that although alpha blockers can relieve symptoms of Raynaud's disease, they are generally ineffective against other peripheral vascular disorders that involve inappropriate vasoconstriction.

Adverse Effects of Alpha Blockade

The most significant adverse effects of the alpha-adrenergic antagonists result from blockade of alpha₁ receptors. Detrimental effects associated with alpha₂ blockade are minor.

Adverse Effects of Alpha₁ Blockade

Orthostatic Hypotension. Orthostatic hypotension is the most serious adverse response to alpha-adrenergic blockade. This hypotension can reduce blood flow to the brain, thereby causing dizziness, lightheadedness, and even syncope (fainting).

The cause of hypotension is blockade of alpha receptors on veins, which reduces muscle tone in the venous wall. Because of reduced venous tone, blood tends to pool (accumulate) in veins when the patient assumes an erect posture. As a result, return of blood to the heart is reduced, which decreases cardiac output, which in turn causes blood pressure to fall.

Patients should be informed about symptoms of hypotension (lightheadedness, dizziness) and advised to sit or lie down if these occur. In addition, patients should be informed that orthostatic hypotension can be minimized by avoiding abrupt transitions from a supine or sitting position to an erect posture.

Reflex Tachycardia. Alpha-adrenergic antagonists can increase heart rate by triggering the baroreceptor reflex. The mechanism is this: (1) blockade of vascular alpha₁ receptors causes vasodilation; (2) vasodilation reduces blood pressure; and (3) baroreceptors sense the reduction in blood pressure and, in an attempt to restore normal pressure, initiate a reflex increase in heart rate via the autonomic nervous system. If necessary, reflex tachycardia can be suppressed with a beta-adrenergic blocking agent.

Nasal Congestion. Alpha blockade can dilate the blood vessels of the nasal mucosa, producing nasal congestion.

Inhibition of Ejaculation. Since activation of alpha₁ receptors is required for ejaculation (see Table 13-3), blockade of these receptors can cause impotence. This form of drug-induced impotence is reversible and resolves when the alpha blocker is withdrawn.

The ability of alpha blockers to inhibit ejaculation can be a major reason for nonadherence to the prescribed regimen. If a patient deems the adverse sexual effects of alpha blockade unacceptable, a change in medication will be required. Because males may be reluctant to discuss such concerns, a tactful interview may be needed to discern if drug-induced impotence is discouraging drug use.

Sodium Retention and Increased Blood Volume. By reducing blood pressure, alpha blockers can promote renal retention of sodium and water, thereby causing blood volume to increase. The steps in this process are as follows: (1) by reducing blood pressure, alpha₁ blockers decrease renal blood flow; (2) in response to reduced perfusion, the kidney excretes less sodium and water; and (3) the resultant retention of sodium and water increases blood volume. As a result, blood pressure is elevated, blood flow to the kidney is increased, and, as far as the kidney is concerned, all is well. Unfortunately, when alpha blockers are used to treat hypertension (which they often are), this compensatory elevation in blood pressure can negate beneficial effects. In order to prevent the kidney from "neutralizing" hypertensive actions, alpha-blocking agents are usually combined with a diuretic when used in patients with hypertension.

Adverse Effects of Alpha₂ Blockade

The most significant adverse effect associated with alpha₂ blockade is potentiation of the reflex tachycardia that can occur in response to blockade of alpha₁ receptors. Why does alpha₂ blockade intensify reflex tachycardia? Recall that peripheral alpha₂ receptors are located presynaptically and that activation of these receptors inhibits norepinephrine release. Hence, if alpha₂ receptors are blocked, release of norepinephrine will increase. Since the reflex tachycardia caused by alpha₁ blockade is ultimately the result of increased firing of the sympathetic nerves to the heart, and since alpha₂ blockade will cause each nerve impulse to release a greater amount of norepinephrine, alpha₂ blockade will potentiate reflex tachycardia initiated by blockade of alpha₁ receptors. Accordingly, drugs such as phentolamine, which block alpha₂ as well as alpha₁ receptors, cause greater reflex tachycardia than do drugs that block alpha₁ receptors only.

PROPERTIES OF INDIVIDUAL ALPHA BLOCKERS

Eight alpha-adrenergic antagonists are employed clinically. Because the alpha blockers often cause postural hypotension, therapeutic uses are limited.

As indicated in Table 18-1, the alpha-adrenergic blocking agents can be subdivided into two major groups. One group, represented by *prazosin*, contains drugs that produce *selective alpha₁ blockade*. The second group, represented by *phentolamine*, consists of *nonselective alpha blockers*, which block alpha₁ and alpha₂ receptors.

Prazosin

Actions and Uses. Prazosin [Minipress] is a competitive antagonist that produces selective blockade of alpha₁-adrenergic receptors. The result is dilation of arterioles and veins, and relaxation of smooth muscle in the bladder neck (trigone and sphincter) and prostatic capsule. Prazosin is approved only for hypertension. However, it can also benefit men with BPH.

Pharmacokinetics. Prazosin is administered orally. Antihypertensive effects peak in 1 to 3 hours and persist for 10 hours. The drug undergoes extensive hepatic metabolism followed by excretion in the bile. Only 10% is eliminated in the urine. The half-life is 2 to 3 hours.

Adverse Effects. Blockade of alpha₁ receptors can cause *orthostatic hypotension*, *reflex tachycardia*, *inhibition of ejaculation*, and *nasal congestion*. The most serious of these is hypotension. Patients should be educated about the symptoms of hypotension (dizziness, lightheadedness) and advised to sit or lie down if they occur. Also, patients should be informed that orthostatic hypotension can be minimized by moving slowly when changing from a supine or sitting position to an upright position.

About 1% of patients lose consciousness 30 to 60 minutes after receiving their initial prazosin dose. This "first-dose" effect is the result of severe postural hypotension. To minimize the first-dose effect, the initial dose should be small (1 mg or less). Subsequent doses can be gradually increased with little risk of fainting. Patients who are starting treatment should be forewarned about the first-dose effect and advised to avoid driving and other hazardous activities for 12 to 24 hours. Administering the initial dose at bedtime eliminates the risk of a first-dose effect.

Preparations, Dosage, and Administration. Prazosin hydrochloride (Minipress) is available in capsules (1, 2, and 5 mg) for oral use. The initial adult dosage for hypertension is 1 mg 2 or 3 times a day. The maintenance dosage is 6 to 15 mg/day taken in divided doses.

Terazosin

Actions and Uses. Like prazosin, terazosin [Hytrin] is a selective, competitive antagonist at alpha₁-adrenergic receptors. The drug is approved for hypertension and BPH. Use in BPH is discussed further in Chapter 66.

Pharmacokinetics. Peak effects develop 1 to 2 hours after oral dosing. The drug's half-life is prolonged (9 to 12 hours), allowing benefits to be maintained with just one dose a day. Terazosin undergoes hepatic metabolism followed by excretion in the bile and urine.

Adverse Effects. Like other alpha-blocking agents, terazosin can cause *orthostatic hypotension*, *reflex tachycardia*, and *nasal congestion*. In addition, terazosin is associated with a high incidence (16%) of *headache*. As with prazosin, the first dose can cause profound hypotension. To minimize this first-dose effect, the initial dose should be administered at bedtime.

Preparations, Dosage, and Administration. Terazosin [Hytrin] is available in tablets and capsules (1, 2, 5, and 10 mg). Antihypertensive therapy is initiated with a 1-mg dose, administered at bedtime to minimize the

first-dose effect. Dosage can be gradually increased as needed and tolerated. The recommended dosage range for maintenance therapy is 1 to 5 mg once daily. Dosing for *benign prostatic hyperplasia* is similar to that for hypertension, except that the maintenance dosage is 10 mg/day for most men.

Doxazosin

Actions and Uses. Doxazosin [Cardura] is a selective, competitive inhibitor of alpha₁-adrenergic receptors. The drug is indicated for hypertension and BPH. Use in BPH is discussed in Chapter 66.

Pharmacokinetics. Doxazosin is administered orally, and peak effects develop in 2 to 3 hours. Its half-life is prolonged (22 hours), so once-a-day dosing is adequate. In the blood, most (98%) of the drug is protein bound. Doxazosin undergoes extensive hepatic metabolism followed by biliary excretion.

Adverse Effects. Like prazosin and terazosin, doxazosin can cause *orthostatic hypotension*, *reflex tachycardia*, and *nasal congestion*. As with prazosin and terazosin, the first dose can cause profound hypotension, which can be minimized by giving the initial dose at bedtime.

Preparations, Dosage, and Administration. Doxazosin is available in two oral formulations: immediate-release tablets (1, 2, 4, and 8 mg), marketed as Cardura, and sustained-release tablets (4 and 8 mg), marketed as Cardura XL. Cardura is approved for hypertension and BPH, whereas Cardura XL is approved for BPH only.

Dosage Using Cardura. The initial dosage for hypertension or BPH is 1 mg once a day. The dosage may be gradually increased as needed, up to a maximum of 16 mg once daily for hypertension or 8 mg once daily for BPH.

Dosage Using Cardura XL. The initial dosage (for BPH) is 4 mg once a day administered with breakfast. If needed, the dosage may be increased to 8 mg once daily 3 to 4 weeks later.

Tamsulosin

Actions and Uses. Tamsulosin [Flomax] is an alpha₁-adrenergic antagonist that causes "selective" blockade of alpha₁ receptors on smooth muscle of the bladder neck (trigone and sphincter), prostatic capsule, and prostatic urethra; blockade of vascular alpha₁ receptors is weak. The drug is approved only for BPH. It is not useful for hypertension. In men with BPH, tamsulosin increases urine flow rate and decreases residual urine volume. Maximum benefits develop within 2 weeks. Use in BPH is discussed further in Chapter 66.

Pharmacokinetics. Tamsulosin is administered orally, and absorption is slow. Food further decreases the rate and extent of absorption. The drug is metabolized in the liver and excreted in the urine.

Adverse Effects. The most common adverse effects are *headache* (20%) and *dizziness* (15%). Between 8% and 18% of patients experience *abnormal ejaculation* (ejaculation failure, ejaculation decrease, retrograde ejaculation). In addition, the drug is associated with increased incidence of *infection*. Because relaxation of vascular smooth muscle is relatively weak, the risk of orthostatic hypotension is much lower than with most other alpha blockers.

Drug Interactions. Combined use with cimetidine increases tamsulosin serum levels, which may cause toxicity. Combined use with hypotensive drugs—including sildenafil [Viagra] and related agents—may cause a significant reduction in blood pressure.

Preparations, Dosage, and Administration. Tamsulosin is available alone in 0.4-mg capsules sold as *Flomax*, and combined with dutasteride (0.4 mg tamsulosin/0.5 mg dutasteride) in capsules sold as *Jalyn*. The usual dosage is 0.4 mg once a day, administered 30 minutes after the same meal each day.

Alfuzosin

Actions and Uses. Like tamsulosin, alfuzosin [Uroxatral, Xatral[♦]] is an alpha₁ blocker with selectivity for alpha₁ receptors in the prostate and urinary tract. At recommended doses, blockade of alpha₁ receptors on blood vessels is weak. Alfuzosin is indicated only for BPH. The drug is of no use for hypertension. Use in BPH is discussed further in Chapter 66.

Pharmacokinetics. Alfuzosin is formulated in extended-release tablets, and hence absorption is slow. Plasma levels peak 8 hours after dosing. Bioavailability is 49%. Alfuzosin undergoes extensive hepatic metabolism, primarily by CYP3A4, an isozyme of cytochrome P450. Most (70%) of each dose is eliminated in the feces as inactive metabolites. A small fraction leaves unchanged in the urine. The half-life is 10 hours.

In patients with moderate to severe hepatic impairment, alfuzosin levels increase three- to fourfold. Accordingly, the drug is contraindicated for these patients.

Adverse Effects. Alfuzosin is generally well tolerated. The most common adverse effect is *dizziness* (5%). Syncope and clinically significant hypotension are rare. Unlike tamsulosin, alfuzosin does not interfere with ejaculation. Doses 4 times greater than recommended can prolong the QT interval, and might thereby pose a risk of ventricular dysrhythmias.

Drug Interactions. Levels of alfuzosin are markedly raised by powerful inhibitors of CYP3A4. Among these are erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, and the HIV protease inhibitors, such as zidovudine. Concurrent use of alfuzosin with these drugs is contraindicated.

Although alfuzosin does not lower blood pressure much by itself, combining it with other hypotensive agents could produce a more dramatic reduction. Accordingly, such combinations should be used with caution. Drugs of concern include organic nitrates, antihypertensive agents, and the type 5 phosphodiesterase inhibitors used for impotence (eg, sildenafil [Viagra]).

Preparations, Dosage, and Administration. Alfuzosin [Uroxatral] is available in 10-mg extended-release tablets. The recommended dosage is 10 mg once a day, taken immediately after the same meal each day.

Silodosin

Actions and Uses. Silodosin [Rapaflo], approved in October 2008, is an alpha-adrenergic antagonist that selectively blocks alpha₁ receptors in the prostate, bladder, and urethra. Blockade of vascular alpha receptors is weak. The drug is indicated only for BPH (see Chapter 66).

Adverse Effects. Silodosin is generally well tolerated. However, like tamsulosin, silodosin can greatly reduce or eliminate release of semen during orgasm. This effect reverses when the drug is discontinued. Although blockade of vascular alpha receptors is usually minimal, silodosin can produce dizziness, lightheadedness, and nasal congestion.

Preparations, Dosage, and Administration. Silodosin is supplied in 4- and 8-mg capsules. The usual dosage is 8 mg once daily, but should be reduced to 4 mg once daily in men with moderate renal or hepatic impairment. Men with severe renal or hepatic impairment should not use the drug.

Phentolamine

Actions and Uses. Like prazosin, phentolamine [OraVerse, Regitine[®]] is a competitive adrenergic antagonist. However, in contrast to prazosin, phentolamine blocks alpha₂ receptors as well as alpha₁ receptors. Phentolamine has three approved applications: (1) diagnosis and treatment of pheochromocytoma; (2) prevention of tissue necrosis following extravasation of drugs that produce alpha₁-mediated vasoconstriction (eg, norepinephrine); and (3) reversal of soft tissue anesthesia (local anesthetics are often combined with epinephrine, which prolongs anesthetic action by causing alpha₁-mediated vasoconstriction; phentolamine blocks epinephrine-mediated vasoconstriction, and thereby increases local blood flow, which increases the rate of anesthetic removal).

Adverse Effects. Like prazosin, phentolamine can produce the typical adverse effects associated with alpha-adrenergic blockade: *orthostatic hypotension, reflex tachycardia, nasal congestion, and inhibition of ejaculation*. Because it blocks alpha₂ receptors, *phentolamine produces greater reflex tachycardia than prazosin*. If reflex tachycardia is especially severe, heart rate can be reduced with a beta blocker. Since tachycardia can aggravate angina pectoris and myocardial infarction (MI), phentolamine is contraindicated for patients with either disorder.

Overdose can produce profound hypotension. If necessary, blood pressure can be elevated with *norepinephrine*. *Epinephrine* should not be used, because the drug can cause blood pressure to drop even further! Why? Because in the presence of alpha₁ blockade, the ability of epinephrine to promote vasodilation (via activation of vascular beta₂ receptors) may outweigh the ability of epinephrine to cause vasoconstriction (via activation of vascular alpha₁ receptors). Further lowering of blood pressure is not a problem with norepinephrine because norepinephrine does not activate beta₂ receptors.

Preparations, Dosage, and Administration. For IM and IV administration, phentolamine is supplied in a concentrated solution that contains 5 mg phentolamine/2 mL fluid. The dose for preventing hypertension during surgical excision of a *pheochromocytoma* is 5 mg (IM or IV) given 1 to 2 hours before surgery. To prevent *necrosis following extravasation* of IV norepinephrine, the region should be infiltrated with 5 to 10 mg of phentolamine diluted in 10 mL of saline.

The *OraVerse* formulation (0.4 mg phentolamine/0.7 mL fluid) is used to reverse local anesthesia (eg, following dental work). The dose employed is based on the dose of the local anesthetic.

Phenoxybenzamine

Actions and Uses. Phenoxybenzamine [Dibenzylin] is an old drug that, like phentolamine, blocks alpha₁ and alpha₂ receptors. However, unlike

all of the other alpha-adrenergic antagonists, phenoxybenzamine is a *non-competitive* receptor antagonist. Hence, receptor blockade is *not reversible*. As a result, the effects of phenoxybenzamine are long lasting. (Responses to a single dose can persist for several days.) Effects subside as newly synthesized receptors replace the ones that have been irreversibly blocked. Phenoxybenzamine is approved only for *pheochromocytoma*.

Adverse Effects. Like the other alpha-adrenergic antagonists, phenoxybenzamine can produce *orthostatic hypotension, reflex tachycardia, nasal congestion, and inhibition of ejaculation*. Reflex tachycardia is greater than that caused by prazosin and about equal to that caused by phentolamine.

If dosage is excessive, phenoxybenzamine, like phentolamine, will cause profound hypotension. Furthermore, since hypotension is the result of *irreversible* alpha₁ blockade, it cannot be corrected with an alpha₁ agonist. To restore blood pressure, patients must be given IV fluids, which elevate blood pressure by increasing blood volume.

Preparations, Dosage, and Administration. Phenoxybenzamine hydrochloride [Dibenzylin] is available in 10-mg tablets for oral use. The initial adult dosage is 10 mg twice a day. The dosage can be increased every other day until the desired level of alpha blockade (blood pressure control) has been achieved. The usual adult maintenance dosage is 20 to 40 mg given 2 or 3 times a day.

BETA-ADRENERGIC ANTAGONISTS

THERAPEUTIC AND ADVERSE RESPONSES TO BETA BLOCKADE

In this section we consider the beneficial and adverse responses that can result from blockade of beta-adrenergic receptors. Properties of individual beta blockers are discussed after that.

Therapeutic Applications of Beta Blockade

Practically all of the therapeutic effects of the beta-adrenergic antagonists result from blockade of beta₁ receptors in the heart. The major consequences of blocking these receptors are (1) reduced heart rate, (2) reduced force of contraction, and (3) reduced velocity of impulse conduction through the atrioventricular (AV) node. Because of these effects, beta blockers are useful in a variety of cardiovascular disorders.

Angina Pectoris. Angina pectoris (paroxysmal pain in the region of the heart) occurs when oxygen supply (blood flow) to the heart is insufficient to meet cardiac oxygen demand. Anginal attacks can be precipitated by exertion, intense emotion, and other factors. Beta-adrenergic blockers are a mainstay of anti-anginal therapy. By blocking beta₁ receptors in the heart, these drugs decrease cardiac work. This brings oxygen demand back into balance with oxygen supply, and thereby prevents pain. Angina pectoris and its treatment are the subject of Chapter 51.

Hypertension. For years, beta blockers were considered drugs of choice for hypertension. However, recent data indicate they are less beneficial than previously believed.

The exact mechanism by which beta blockers reduce blood pressure is not known. Older proposed mechanisms include reduction of cardiac output through blockade of beta₁ receptors in the heart and suppression of renin release through blockade of beta₁ receptors in the kidney (see Chapter 44 for a discussion of the role of renin in blood pressure control). More recently, we have learned that, with long-term use, beta blockers reduce peripheral vascular resistance, which could account for much of their antihypertensive effects. The role of beta-adrenergic blocking agents in hypertension is discussed further in Chapter 47.

Cardiac Dysrhythmias. Beta-adrenergic blocking agents are especially useful for treating dysrhythmias that involve

excessive electrical activity in the sinus node and atria. By blocking cardiac beta₁ receptors, these drugs can (1) decrease the rate of sinus nodal discharge and (2) suppress conduction of atrial impulses through the AV node, thereby preventing the ventricles from being driven at an excessive rate. The use of beta-adrenergic blockers to treat dysrhythmias is discussed at length in Chapter 49.

Myocardial Infarction. An MI is a region of myocardial necrosis caused by localized interruption of blood flow to the heart wall. Treatment with a beta blocker can reduce pain, infarct size, mortality, and the risk of reinfarction. To be effective, therapy with a beta blocker must commence soon after an MI has occurred, and should be continued for several years. The role of beta blockers in treating MI is discussed further in Chapter 53.

Reduction of Perioperative Mortality. Beta blockers may decrease the risk for mortality associated with noncardiac surgery in high-risk patients. In the DECREASE-IV trial, pretreatment with bisoprolol reduced the incidence of perioperative MI and death. However, for treatment to be both safe and effective, dosing should begin *early* (several days to weeks before surgery) and *doses should be low initially and then titrated up* (to achieve a resting heart rate of 60 to 80 beats/min). In addition, treatment should continue for 1 month after surgery. As shown in an earlier trial, known as POISE, if the beta blocker is started *late* (just prior to surgery), and if the doses are *large*, such treatment can actually increase the risk of perioperative mortality.

Heart Failure. Beta blockers are now considered standard therapy for heart failure. This application is relatively new and may come as a surprise to some readers. Why? Because, until recently, heart failure was considered an absolute *contraindication* to beta blockers. At this time, only three beta blockers—carvedilol, bisoprolol, and metoprolol—have been shown effective for heart failure. Use of beta blockers for heart failure is discussed at length in Chapter 48.

Hyperthyroidism. Hyperthyroidism (excessive production of thyroid hormone) is associated with an increase in the sensitivity of the heart to catecholamines (eg, norepinephrine, epinephrine). As a result, normal levels of sympathetic activity to the heart can generate tachydysrhythmias and angina pectoris. Blockade of cardiac beta₁ receptors suppresses these responses.

Migraine Prophylaxis. When taken prophylactically, beta-adrenergic blocking agents can reduce the frequency and intensity of migraine attacks. However, although beta blockers are effective as prophylaxis, these drugs are not able to abort a migraine headache once it has begun. The mechanism by which beta blockers prevent migraine is not known. Treatment of migraine and other headaches is the subject of Chapter 30.

Stage Fright. Public speakers and other performers sometimes experience “stage fright.” Prominent symptoms are tachycardia and sweating brought on by generalized discharge of the sympathetic nervous system. Beta blockers help by preventing beta₁-mediated tachycardia.

Pheochromocytoma. As discussed above, a pheochromocytoma secretes large amounts of catecholamines, which can cause excessive stimulation of the heart. Cardiac stimulation can be prevented by beta₁ blockade.

Glaucoma. Beta blockers are important drugs for treating glaucoma, a condition characterized by elevated intraocular pressure with subsequent injury to the optic nerve. The group of beta blockers used in glaucoma (see Table 104-2) is differ-

ent from the group of beta blockers discussed in this chapter. Glaucoma and its treatment are addressed in Chapter 104 (Drugs for the Eye).

Adverse Effects of Beta Blockade

Although therapeutic responses to beta blockers are due almost entirely to blockade of beta₁ receptors, adverse effects involve both beta₁ and beta₂ blockade. Consequently, the nonselective beta-adrenergic blocking agents (drugs that block beta₁ and beta₂ receptors) produce a broader spectrum of adverse effects than do the “cardioselective” beta-adrenergic antagonists (drugs that block beta₁ receptors only at therapeutic doses).

Adverse Effects of Beta₁ Blockade

All of the adverse effects of beta₁ blockade are the result of blocking beta₁ receptors in the heart. Blockade of renal beta₁ receptors is not a concern.

Bradycardia. Blockade of cardiac beta₁ receptors can produce bradycardia (excessively slow heart rate). If necessary, heart rate can be increased using a combination of isoproterenol (a beta-adrenergic agonist) and atropine (a muscarinic antagonist). Isoproterenol competes with the beta blocker for cardiac beta₁ receptors, thereby promoting cardiac stimulation. By blocking muscarinic receptors on the heart, atropine prevents slowing of the heart by the parasympathetic nervous system.

Reduced Cardiac Output. Beta₁ blockade can reduce cardiac output by decreasing heart rate and the force of myocardial contraction. Because they can decrease cardiac output, *beta blockers must be used with great caution in patients with heart failure or reduced cardiac reserve*. In both cases, any further decrease in cardiac output could result in insufficient tissue perfusion.

Precipitation of Heart Failure. In some patients, suppression of cardiac function with a beta blocker can be so great as to cause heart failure. Patients should be informed about the early signs of heart failure (shortness of breath, night coughs, swelling of the extremities) and instructed to notify the prescriber if these occur. It is important to appreciate that, although beta blockers can precipitate heart failure, they are also used to *treat* heart failure.

AV Heart Block. Atrioventricular heart block is defined as suppression of impulse conduction through the AV node. In its most severe form, AV block prevents *all* atrial impulses from reaching the ventricles. Because blockade of cardiac beta₁ receptors can suppress AV conduction, production of AV block is a potential complication of beta-blocker therapy. These drugs are contraindicated for patients with pre-existing AV block.

Rebound Cardiac Excitation. Long-term use of beta blockers can sensitize the heart to catecholamines. As a result, if a beta blocker is withdrawn *abruptly*, anginal pain or ventricular dysrhythmias may develop. This phenomenon of increased cardiac activity in response to abrupt cessation of beta-blocker therapy is referred to as *rebound excitation*. The risk of rebound excitation can be minimized by withdrawing these drugs gradually (eg, by tapering the dosage over a period of 1 to 2 weeks). If rebound excitation occurs, dosing should be temporarily resumed. Patients should be warned against abrupt cessation of treatment. Also, they should be advised to carry an adequate supply of their beta blocker when traveling.

Adverse Effects of Beta₂ Blockade

Bronchoconstriction. Blockade of beta₂ receptors in the lung can cause constriction of the bronchi. (Recall that activation of these receptors promotes bronchodilation.) For most people, the degree of bronchoconstriction is insignificant. However, when bronchial beta₂ receptors are blocked in patients with asthma, the resulting increase in airway resistance can be life threatening. Accordingly, *drugs that block beta₂ receptors* are contraindicated for people with asthma. If these individuals must use a beta blocker, they should use an agent that is beta₁ selective (eg, metoprolol).

Hypoglycemia from Inhibition of Glycogenolysis. As noted in Chapter 13, epinephrine, acting at beta₂ receptors in skeletal muscle and the liver, can stimulate glycogenolysis (breakdown of glycogen into glucose). Beta₂ blockade will inhibit this process, posing a risk of hypoglycemia. Although suppression of beta₂-mediated glycogenolysis is inconsequential for most people, interference with this process can be detrimental to patients with *diabetes*. Why? Because these people are especially dependent on beta₂-mediated glycogenolysis as a way to overcome severe reductions in blood glucose levels (caused by overdosing with insulin). If the diabetic patient requires a beta blocker, a beta₁-selective agent should be chosen.

Adverse Effects in Neonates from Beta₁ and Beta₂ Blockade

Use of beta blockers during pregnancy can have residual effects on the newborn infant. Specifically, because beta blockers can remain in the circulation for several days after birth, neonates may be at risk for bradycardia (from beta₁ blockade), respiratory distress (from beta₂ blockade), and hypoglycemia (from beta₂ blockade). Accordingly, for 3 to 5 days after birth, newborns should be closely monitored for these effects. Adverse neonatal effects have been observed with at least one beta blocker (betaxolol), and may be a risk with others as well.

PROPERTIES OF INDIVIDUAL BETA BLOCKERS

The beta-adrenergic antagonists can be subdivided into three groups:

- *First-generation (nonselective) beta blockers* (eg, propranolol), which block beta₁ and beta₂ receptors
- *Second-generation (cardioselective) beta blockers* (eg, metoprolol), which produce selective blockade of beta₁ receptors (at usual doses)
- *Third-generation (vasodilating) beta blockers* (eg, carvedilol), which act on blood vessels to cause dilation, but may produce nonselective or cardioselective beta blockade

Our discussion of the individual beta blockers focuses on two prototypes: propranolol and metoprolol. Properties of these and other beta blockers are summarized in Tables 18-2 and 18-3.

Propranolol

Propranolol [Inderal LA, InnoPran XL], our prototype of the first-generation beta blockers, produces *nonselective* beta blockade. That is, this drug blocks both beta₁- and beta₂-adrenergic receptors. Propranolol was the first beta blocker to

receive widespread clinical use and remains one of our most important beta-blocking agents.

Pharmacologic Effects

By blocking *cardiac* beta₁ receptors, propranolol can *reduce heart rate, decrease the force of ventricular contraction, and suppress impulse conduction through the AV node*. The net effect is a reduction in cardiac output.

By blocking *renal* beta₁ receptors, propranolol can *suppress secretion of renin*.

By blocking beta₂ receptors, propranolol can produce three major effects: (1) *bronchoconstriction* (through beta₂ blockade in the lung), (2) *vasoconstriction* (through beta₂ blockade on certain blood vessels), and (3) *reduced glycogenolysis* (through beta₂ blockade in skeletal muscle and liver).

Pharmacokinetics

Propranolol is *highly lipid soluble* and therefore can readily cross membranes. The drug is well absorbed following oral administration, but, because of extensive metabolism on its first pass through the liver, less than 30% of each dose reaches the systemic circulation. Because of its ability to cross membranes, propranolol is widely distributed to all tissues and organs, including the central nervous system (CNS). Propranolol undergoes hepatic metabolism followed by excretion in the urine.

Therapeutic Uses

Practically all of the applications of propranolol are based on blockade of beta₁ receptors in the heart. The most important indications are *hypertension, angina pectoris, cardiac dysrhythmias, and myocardial infarction*. The role of propranolol and other beta blockers in these disorders is discussed in Chapter 47 (Drugs for Hypertension), Chapter 49 (Antidysrhythmic Drugs), Chapter 51 (Drugs for Angina Pectoris), and Chapter 53 (Management of ST-Elevation Myocardial Infarction). Additional indications include *prevention of migraine headache* and "*stage fright*."

Adverse Effects

The most serious adverse effects result from blockade of beta₁ receptors in the heart and blockade of beta₂ receptors in the lung.

Bradycardia. Beta₁ blockade in the heart can cause bradycardia. Heart rate should be assessed before each dose. If necessary, heart rate can be increased by administering atropine and isoproterenol.

AV Heart Block. By slowing conduction of impulses through the AV node, propranolol can cause AV heart block. The drug is contraindicated for patients with pre-existing AV block (if the block is greater than first degree).

Heart Failure. In patients with heart disease, suppression of myocardial contractility by propranolol can result in heart failure. Patients should be informed about the early signs of heart failure (shortness of breath, night coughs, swelling of the extremities) and instructed to notify the prescriber if these occur. Propranolol is generally contraindicated for patients with pre-existing heart failure (although other beta blockers are used to *treat* heart failure).

Rebound Cardiac Excitation. Abrupt withdrawal of propranolol can cause rebound excitation of the heart, resulting in tachycardia and ventricular dysrhythmias. This problem is

TABLE 18-2 • Clinical Pharmacology of the Beta-Adrenergic Blocking Agents

Generic Name	Trade Name	Receptors Blocked	ISA	Lipid Solubility	Half-Life (hr)	Route*	Maintenance Dosage in Hypertension†
First-Generation: Nonselective Beta Blockers							
Carteolol	Cartrol	Beta ₁ , Beta ₂	++	Low	6	PO	2.5 mg once/day
Nadolol	Corgard	Beta ₁ , Beta ₂	0	Low	20–24	PO	40 mg once/day
Penbutolol	Levitol	Beta ₁ , Beta ₂	+	Moderate	5	PO	20 mg once/day
Pindolol	Visken	Beta ₁ , Beta ₂	+++	Moderate	3–4	PO	10 mg twice/day
Propranolol (IR)	generic only	Beta ₁ , Beta ₂	0	High	3–5	PO, IV	60 mg twice/day
Propranolol (SR)	Inderal LA, InnoPran XL					PO	80 mg once/day
Sotalol	Betapace	Beta ₁ , Beta ₂	0	High	12	PO	Not for hypertension
Timolol	Blocadren	Beta ₁ , Beta ₂	0	Low	4	PO	20 mg twice/day
Second-Generation: Cardioselective Beta Blockers							
Acebutolol	Sectral	Beta ₁	+	Moderate	3–4	PO	400 mg once/day
Atenolol	Tenormin	Beta ₁	0	Low	6–9	PO, IV	50 mg once/day
Betaxolol	Kerlone	Beta ₁	0	Low	14–22	PO	10 mg once/day
Bisoprolol	Zebeta, Monacor*	Beta ₁	0	Moderate	9–12	PO	5 mg once/day
Esmolol	Brevibloc	Beta ₁	0	Low	0.15	IV	Not for hypertension
Metoprolol (IR)	Lopressor, Betaloc*	Beta ₁	0	High	3–7	PO, IV	100 mg once/day
Metoprolol (SR)	Toprol XL, Betaloc CR*	Beta ₁				PO	100 mg once/day
Third-Generation: Beta Blockers with Vasodilating Actions							
Carvedilol (IR)	Coreg	Beta ₁ , Beta ₂ , Alpha ₁	0	Moderate	5–11	PO	12.5 mg twice/day
Carvedilol (SR)	Coreg CR					PO	40 mg once/day
Labetalol	Normodyne, Trandate	Beta ₁ , Beta ₂ , Alpha ₁	0	Low	6–8	PO, IV	300 mg twice/day
Nebivolol	Bystolic	Beta ₁	0	High	12–19	PO	20 mg once/day

IR = immediate release, ISA = intrinsic sympathomimetic activity (partial agonist activity), SR = sustained release.

*Oral administration is used for essential hypertension. Intravenous administration is reserved for acute myocardial infarction (atenolol, metoprolol), cardiac dysrhythmias (esmolol, propranolol), and severe hypertension (labetalol).

†These are the lowest doses normally used for maintenance in hypertension.

especially dangerous for patients with pre-existing cardiac ischemia. To avoid rebound excitation, propranolol should be withdrawn slowly (ie, by giving progressively smaller doses over 1 to 2 weeks). Patients should be warned against abrupt cessation of treatment. In addition, they should be advised to carry an adequate supply of propranolol when traveling.

Bronchoconstriction. Blockade of beta₂ receptors in the lung can cause bronchoconstriction. As a rule, increased airway resistance is hazardous only to patients with asthma and other obstructive pulmonary disorders.

Inhibition of Glycogenolysis. Blockade of beta₂ receptors in skeletal muscle and the liver can inhibit glycogenolysis. This effect can be dangerous for people with diabetes (see below).

CNS Effects. Because of its lipid solubility, propranolol can readily cross the blood-brain barrier, and hence has ready access sites in the CNS. However, although propranolol is reputed to cause a variety of CNS reactions—depression, insomnia, nightmares, and hallucinations—these reactions are,

in fact, very rare. Because of the possible risk of depression, prudence dictates avoiding propranolol in patients who already have this disorder.

Effects in Neonates. Use of propranolol and other beta blockers during pregnancy may put the newborn infant at risk of bradycardia, respiratory distress, and hypoglycemia. Neonates should be closely monitored for these effects.

Precautions, Warnings, and Contraindications

Severe Allergy. Propranolol should be avoided in patients with a history of severe allergic reactions (anaphylaxis). Why? Recall that epinephrine, the drug of choice for anaphylaxis, relieves symptoms in large part by activating beta₁ receptors in the heart and beta₂ receptors in the lung. If these receptors are blocked by propranolol, the ability of epinephrine to help will be dangerously impaired.

Diabetes. Propranolol can be detrimental to diabetic patients in two ways. First, by blocking beta₂ receptors in muscle

TABLE 18-3 • Beta-Adrenergic Blocking Agents: Summary of Therapeutic Uses*

	Hypertension	Angina Pectoris	Cardiac Dysrhythmias	Myocardial Infarction	Migraine Prophylaxis	Stage Fright	Heart Failure
First-Generation: Nonselective Beta Blockers							
Carteolol	A	I			I	I	
Nadolol	A	A	I				
Penbutolol	A					I	
Pindolol	A	I	I		A	I	
Propranolol	A	A	A	A			
Sotalol			A				
Timolol	A	I	I	A	A	I	
Second-Generation: Cardioselective Beta Blockers							
Acebutolol	A	I	A	I			
Atenolol	A	A	I	A	I	I	
Betaxolol	A	I					
Bisoprolol	A	I	I				I
Esmolol		I	A				
Metoprolol	A	A	I	A	I		A
Third-Generation: Beta Blockers with Vasodilating Actions							
Carvedilol	A	I		A			A
Labetalol	A	I					
Nebivolol	A						I

A = FDA-approved use, I = Investigational use.

*Beta blockers used for glaucoma are discussed in Chapter 104 (Drugs for the Eye).

and liver, propranolol can suppress glycogenolysis, thereby eliminating an important mechanism for correcting hypoglycemia (which can occur when insulin dosage is excessive). Second, by blocking beta₁ receptors, propranolol can suppress tachycardia, which normally serves as an early warning signal that blood glucose levels are falling too low. (When glucose drops below a safe level, the sympathetic nervous system is activated, causing an increase in heart rate.) By "masking" tachycardia, propranolol can delay awareness of hypoglycemia, thereby compromising the patient's ability to correct the problem in a timely fashion. Diabetic patients who are taking propranolol should be warned that tachycardia may no longer be a reliable indicator of hypoglycemia. In addition, they should be taught to recognize alternative signs (sweating, hunger, fatigue, poor concentration) that blood glucose is falling perilously low.

Cardiac, Respiratory, and Psychiatric Disorders. Propranolol can exacerbate *heart failure*, *AV heart block*, *sinus bradycardia*, *asthma*, and *bronchospasm*. Accordingly, the drug is contraindicated for patients with these disorders. In addition, propranolol should be used with caution in patients with a history of *depression*.

Drug Interactions

Calcium Channel Blockers. The cardiac effects of two calcium channel blockers—verapamil and diltiazem—are identical to those of propranolol: reduction of heart rate, suppression of AV conduction, and suppression of myocardial contractility. When propranolol and these drugs are combined, excessive cardioppression may result.

Insulin. As discussed above, propranolol can impede early recognition of insulin-induced hypoglycemia. In addition, propranolol can block glycogenolysis, the body's mechanism for correcting hypoglycemia.

Preparations, Dosage, and Administration

General Dosing Considerations. Establishing an effective propranolol dosage is difficult for two reasons: (1) patients vary widely in their requirements for propranolol and (2) there is a poor correlation between blood levels of propranolol and therapeutic responses. The explanation for these observations is that responses to propranolol are dependent on the activity of the sympathetic nervous system. If sympathetic activity is high, then the dose needed to reduce receptor activation will be high too. Conversely, if sympathetic activity is low, then low doses will be sufficient to produce receptor blockade. Since sympathetic activity varies among patients, propranolol requirements vary also. Accordingly, the dosage must be adjusted by monitoring the patient's response, and not by relying on dosing information in a drug reference.

Preparations. Propranolol hydrochloride is available in three oral formulations: (1) immediate-release (IR) tablets (10 to 80 mg) sold generically, (2) extended-release (ER) capsules (60 to 160 mg) sold as Inderal LA and InnoPran XL, and (3) solution (4 and 8 mg/mL) sold generically. The drug is also available in solution (1 mg/mL) for IV administration.

Dosage. For treatment of *hypertension*, the initial dosage is 40 mg twice a day (using IR tablets) or 80 mg once a day (using ER capsules). Usual maintenance dosages are 120 to 240 mg/day in two, three, or four divided doses (using IR tablets) or 80 to 160 mg once a day (using ER capsules).

For *angina pectoris*, the initial dosage is 80 mg once a day (using ER capsules). The usual maintenance dosage is 160 mg once a day (using ER capsules) or 80 to 320 mg/day in two, three, or four divided doses (using IR tablets).

Metoprolol

Metoprolol [Lopressor, Toprol XL, Betaloc \clubsuit], our prototype of the second-generation beta blockers, produces selective blockade of beta₁ receptors in the heart. At usual therapeutic doses, the drug does not cause beta₂ blockade. Please note, however, that selectivity for beta₁ receptors is not absolute: At higher doses, metoprolol and the other "cardioselective" agents will block beta₂ receptors as well. Because their effects on beta₂ receptors are normally minimal, the cardioselective agents are not likely to cause bronchoconstriction or hypoglycemia. Accordingly, these drugs are preferred to the nonselective beta blockers for patients with asthma or diabetes.

Pharmacologic Effects. By blocking cardiac beta₁ receptors, metoprolol has the same impact on the heart as propranolol: it reduces heart rate, force of contraction, and conduction velocity through the AV node. Also like propranolol, metoprolol reduces secretion of renin by the kidney. In contrast to propranolol, metoprolol does not block bronchial beta₂ receptors (at usual doses), and therefore does not increase airway resistance.

Pharmacokinetics. Metoprolol is very lipid soluble and well absorbed following oral administration. Like propranolol, metoprolol undergoes extensive metabolism on its first pass through the liver. As a result, only 40% of an oral dose reaches the systemic circulation. Elimination is by hepatic metabolism and renal excretion.

Therapeutic Uses. The primary indication for metoprolol is *hypertension*. The drug is also approved for *angina pectoris*, *heart failure*, and *myocardial infarction*.

Adverse Effects. Major adverse effects involve the heart. Like propranolol, metoprolol can cause *bradycardia*, *reduced cardiac output*, *AV heart block*, and *rebound cardiac excitation following abrupt withdrawal*. Also, even though metoprolol is approved for *treating heart failure*, it can *cause heart failure* if used incautiously. In contrast to propranolol, metoprolol causes minimal bronchoconstriction and does not interfere with beta₂-mediated glycogenolysis.

Precautions, Warnings, and Contraindications. Like propranolol, metoprolol is contraindicated for patients with *sinus bradycardia* and *AV block greater than first degree*. In addition, it should be used with great care in patients with *heart failure*. Because metoprolol produces only minimal blockade of beta₂ receptors, the drug is safer than propranolol for patients with asthma or a history of severe allergic reactions. In addition, since metoprolol does not suppress beta₂-mediated glycogenolysis, it can be used more safely than propranolol by patients with diabetes. Please note, however, that metoprolol, like propranolol, will "mask" tachycardia, thereby depriving the diabetic patient of an early indication that hypoglycemia is developing.

Preparations, Dosage, and Administration. Metoprolol is available in IR tablets (20, 50, and 100 mg) under the trade name Lopressor and in sustained-release (SR) tablets (25, 50, 100, and 200 mg) under the trade name Toprol XL. The drug is also available in solution (1 mg/mL) for IV administration. The initial dosage for *hypertension* is 100 mg/day in single or divided doses. Dosages for maintenance therapy range from 100 to 450 mg/day in divided doses. Intravenous administration is reserved for *myocardial infarction*.

Other Beta-Adrenergic Blockers

In the United States, 16 beta blockers are approved for cardiovascular disorders (*hypertension*, *angina pectoris*, *cardiac dysrhythmias*, *MI*). Principal differences among these drugs

concern receptor specificity, pharmacokinetics, indications, side effects, intrinsic sympathomimetic activity, and the ability to cause vasodilation.

In addition to the agents used for cardiovascular disorders, there is a group of beta blockers used for glaucoma (see Chapter 104, *Drugs for the Eye*).

Properties of the beta blockers employed for cardiovascular disorders are discussed below.

Receptor Specificity. With regard to receptor specificity, beta blockers fall into two groups: nonselective agents and cardioselective agents. The nonselective agents block beta₁ and beta₂ receptors, whereas the cardioselective agents block beta₁ receptors only (at usual doses). Because of their limited side effects, the cardioselective agents are preferred for patients with asthma or diabetes. Two beta blockers—*labetalol* and *carvedilol*—differ from all the others in that they block *alpha*-adrenergic receptors in addition to beta receptors. The receptor specificity of individual beta blockers is indicated in Tables 18-1 and 18-2.

Pharmacokinetics. Pharmacokinetic properties of the beta blockers are summarized in Table 18-2. The relative lipid solubility of these agents is of particular importance. The drugs with high solubility (eg, propranolol, metoprolol) have two prominent features: (1) they penetrate the blood-brain barrier with ease and (2) they are eliminated primarily by hepatic metabolism. Conversely, the drugs with low lipid solubility (eg, nadolol, atenolol) penetrate the blood-brain barrier poorly and are eliminated primarily by renal excretion.

Therapeutic Uses. Principal indications for the beta-adrenergic blockers are *hypertension*, *angina pectoris*, and *cardiac dysrhythmias*. Other uses include prophylaxis of *migraine headache*, treatment of *myocardial infarction*, symptom suppression in individuals with *situational anxiety* (eg, stage fright), and treatment of *heart failure* (see Chapter 48). Approved and investigational uses of the beta blockers are summarized in Table 18-3.

Esmolol and *sotalol* differ from the other beta blockers in that they are not used for hypertension. Because of its very short half-life (15 minutes), *esmolol* is clearly unsuited for treating hypertension, which requires maintenance of blood levels throughout the day, every day, for an indefinite time. The only approved indication for *esmolol* is emergency IV therapy of *supraventricular tachycardia*. *Sotalol* is approved only for *ventricular dysrhythmias*. *Esmolol* and *sotalol* are discussed further in Chapter 49 (*Antidysrhythmic Drugs*).

Adverse Effects. By blocking beta₁ receptors in the heart, all of the beta blockers can cause *bradycardia*, *AV heart block*, and, rarely, *heart failure*. By blocking beta₂ receptors in the lung, the nonselective agents can cause significant *bronchoconstriction* in patients with asthma or chronic obstructive pulmonary disease. In addition, by blocking beta₂ receptors in the liver and skeletal muscle, the nonselective agents can *inhibit glycogenolysis*, thereby compromising the ability of diabetic patients to compensate for insulin-induced hypoglycemia. Because of their ability to block *alpha*-adrenergic receptors, *carvedilol* and *labetalol* can cause *postural hypotension*.

Although *CNS effects* (insomnia, depression) can occur with all beta blockers, these effects are rare, and are most likely with the more lipid-soluble agents. Abrupt discontinuation of any beta blocker can produce *rebound cardiac excita-*

tion. Accordingly, all beta blockers should be withdrawn slowly (by tapering the dosage over 1 to 2 weeks).

Intrinsic Sympathomimetic Activity (Partial Agonist Activity). The term *intrinsic sympathomimetic activity* (ISA) refers to the ability of certain beta blockers—especially *pin-dolol*—to act as *partial agonists* at beta-adrenergic receptors. (As discussed in Chapter 5, a partial agonist is a drug that, when bound to a receptor, produces a limited degree of receptor activation while preventing strong agonists from binding to that receptor to cause full activation.)

In contrast to other beta blockers, agents with ISA have very little effect on resting heart rate and cardiac output. When patients are at rest, stimulation of the heart by the sympathetic nervous system is low. If an ordinary beta blocker is given, it will block sympathetic stimulation, causing heart rate and cardiac output to decline. However, if a beta blocker has ISA, its own ability to cause limited receptor activation will compensate for blocking receptor activation by the sympathetic nervous system and, consequently, resting heart rate and cardiac output are not reduced.

Because of their ability to provide a low level of cardiac stimulation, beta blockers with ISA are preferred to other beta blockers for use in patients with bradycardia. Conversely, these agents should not be given to patients with myocardial infarction. Why? Because their ability to cause even limited cardiac stimulation can be detrimental.

Vasodilation. The third-generation beta blockers—*carvedilol*, *labetalol*, and *nebivolol*—can dilate blood vessels. Two mechanisms are employed: Carvedilol and labetalol block vascular alpha₁ receptors; nebivolol promotes synthesis and release of nitric oxide from the vascular epithelium. The exact clinical benefit of vasodilation by these drugs has not been clarified.

Dosage and Administration. With the exception of *esmolol*, all of the beta blockers discussed in this chapter can be administered orally. These drugs—*atenolol*, *labetalol*, and *propranolol*—may be given intravenously as well as orally. *Esmolol* is administered only by IV injection.

Maintenance dosages for hypertension are summarized in Table 18-2. For most beta blockers, dosing can be done just once a day. For the drugs with especially short half-lives, twice-a-day dosing is required (unless an extended-release formulation is available).

KEY POINTS

- Most beneficial responses to alpha blockers, including reduction of blood pressure in patients with hypertension, result from blockade of alpha₁ receptors on blood vessels.
- Alpha blockers reduce symptoms of BPH by blocking alpha₁ receptors in the bladder neck and prostatic capsule, which causes smooth muscle at those sites to relax.
- The major adverse effects of alpha blockers are *orthostatic hypotension* (caused by blocking alpha₁ receptors on veins); *reflex tachycardia* (caused by blocking alpha₁ receptors on arterioles); *nasal congestion* (caused by blocking alpha₁ receptors in blood vessels of the nasal mucosa); and *inhibition of ejaculation* (caused by blocking alpha₁ receptors in male sex organs).
- The first dose of an alpha blocker can cause fainting from profound orthostatic hypotension, the so-called *first-dose effect*.
- The alpha blockers used most frequently—prazosin, doxazosin, and terazosin—produce selective blockade of alpha₁ receptors.
- Beta blockers produce most of their beneficial effects by blocking beta₁ receptors in the heart, thereby reducing heart rate, force of contraction, and AV conduction.
- Principal indications for the beta blockers are cardiovascular: hypertension, angina pectoris, heart failure, and supraventricular tachydysrhythmias.
- Potential adverse effects from beta₁ blockade are bradycardia, reduced cardiac output, AV block, and precipitation of heart failure (even though some beta blockers are used to *treat* heart failure).
- Potential adverse effects from beta₂ blockade are bronchoconstriction (a concern for people with asthma) and reduced glycogenolysis (a concern for people with diabetes).
- Beta blockers can be divided into three groups: (1) first-generation agents (ie, nonselective beta blockers, such as propranolol, which block beta₁ and beta₂ receptors); (2) second-generation agents (ie, cardioselective beta blockers, such as metoprolol, which block beta₁ receptors only at usual doses); and (3) third-generation agents (ie, vasodilating beta blockers, which may be cardioselective or nonselective).
- Beta blockers can be hazardous to patients with severe allergies because they can block beneficial actions of epinephrine, the drug of choice for treating anaphylactic shock.
- Beta blockers can be detrimental to diabetic patients because they suppress glycogenolysis (an important mechanism for correcting insulin-induced hypoglycemia), and they suppress tachycardia (an early warning signal that glucose levels are falling too low).
- Combining a beta blocker with a calcium channel blocker can produce excessive cardiosuppression.
- Cardioselective beta blockers are preferred to nonselective beta blockers for patients with asthma or diabetes.

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Summary of Major Nursing Implications*

ALPHA-ADRENERGIC ANTAGONISTS

Alfuzosin
Doxazosin
Prazosin
Silodosin
Tamsulosin
Terazosin

Preadministration Assessment

Therapeutic Goal

Doxazosin, Prazosin, Terazosin. Reduction of blood pressure in patients with *essential hypertension*.
Doxazosin, Terazosin, Alfuzosin, Silodosin, Tamsulosin. Reduction of symptoms in patients with *benign prostatic hyperplasia*.

Baseline Data

Essential Hypertension. Determine blood pressure and heart rate.
Benign Prostatic Hyperplasia. Determine the degree of nocturia, daytime frequency, hesitancy, intermittency, terminal dribbling (at the end of voiding), urgency, impairment of size and force of urinary stream, dysuria, and sensation of incomplete voiding.

Identifying High-Risk Patients

The only contraindication is hypersensitivity to these drugs.

Implementation: Administration

Route

Oral.

Administration

Instruct patients to take the initial dose at bedtime to minimize the "first-dose" effect. Except for *tamsulosin*, which is administered *after* eating, these drugs may be taken with food.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Essential Hypertension. Evaluate by monitoring blood pressure.
Benign Prostatic Hyperplasia. Evaluate for improvement in the symptoms listed under *Baseline Data*.

Minimizing Adverse Effects

Orthostatic Hypotension. Alpha₁ blockade can cause postural hypotension. Inform patients about the symptoms of hypotension (dizziness, lightheadedness) and advise them to sit or lie down if these occur. Advise patients to move slowly when changing from a supine or sitting position to an upright posture.
First-Dose Effect. The first dose may cause fainting from severe orthostatic hypotension. Forewarn patients

about first-dose hypotension and advise them to avoid driving and other hazardous activities for 12 to 24 hours after the initial dose. To minimize risk, advise patients to take the first dose at bedtime.

BETA-ADRENERGIC ANTAGONISTS

Acebutolol
Atenolol
Beixolol
Bisoprolol
Carteolol
Carvedilol
Labetalol
Metoprolol
Nadolol
Nebivolol
Pembolol
Pindolol
Propranolol
Timolol

Except where noted, the implications summarized here apply to all beta-adrenergic blocking agents.

Preadministration Assessment

Therapeutic Goal

Principal indications are *hypertension*, *angina pectoris*, *heart failure*, and *cardiac dysrhythmias*. Indications for individual agents are summarized in Table 18-3.

Baseline Data

All Patients. Determine heart rate.
Hypertension. Determine standing and supine blood pressure.
Angina Pectoris. Determine the incidence, severity, and circumstances of anginal attacks.
Cardiac Dysrhythmias. Obtain a baseline electrocardiogram (ECG).

Identifying High-Risk Patients

All beta blockers are *contraindicated* for patients with sinus bradycardia or AV heart block greater than first degree, and must be used with *great caution* in patients with heart failure. Use with *caution* (especially the nonselective agents) in patients with asthma, bronchospasm, diabetes, or a history of severe allergic reactions. Use all beta blockers with *caution* in patients with a history of depression and in those taking calcium channel blockers.

Implementation: Administration

Routes

Oral. All beta blockers listed above.
Intravenous. Atenolol, labetalol, metoprolol, and propranolol.

Continued

Summary of Major Nursing Implications—cont'd

Administration

For maintenance therapy of hypertension, administer one or more times daily (see Table 18-2 and text).

Warn patients against abrupt discontinuation of treatment.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Hypertension. Monitor blood pressure and heart rate prior to each dose. Advise outpatients to monitor blood pressure and heart rate daily.

Angina Pectoris. Advise patients to record the incidence, circumstances, and severity of anginal attacks.
Cardiac Dysrhythmias. Monitor for improvement in the ECG.

Minimizing Adverse Effects

Bradycardia. Beta₁ blockade can reduce heart rate. If bradycardia is severe, withhold medication and notify the physician. If necessary, administer atropine and isoproterenol to restore heart rate.

AV Heart Block. Beta₁ blockade can decrease AV conduction. Do not give beta blockers to patients with AV block greater than first degree.

Heart Failure. Suppression of myocardial contractility can cause heart failure. Inform patients about early signs of heart failure (shortness of breath, night coughs, swelling of the extremities), and instruct them to notify the prescriber if these occur.

Rebound Cardiac Excitation. Abrupt withdrawal of beta blockers can cause tachycardia and ventricular dysrhythmias. Warn patients against abrupt discontinuation of drug use. Also, advise patients, when traveling, to carry an adequate supply of medication plus a copy of their prescription.

Postural Hypotension. By blocking alpha-adrenergic receptors, *carvedilol* and *labetalol* can cause postural hypotension. Inform patients about signs of hypotension (lightheadedness, dizziness) and advise them to sit or lie down if these develop.

headiness, dizziness) and advise them to sit or lie down if these develop. Advise patients to move slowly when changing from a supine or sitting position to an upright position.
Bronchoconstriction. Beta₂ blockade can cause substantial airway constriction in patients with asthma. The risk of bronchoconstriction is much lower with the cardioselective agents than with the nonselective agents.

Effects in Diabetic Patients. Beta₁ blockade can "mask" tachycardia, an early sign of hypoglycemia. Warn patients that tachycardia cannot be relied on as an indicator of impending hypoglycemia, and teach them to recognize other indicators (sweating, hunger, fatigue, poor concentration) that blood glucose is falling dangerously low. Beta₁ blockade can prevent glycogenolysis, an emergency means of increasing blood glucose. Patients may need to reduce their insulin dosage. Cardioselective beta blockers are preferred to nonselective agents in patients with diabetes.

Effects in Neonates. Maternal use of *betaxolol* during pregnancy may cause bradycardia, respiratory distress, and hypoglycemia in the infant. Accordingly, for 3 to 5 days after birth, newborns should be closely monitored for these effects. Beta blockers other than *betaxolol* may pose a similar risk.

CNS Effects. Rarely, beta blockers cause depression, insomnia, and nightmares. If these occur, switching to a beta blocker with low lipid solubility may help (see Table 18-2).

Minimizing Adverse Interactions

Calcium Channel Blockers. Two calcium channel blockers—*verapamil* and *diltiazem*—can intensify the cardio-suppressant effects of the beta blockers. Use these combinations with caution.

Insulin. Beta blockers can prevent the compensatory glycogenolysis that normally occurs in response to insulin-induced hypoglycemia. Diabetic patients may need to reduce their insulin dosage.

Indirect-Acting Antiadrenergic Agents

Centrally Acting Alpha₂ Agonists

Clonidine

Guanabenz and Guanfacine

Methyldopa and Methyldopate

Adrenergic Neuron-Blocking Agents

Reserpine

The indirect-acting antiadrenergic agents are drugs that prevent the activation of peripheral adrenergic receptors, but by mechanisms that do not involve direct interaction with peripheral receptors. There are two categories of indirect-acting antiadrenergic drugs. The first group—*centrally acting alpha₂ agonists*—consists of drugs that act within the central nervous system (CNS) to reduce the outflow of impulses along sympathetic neurons. The second group—*adrenergic neuron-blocking agents*—consists of drugs that act within the terminals of sympathetic neurons to decrease norepinephrine (NE) release. With both groups, the net result is reduced activation of peripheral adrenergic receptors. Hence, the pharmacologic effects of the indirect-acting adrenergic blocking agents are very similar to those of drugs that block adrenergic receptors directly.

CENTRALLY ACTING ALPHA₂ AGONISTS

The drugs discussed in this section act within the CNS to reduce the firing of sympathetic neurons. Their primary use is hypertension.

Why are we discussing centrally acting drugs in a unit on peripheral nervous system pharmacology? Because the effects of these drugs are ultimately the result of decreased activation of alpha- and beta-adrenergic receptors in the periphery. That is, by inhibiting the firing of sympathetic neurons, the centrally acting agents decrease the release of NE from sympathetic nerves, and thereby decrease activation of peripheral adrenergic receptors. Hence, although these drugs act within the CNS, their effects are like those of the direct-acting adrenergic receptor blockers. Accordingly, it seems appropriate to discuss these agents in the context of peripheral nervous system pharmacology, rather than presenting them in the context of CNS drugs.

Clonidine

Clonidine [Catapres, Catapres-TTS, Jenloga] is a centrally acting alpha₂ agonist with two approved indications: *hypertension* and *severe pain*. For treatment of hypertension, the

drug is sold as *Catapres* and *Jenloga*. For treatment of pain it's sold as *Duraclon*. Use for hypertension is discussed here. Use against pain is discussed in Chapter 28.

Clonidine is a widely used antihypertensive drug. Why? Because it's both effective and safe. Except for rare instances of rebound hypertension, the drug is generally free of serious adverse effects. Dosing is done orally or by transdermal patch.

Mechanism of Antihypertensive Action

Clonidine is an alpha₂-adrenergic agonist that causes "selective" activation of alpha₂ receptors in the CNS—specifically, in brainstem areas associated with autonomic regulation of the cardiovascular system. By activating central alpha₂ receptors, clonidine reduces sympathetic outflow to blood vessels and to the heart.

Pharmacologic Effects

The most significant effects of clonidine concern the heart and vascular system. By suppressing the firing of sympathetic nerves to the heart, clonidine can cause *bradycardia* and a *decrease in cardiac output*. By suppressing sympathetic regulation of blood vessels, the drug promotes *vasodilation*. The net result of cardiac suppression and vasodilation is *decreased blood pressure*. Blood pressure is reduced in both supine and standing subjects. (Note that the effect of clonidine on blood pressure is unlike that of the peripheral alpha-adrenergic blockers, which tend to decrease blood pressure only when the patient is standing.) Because the hypotensive effects of clonidine are not posture dependent, orthostatic hypotension is minimal.

Pharmacokinetics

Clonidine is very lipid soluble. As a result, the drug is readily absorbed after oral dosing and is widely distributed throughout the body, including the CNS. Hypotensive responses begin 30 to 60 minutes after administration and peak in 4 hours. Effects of a single dose may persist as long as 1 day. Clonidine is eliminated by a combination of hepatic metabolism and renal excretion.

Therapeutic Uses

Clonidine has two *approved* applications: treatment of hypertension (its main use) and relief of severe pain (see Chapter 28). *Investigational* uses include treating attention-deficit/hyperactivity disorder (ADHD), managing opioid withdrawal, facilitating smoking cessation, and treating Tourette's syndrome, a CNS disease characterized by uncontrollable tics and verbal outbursts that are frequently obscene.

Adverse Effects

Drowsiness. CNS depression is common. About 35% of patients experience drowsiness; an additional 8% experience

outright sedation. These responses become less intense with continued drug use. Patients in their early weeks of treatment should be advised to avoid hazardous activities if alertness is impaired.

Xerostomia. Xerostomia (dry mouth) is common, occurring in about 40% of patients. The reaction usually diminishes over the first 2 to 4 weeks of therapy. Although not dangerous, xerostomia can be annoying enough to discourage drug use. Patients should be advised that discomfort can be reduced by chewing gum, sucking hard candy, and taking frequent sips of fluids.

Rebound Hypertension. Rebound hypertension is characterized by a large increase in blood pressure occurring in response to abrupt clonidine withdrawal. This rare but serious reaction is caused by overactivity of the sympathetic nervous system, and can be accompanied by nervousness, tachycardia, and sweating. Left untreated, the reaction may persist for a week or more. If blood pressure climbs dangerously high, it should be lowered with a combination of alpha- and beta-adrenergic blocking agents. Rebound effects can be avoided by withdrawing clonidine slowly (over 2 to 4 days). Patients should be informed about rebound hypertension and warned not to discontinue clonidine without consulting the prescriber.

Use in Pregnancy. Clonidine is embryotoxic in animals. Because of the possibility of fetal harm, clonidine is not recommended for pregnant women. Pregnancy should be ruled out before clonidine is given.

Abuse. People who abuse cocaine, opioids (eg, morphine, heroin), and other drugs frequently abuse clonidine as well. Why? Because at high doses, clonidine can cause subjective effects—euphoria, sedation, hallucinations—that some individuals find desirable. In addition, clonidine can intensify the subjective effects of some abused drugs, including benzodiazepines, cocaine, and opioids. Since clonidine costs less than these drugs, the combination allows abusers to get high for less money.

Other Adverse Effects. Clonidine can cause a variety of adverse effects, including constipation, impotence, gynecomastia, and adverse CNS effects (eg, vivid dreams, nightmares, anxiety, depression). Localized skin reactions are common with transdermal clonidine patches.

Preparations, Dosage, and Administration

Preparations. Clonidine hydrochloride is available in oral and transdermal formulations. Oral clonidine is available in standard tablets (0.1, 0.2, and 0.3 mg) marketed as *Catapres*, and in modified-release tablets (0.1 mg) marketed as *Jenloga*. Transdermal clonidine [*Catapres-TTS*] is available in 2.5-, 5-, and 7.5-mg patches that deliver 0.1, 0.2, and 0.3 mg/24 hr, respectively.

Dosage and Administration. Oral. For treatment of hypertension, the initial adult dosage is 0.1 mg twice a day. The usual maintenance dosage is 0.2 to 0.6 mg/day, administered in divided doses. By taking the majority of the daily dose at bedtime, daytime sedation can be minimized.

Transdermal. Transdermal patches are applied to a region of hairless, intact skin on the upper arm or torso. A new patch is applied every 7 days.

Guanabenz and Guanfacine

The pharmacology of guanabenz [*Wyntensin*] and guanfacine [*Tenex*] is very similar to that of clonidine. Like clonidine, both drugs are indicated for hypertension. In addition, guanfacine, marketed as *Intuniv*, is used for ADHD (see Chapter 36). Benefits in hypertension derive from activating brainstem alpha₂-adrenergic receptors, an action that reduces sympathetic outflow to the heart and blood vessels. The result is a reduction in cardiac output and blood pressure. Both drugs have the same major adverse effects

as clonidine: sedation and dry mouth. In addition, both can cause rebound hypertension following abrupt withdrawal. Guanabenz is available in 4- and 8-mg tablets. Dosing is begun at 4 mg twice daily and can be increased to 32 mg twice daily. For treatment of hypertension, guanfacine is available in 1- and 2-mg tablets. The usual dosage is 1 mg/day, taken at bedtime to minimize daytime sedation. Preparations and dosage for ADHD are presented in Chapter 36.

Methyldopa and Methyldopate

Methyldopa is an oral antihypertensive agent that lowers blood pressure by acting at sites within the CNS. Two side effects—hemolytic anemia and hepatic necrosis—can be severe. Methyldopate, an intravenous agent, is nearly identical to methyldopa in structure and pharmacologic effects. In the discussion below, the term *methyldopa* is used in reference to both methyldopate and methyldopa itself.

Mechanism of Action

Methyldopa works much like clonidine. Like clonidine, methyldopa inhibits sympathetic outflow from the CNS by causing alpha₂ activation in the brain. However, methyldopa differs from clonidine in that methyldopa itself is not an alpha₂ agonist. Hence, before it can act, methyldopa must first be taken up into brainstem neurons, where it is then converted to methylnorepinephrine, a compound that is an effective alpha₂ agonist. Release of methylnorepinephrine results in alpha₂ activation.

Pharmacologic Effects

The most prominent response to methyldopa is a drop in blood pressure. The principal mechanism is vasodilation, not cardiosuppression. Vasodilation occurs because of reduced sympathetic traffic to blood vessels. At usual therapeutic doses, methyldopa does not decrease heart rate or cardiac output. Hence, hypotensive actions cannot be ascribed to cardiac depression. The hemodynamic effects of methyldopa are very much like those of clonidine: Both drugs lower blood pressure in supine and standing subjects, and both produce relatively little orthostatic hypotension.

Therapeutic Use

The only indication for methyldopa is *hypertension*. Methyldopa was one of the earliest antihypertensive agents available and remains in wide use. Methyldopate may be used for hypertensive crisis, but other drugs are preferred.

Adverse Effects

Positive Coombs' Test and Hemolytic Anemia. A positive Coombs' test* develops in 10% to 20% of patients who take methyldopa chronically. The test usually turns positive between the 6th and 12th month of treatment. Of the patients who have a positive Coombs' test, only a few (about 5%) develop hemolytic anemia. Coombs-positive patients who do not develop hemolytic anemia may continue methyldopa treatment. However, if hemolytic anemia does develop, methyldopa should be withdrawn immedi-

*The Coombs' test detects the presence of antibodies directed against the patient's own red blood cells. These antibodies can cause hemolysis (ie, red blood cell lysis).

ately. For most patients, hemolytic anemia then quickly resolves, although the Coombs' test may remain positive for months. A Coombs' test should be performed prior to treatment and 6 to 12 months later. Blood counts (hematocrit, hemoglobin, or red cell count) should be obtained prior to treatment and periodically thereafter.

Hepatotoxicity. Methyldopa has been associated with hepatitis, jaundice, and, rarely, fatal hepatic necrosis. All patients should undergo periodic assessment of liver function. If signs of hepatotoxicity appear, methyldopa should be discontinued immediately. Liver function usually normalizes after drug withdrawal.

Other Adverse Effects. Methyldopa can cause *xerostomia*, *sexual dysfunction*, *orthostatic hypotension*, and a variety of *CNS effects*, including drowsiness, reduced mental acuity, nightmares, and depression. These responses are not usually dangerous, but they can detract from adherence.

Preparations, Dosage, and Administration

Preparations. *Methyldopa* is available in tablets (250 and 500 mg) for oral use. *Methyldopate* is available in solution (50 mg/mL) for IV use.

Oral Therapy with Methyldopa. For treatment of hypertension, the initial adult dosage is 250 mg 2 to 3 times a day. Daily maintenance dosages usually range from 0.5 to 2 gm administered in two to four divided doses.

Intravenous Therapy with Methyldopate. Methyldopate, administered by slow IV infusion, is indicated for hypertensive emergencies. However, since faster acting drugs are available, use of methyldopate is rare. Methyldopate for infusion should be diluted in 5% dextrose to a concentration of 10 mg/mL. The usual adult dose is 250 to 500 mg infused over 30 to 60 minutes. Dosing may be repeated every 6 hours as required.

ADRENERGIC NEURON-BLOCKING AGENTS

The adrenergic neuron-blocking agents act presynaptically to reduce the release of NE from sympathetic neurons. These drugs have little or no effect on the release of epinephrine from the adrenal medulla. At this time, *reserpine* is the only adrenergic neuron blocker available. Two others—*guanadrel* [Hylorel] and *guanethidine* [Ismelin]—have been withdrawn.

Reserpine

Reserpine is a naturally occurring compound prepared from the root of *Rauwolfia serpentina*, a shrub indigenous to India. Because of its source, reserpine is classified as a *Rauwolfia alkaloid*. The primary indication for reserpine is hypertension. The side effect of greatest concern is severe depression.

Mechanism of Action

Reserpine causes *depletion of NE from postganglionic sympathetic neurons*. By doing so, the drug can decrease activation of practically all adrenergic receptors. Hence, the effects of reserpine closely resemble those produced by a combination of alpha- and beta-adrenergic blockade.

Reserpine depletes NE in two ways. First, the drug acts on vesicles within the nerve terminal to cause displacement of stored NE, thereby exposing the transmitter to destruction by monoamine oxidase. Second, reserpine suppresses NE synthesis. How? By blocking the uptake of dopamine (the immediate precursor of NE) into presynaptic vesicles, which contain the enzymes needed to convert dopamine into NE (Fig. 19-1). A week or two may be required to produce maximal transmitter depletion.

In addition to its peripheral effects, reserpine can cause depletion of transmitters (serotonin, catecholamines) from neurons in the CNS. Depletion of these CNS transmitters underlies the most serious side effect of reserpine—deep emotional depression—and also explains the occasional use of reserpine in psychiatry.

Pharmacologic Effects

Peripheral Effects. By depleting sympathetic neurons of NE, reserpine decreases the activation of alpha- and beta-adrenergic receptors. Decreased activation of beta receptors slows heart rate and reduces cardiac output. Decreased alpha activation promotes vasodilation. All three effects cause a *decrease in blood pressure*.

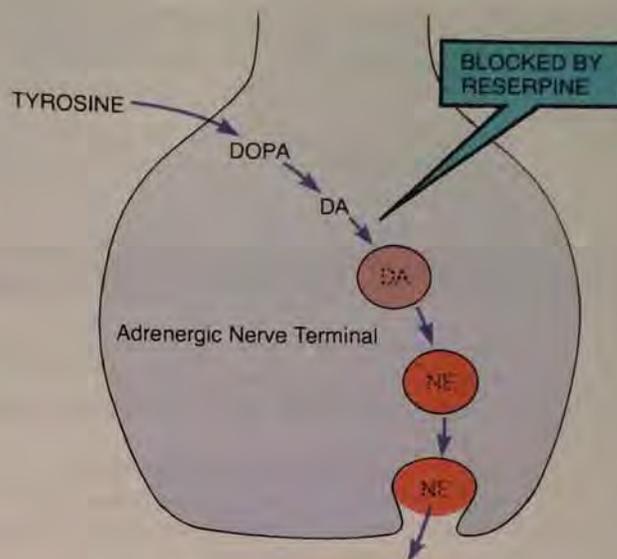


Figure 19-1 • Mechanism of reserpine action.

Reserpine depletes neurons of norepinephrine (NE) by two mechanisms. (1) As indicated in this figure, reserpine blocks the uptake of dopamine (DA) into vesicles, thereby preventing NE synthesis. (2) Reserpine also displaces NE from vesicles, thereby allowing degradation of NE by monoamine oxidase present in the nerve terminal (not shown).

Effects on the CNS. Reserpine produces sedation and a state of indifference to the environment. In addition, the drug can cause severe depression. These effects are thought to result from depletion of certain neurotransmitters (catecholamines, serotonin) from neurons in the brain.

Therapeutic Uses

Hypertension. The principal indication for reserpine is hypertension. Benefits result from vasodilation and reduced cardiac output. Since these effects occur secondary to depletion of NE, and since transmitter depletion occurs slowly, full antihypertensive responses can take a week or more to develop. Conversely, when reserpine is discontinued, effects may persist for several weeks as the NE content of sympathetic neurons becomes replenished. Because its side effects can be severe, and because more desirable drugs are available (see Chapter 47), reserpine is not a preferred drug for hypertension.

Psychotic States. Reserpine can be used to treat agitated psychotic patients, such as those suffering from certain forms of schizophrenia. However, since superior drugs are available, reserpine is rarely employed in psychotherapy.

Adverse Effects

Depression. Reserpine can produce severe depression that may persist for months after the drug is withdrawn. Suicide has occurred. All patients should be informed about the risk of depression. Also, they should be educated about signs of depression (eg, early morning insomnia, loss of appetite, change in mood) and instructed to notify the prescriber immediately if these develop. Because of the risk of suicide, patients who develop depression may require hospitalization. *Reserpine is contraindicated for patients with a history of depressive disorders.* The risk of depression can be minimized by keeping the dosage low (0.25 mg/day or less).

Cardiovascular Effects. Depletion of NE from sympathetic neurons can result in *bradycardia*, *orthostatic hypotension*, and *nasal congestion*. Bradycardia is caused by decreased activation of beta₁ receptors in the heart. Hypotension and nasal congestion result from vasodilation secondary to decreased activation of alpha receptors on blood vessels. Patients should be informed that orthostatic hypotension, the most serious cardiovascular effect, can be minimized by moving slowly when changing from a seated or supine position to an upright position. In addition, patients should be advised to sit or lie down if lightheadedness or dizziness occurs.

CHAPTER 19 Indirect-Acting Antidiadrenergic Agents

GI Effects. By mechanisms that are not understood, reserpine can stimulate several aspects of GI function. The drug can increase secretion of gastric acid which may result in *ulcer formation*. In addition, reserpine can increase the tone and motility of intestinal smooth muscle, thereby causing *cramps and diarrhea*.

KEY POINTS

- All of the drugs discussed in this chapter reduce activation of peripheral alpha- and beta-adrenergic receptors, but they do so by mechanisms other than direct receptor blockade.
- The principal indication for these drugs is hypertension.
- Clonidine and methyldopa reduce sympathetic outflow to the heart and blood vessels by causing activation of alpha₂-adrenergic receptors in the brainstem.

Preparations, Dosage, and Administration

Reserpine is available in 0.1- and 0.25-mg tablets, which may be administered with food if GI upset occurs. The usual initial dosage for hypertension in adults is 0.5 mg/day for 1 to 2 weeks. The usual maintenance dosage is 0.25 mg/day.

- The principal adverse effects of clonidine are drowsiness and dry mouth. Rebound hypertension can occur if the drug is abruptly withdrawn.
- The principal adverse effects of methyldopa are hemolytic anemia and liver damage.

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Summary of Major Nursing Implications—cont'd

Administration

Most patients on oral therapy require divided (two to four) daily doses. For some patients, blood pressure can be controlled with a single daily dose at bedtime.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor blood pressure.

Minimizing Adverse Effects

Hemolytic Anemia. If hemolysis occurs, withdraw methyldopa immediately; hemolytic anemia usually resolves soon. Obtain a Coombs' test prior to treatment and 6 to 12 months later. Obtain blood counts (hematocrit, hemoglobin, or red cell count) prior to treatment and periodically thereafter.

Hepatotoxicity. Methyldopa can cause hepatitis, jaundice, and fatal hepatic necrosis. Assess liver function prior to treatment and periodically thereafter. If liver dysfunction develops, discontinue methyldopa immediately. In most cases, liver function returns to normal soon.

Summary of Major Nursing Implications*

CLONIDINE

Preadministration Assessment

Therapeutic Goal

Reduction of blood pressure in hypertensive patients.¹

Baseline Data

Determine blood pressure and heart rate.

Identifying High-Risk Patients

Clonidine is embryotoxic to animals and should not be used during pregnancy. Rule out pregnancy before initiating treatment.

Implementation: Administration

Routes

Oral, transdermal.

Administration

Oral. Advise the patient to take the major portion of the daily dose at bedtime to minimize daytime sedation.

Transdermal. Instruct the patient to apply transdermal patches to hairless, intact skin on the upper arm or torso, and to apply a new patch every 7 days.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor blood pressure.

Minimizing Adverse Effects

Drowsiness and Sedation. Inform patients about possible CNS depression and warn them to avoid hazardous activities if alertness is reduced.

*Patient education information is highlighted as blue text.

¹As discussed in Chapter 28, clonidine is also used to relieve severe pain.

Xerostomia. Dry mouth is common. Inform patients that discomfort can be reduced by chewing gum, sucking hard candy, and taking frequent sips of fluids.

Rebound Hypertension. Severe hypertension occurs rarely following abrupt clonidine withdrawal. Treat with a combination of alpha- and beta-adrenergic blockers. To avoid rebound hypertension, withdraw clonidine slowly (over 2 to 4 days). Inform patients about rebound hypertension and warn them against abrupt discontinuation of treatment.

Abuse. People who abuse cocaine, opioids, and other drugs frequently abuse clonidine as well. Be alert for signs of clonidine abuse (eg, questionable or frequent requests for a prescription).

METHYLDOPA

Preadministration Assessment

Therapeutic Goal

Reduction of blood pressure in hypertensive patients.

Baseline Data

Obtain baseline values for blood pressure, heart rate, blood counts (hematocrit, hemoglobin, or red cell count), Coombs' test, and liver function tests.

Identifying High-Risk Patients

Methyldopa is *contraindicated* for patients with active liver disease or a history of methyldopa-induced liver dysfunction.

Implementation: Administration

Routes

Oral. For routine management of hypertension **Intravenous.** For hypertensive emergencies.

Introduction to Central Nervous System Pharmacology

Transmitters of the CNS

The Blood-Brain Barrier

How Do CNS Drugs Produce Therapeutic Effects?

Adaptation of the CNS to Prolonged Drug Exposure

Development of New Psychotherapeutic Drugs

Approaching the Study of CNS Drugs

The central nervous system (CNS) drugs—agents that act on the brain and spinal cord—are used widely for medical and nonmedical purposes. Medical applications include relief of pain, suppression of seizures, production of anesthesia, and treatment of psychiatric disorders. CNS drugs are used non-medically for their stimulant, depressant, euphoriant, and other “mind-altering” abilities.

Despite the widespread use of CNS drugs, knowledge of these agents is limited. Much of our ignorance stems from the anatomic and neurochemical complexity of the brain and spinal cord. (There are more than 50 billion neurons in the cerebral hemispheres alone.) Because of this complexity, we are a long way from fully understanding both the CNS itself and the drugs used to affect it.

TRANSMITTERS OF THE CNS

In contrast to the peripheral nervous system, in which only three compounds—acetylcholine, norepinephrine, and epinephrine—serve as neurotransmitters, the CNS contains at least 21 compounds that serve as neurotransmitters (Table 20-1). Furthermore, since there are numerous sites within the CNS for which no transmitter has been identified, it is clear that additional compounds, yet to be discovered, also mediate central neurotransmission.

It is important to note that none of the compounds that are thought to be CNS neurotransmitters has actually been *proved* to serve this function. The reason for uncertainty lies with the technical difficulties involved in CNS research. However, although absolute proof may be lacking, the evidence supporting a neurotransmitter role for several compounds (eg, dopamine, norepinephrine, serotonin, enkephalins) is completely convincing.

Although much is known about the actions of CNS transmitters at various sites in the brain and spinal cord, it is not usually possible to relate these known actions in a precise way to behavioral or psychologic processes. For example, although we know the locations of specific CNS sites at which

TABLE 20-1 • Neurotransmitters of the CNS

Monoamines	Opioid Peptides
Norepinephrine	Dynorphins
Epinephrine	Endorphins
Dopamine	Enkephalins
Serotonin	
Amino Acids	Nonopioid Peptides
Aspartate	Neurotensin
Glutamate	Somatostatin
GABA	Substance P
Glycine	Oxytocin
	Vasopressin
Purines	Others
Adenosine	Acetylcholine
Adenosine monophosphate	Histamine
Adenosine triphosphate	

GABA = gamma-aminobutyric acid.

norepinephrine appears to act as a transmitter, and although we know the effect of norepinephrine at most of these sites (suppression of neuronal excitability), we do not know the precise relationship between suppression of neuronal excitability at each of these sites and the impact of that suppression on the overt function of the organism. This example illustrates the general state of our knowledge of CNS transmitter function: We have a great deal of detailed information about the biochemistry and electrophysiology of CNS transmitters, but we are as yet unable to assemble those details into a completely meaningful picture.

THE BLOOD-BRAIN BARRIER

As discussed in Chapter 4, the blood-brain barrier impedes the entry of drugs into the brain. Passage across the barrier is limited to lipid-soluble agents and to drugs that are able to cross by way of specific transport systems. Drugs that are protein bound and drugs that are highly ionized cannot cross.

From a therapeutic perspective, the blood-brain barrier is a mixed blessing. The good news is that the barrier protects the brain from injury by potentially toxic substances. The bad news is that the barrier can be a significant obstacle to entry of therapeutic agents.

The blood-brain barrier is not fully developed at birth. Accordingly, infants are much more sensitive to CNS drugs than are older children and adults.

HOW DO CNS DRUGS PRODUCE THERAPEUTIC EFFECTS?

Although much is known about the biochemical and electrophysiologic effects of CNS drugs, in most cases we cannot state with certainty the relationship between these effects and production of beneficial responses. Why? In order to fully understand how a drug alters symptoms, we need to understand, at a biochemical and physiologic level, the pathophysiology of the disorder being treated. In the case of most CNS disorders, our knowledge is limited. That is, we do not fully understand the brain in either health or disease. Given our incomplete understanding of the CNS itself, we must exercise caution when attempting to assign a precise mechanism for a drug's therapeutic effects.

Although we can't state with certainty how CNS drugs act, we do have sufficient data to permit formulation of plausible hypotheses. Consequently, as we study CNS drugs in the chapters that follow, proposed mechanisms of action are presented. Keep in mind, however, that these mechanisms are tentative, representing our best guess based on data available today. As we learn more, it is almost certain that these concepts will be modified, if not discarded entirely.

ADAPTATION OF THE CNS TO PROLONGED DRUG EXPOSURE

When CNS drugs are taken chronically, their effects may differ from those produced during initial use. These altered effects are the result of adaptive changes that occur in the brain in response to prolonged drug exposure. The brain's ability to adapt to drugs can produce alterations in therapeutic effects and side effects. Adaptive changes are often beneficial, although they can also be detrimental.

Increased Therapeutic Effects. Certain drugs used in psychiatry—antipsychotics and antidepressants—must be taken for several weeks before full therapeutic effects develop. It would appear that beneficial responses are delayed because they result from adaptive changes—and not from the direct effects of drugs on synaptic function. Hence, full therapeutic effects are not seen until the CNS has had time to modify itself in response to prolonged drug exposure.

Decreased Side Effects. When CNS drugs are taken chronically, the intensity of side effects may decrease (while therapeutic effects remain undiminished). For example, phenobarbital (an antiseizure drug) produces sedation during the initial phase of therapy; however, with continued treatment, sedation declines while full protection from seizures is retained. Similarly, when morphine is given to control pain, nausea is a common side effect early on; however, as treatment continues, nausea diminishes while analgesic effects persist. Adaptations within the brain are believed to underlie these phenomena.

Tolerance and Physical Dependence. Tolerance and physical dependence are special manifestations of CNS adaptation. *Tolerance* is defined as a decreased response occurring in the course of prolonged drug use. *Physical dependence* is defined as a state in which abrupt discontinuation of drug use will precipitate a withdrawal syndrome. Research indicates that the kinds of adaptive changes that underlie tolerance and dependence are such that, once they have taken place, contin-

ued drug use is required for the brain to function "normally." If drug use is stopped, the drug-adapted brain can no longer function properly, and hence a withdrawal syndrome ensues. The withdrawal reaction continues until the adaptive changes have had time to revert, thereby restoring the CNS to its pre-treatment state.

DEVELOPMENT OF NEW PSYCHOTHERAPEUTIC DRUGS

Because of deficiencies in our knowledge of the neurochemical and physiologic changes that underlie mental disease, it is impossible to take a rational approach to the development of truly new (nonderivative) psychotherapeutic agents. History bears this out: Virtually all of the major advances in psychopharmacology have been happy accidents.

In addition to our relative ignorance about the neurochemical and physiologic correlates of mental illness, two other factors contribute to the difficulty in generating truly new psychotherapeutic agents. First, in contrast to many other diseases, we lack adequate animal models of mental illness. Accordingly, animal research is not likely to reveal new types of psychotherapeutic agents. Second, mentally healthy individuals cannot be used as subjects to assess potential psychotherapeutic agents. Why? Because most psychotherapeutic drugs either have no effect on healthy individuals or produce paradoxical effects.

Once a new drug has been stumbled upon, variations on that agent can be developed systematically. The following process can be employed: (1) structural analogs of the new agent are synthesized, (2) these analogs are run through biochemical and physiologic screening tests to determine whether or not they possess activity similar to that of the parent compound, and (3) after serious toxicity has been ruled out, promising agents are tested in humans for possible psychotherapeutic activity. By following this procedure, it is possible to develop drugs that have fewer side effects than the original drug and perhaps even superior therapeutic effects. However, although this procedure may produce small advances, it is not likely to yield a major therapeutic breakthrough.

APPROACHING THE STUDY OF CNS DRUGS

Because our understanding of the CNS is less complete than our understanding of the peripheral nervous system, our approach to studying CNS drugs differs from the approach we took with peripheral nervous system agents. When we studied the pharmacology of the peripheral nervous system, we emphasized the importance of understanding transmitters and their receptors prior to embarking on a study of drugs. Since our knowledge of CNS transmitters is insufficient to allow this approach, rather than making a detailed examination of CNS transmitters before we study CNS drugs, we will discuss drugs and transmitters concurrently. Hence, for now, all that you need to know about CNS transmitters is that (1) there are a lot of them, (2) their precise functional roles are not clear, and (3) their complexity makes it difficult for us to know with certainty just how CNS drugs produce their beneficial effects.

KEY POINTS

- In the CNS, at least 21 compounds appear to act as neurotransmitters, whereas in the periphery, only three compounds act as neurotransmitters.
- As a rule, we do not understand with precision how CNS drugs produce their effects.
- The blood-brain barrier can protect the CNS from toxic substances, but can also block entry of medicines into the CNS.

- The CNS often undergoes adaptive changes during prolonged drug exposure. The result can be increased therapeutic effects, decreased side effects, tolerance, and physical dependence.

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Drugs for Parkinson's Disease

Pathophysiology That Underlies Motor Symptoms
 Overview of Motor Symptom Management
 Pharmacology of the Drugs Used for Motor Symptoms

Levodopa

Levodopa/Carbidopa

Dopamine Agonists

COMT Inhibitors

Levodopa/Carbidopa/Entacapone

MAO-B Inhibitors

Amantadine

Centrally Acting Anticholinergic Drugs

Nonmotor Symptoms and Their Management

Box 21-1. Surgical and Electrical Treatments for Parkinson's Disease

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder first described in 1817 by Dr. James Parkinson, a London physician. The disease afflicts over 1 million Americans, making it second only to Alzheimer's disease as the most common degenerative disease of neurons. Cardinal symptoms are tremor, rigidity, postural instability, and slowed movement. In addition to these motor symptoms, most patients also experience nonmotor symptoms, especially autonomic disturbances, sleep disturbances, depression, psychosis, and dementia. Years before functional impairment develops, patients may experience early symptoms of PD, including loss of smell, excessive salivation, clumsiness of the hands, worsening of handwriting, bothersome tremor, slower gait, and reduced voice volume. As a rule, symptoms first appear in middle age and progress relentlessly. The underlying cause of motor symptoms is loss of dopaminergic neurons in the substantia nigra. Although there is no cure for motor symptoms, drug therapy can maintain functional mobility for years, and can thereby substantially prolong quality of life and life expectancy. The most effective drug for PD is levodopa, given in combination with carbidopa. Unfortunately, as neurodegeneration progresses, levodopa eventually becomes ineffective.

PATHOPHYSIOLOGY THAT UNDERLIES MOTOR SYMPTOMS

Motor symptoms result from damage to the *extrapyramidal system*, a complex neuronal network that helps regulate movement. When extrapyramidal function is disrupted, *dyskinesias*

(disorders of movement) result. The dyskinesias that characterize PD are tremor at rest, rigidity, postural instability, and bradykinesia (slowed movement). In severe PD, bradykinesia may progress to *akinesia*—complete absence of movement.

In people with PD, neurotransmission is disrupted primarily in the *striatum*, an important component of the extrapyramidal system. A simplified model of striatal neurotransmission is depicted in Figure 21-1A. As indicated, proper function of the striatum requires a balance between two neurotransmitters: *dopamine* and *acetylcholine* (ACh). Dopamine is an *inhibitory* transmitter; ACh is *excitatory*. According to the model, the neurons that release dopamine inhibit neurons that release gamma-aminobutyric acid (GABA, another inhibitory transmitter). In contrast, the neurons that release ACh excite the neurons that release GABA. Movement is normal when the inhibitory influence of dopamine and the excitatory influence of ACh are in balance. Note that the neurons that supply dopamine to the striatum originate in the *substantia nigra*. Between 70% and 80% of these neurons must be lost before PD becomes clinically recognizable. This loss takes place over 5 to 20 years. Put another way, neuronal degeneration begins long before overt motor symptoms appear.

In PD, there is an imbalance between dopamine and ACh in the striatum (Fig. 21-1B). As noted, the imbalance results from *degeneration of the neurons that supply dopamine to the striatum*. In the absence of dopamine, the excitatory influence of ACh goes unopposed, causing excessive stimulation of the neurons that release GABA. Overactivity of these GABAergic neurons contributes to the motor symptoms that characterize PD.

What causes degeneration of dopaminergic neurons? No one knows for sure. However, some evidence strongly implicates *alpha-synuclein*—a potentially toxic protein synthesized by dopaminergic neurons. Under normal conditions, alpha-synuclein is rapidly degraded. As a result, it doesn't accumulate and no harm occurs. Degradation of alpha-synuclein requires two other proteins: *parkin* and *ubiquitin*. (Parkin is an enzyme that catalyzes the binding of alpha-synuclein to ubiquitin. Once bound to ubiquitin, alpha-synuclein can be degraded.) If any of these proteins—alpha-synuclein, parkin, or ubiquitin—is defective, degradation of alpha-synuclein cannot take place. When this occurs, alpha-synuclein accumulates inside the cell, forming neurotoxic fibrils. At autopsy, these fibrils are visible as so-called *Lewy bodies*, which are characteristic of PD pathology. Failure to degrade alpha-synuclein appears to result from two causes: genetic vulnerability and toxins in the environment. Defective genes coding for all three proteins have been found in families with inherited forms of PD. In people with PD that is not inherited, environmental toxins may explain the inability to degrade alpha-synuclein.

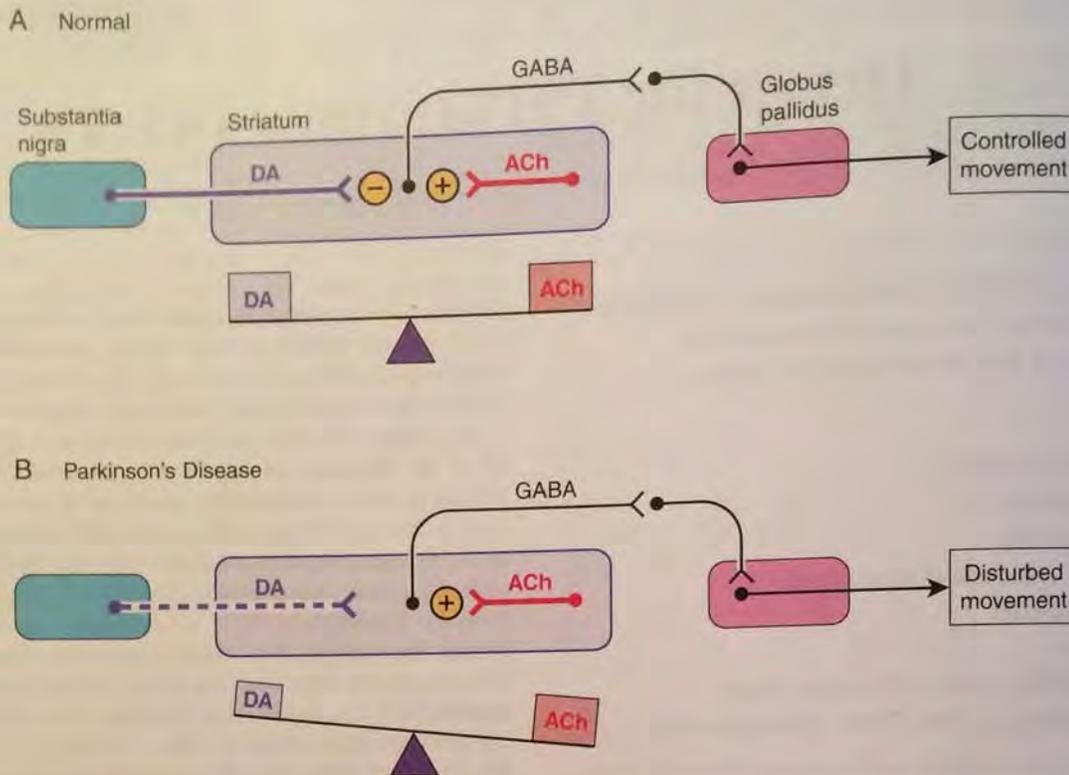


Figure 21-1 • A model of neurotransmission in the healthy striatum and parkinsonian striatum.

A. In the healthy striatum, dopamine (DA) released from neurons originating in the substantia nigra *inhibits* the firing of neurons in the striatum that release gamma-aminobutyric acid (GABA). Conversely, neurons located within the striatum, which release acetylcholine (ACh), *excite* the GABAergic neurons. Hence, under normal conditions, the inhibitory actions of DA are balanced by the excitatory actions of ACh, and controlled movement results. **B.** In Parkinson's disease, the neurons that supply DA to the striatum degenerate. In the absence of sufficient DA, the excitatory effects of ACh go unopposed, and disturbed movement results.

As discussed in Chapter 31, movement disorders similar to those of PD can occur as side effects of antipsychotic drugs. These dyskinesias, which are referred to as *extrapyramidal side effects*, result from blockade of dopamine receptors in the striatum. This drug-induced parkinsonism can be managed with some of the drugs used to treat PD.

OVERVIEW OF MOTOR SYMPTOM MANAGEMENT

Therapeutic Goal

Ideally, treatment would reverse neuronal degeneration, or at least prevent further degeneration, and control symptoms. Unfortunately, the ideal treatment doesn't exist: We have no drugs that can prevent neuronal damage or reverse damage that has already occurred. Hence, the goal with current drugs is simply to improve the patient's ability to carry out activities of daily life. Drug selection and dosage are determined by the extent to which PD interferes with work, walking, dressing, eating, bathing, and other activities. Drugs benefit the patient primarily by improving bradykinesia, gait disturbance, and postural instability. Tremor and rigidity, although disturbing,

are less disabling. It is important to note that drugs only provide symptomatic relief; they do not cure PD. Furthermore, there is no convincing proof that any current drug can delay disease progression.

Drugs Employed

Given the neurochemical basis of parkinsonism—too little striatal dopamine and too much ACh—the approach to treatment is obvious: Give drugs that can restore the functional balance between dopamine and ACh. To accomplish this, two types of drugs are used: (1) *dopaminergic agents* (ie, drugs that directly or indirectly cause activation of dopamine receptors); and (2) *anticholinergic agents* (ie, drugs that block receptors for ACh). Of the two groups, dopaminergic agents are by far the more widely employed.

As shown in Table 21-1, dopaminergic drugs act by several mechanisms: levodopa promotes dopamine synthesis; the dopamine agonists activate dopamine receptors directly; inhibitors of monoamine oxidase-B (MAO-B) prevent dopamine breakdown; amantadine promotes dopamine release (and may also block dopamine reuptake); and the inhibitors of catechol-*O*-methyltransferase (COMT) enhance the effects of levodopa by blocking its degradation.

TABLE 21-1 Dopaminergic Agents for Parkinson's Disease

Drug	Mechanism of Action	Therapeutic Role
Dopamine Replacement		
Levodopa/carbidopa	Levodopa undergoes conversion to DA in the brain and then activates DA receptors (carbidopa blocks destruction of levodopa in the periphery)	First-line drug, or supplement to a dopamine agonist
Dopamine Agonists		
Nonergot Derivatives		
Apomorphine Pramipexole Ropinirole	Directly activate DA receptors	Pramipexole and ropinirole are first-line drugs, or supplements to levodopa. Apomorphine—a subQ nonergot agent—is reserved for rescue therapy during “off” times. Ergot derivatives are generally avoided
Ergot Derivatives		
Bromocriptine Cabergoline		
COMT Inhibitors		
Entacapone Tolcapone	Inhibit breakdown of levodopa by COMT	Adjunct to levodopa to decrease “wearing off”; entacapone is more effective and safer than tolcapone
MAO-B Inhibitors		
Selegiline Rasagiline	Inhibit breakdown of DA by MAO-B	Used in newly diagnosed patients and for managing “off” times during levodopa therapy
Dopamine Releaser		
Amantadine	Promotes release of DA from remaining DA neurons; may also block DA reuptake	May help reduce levodopa-induced dyskinesias

COMT = catechol-*O*-methyltransferase; DA = dopamine; MAO-B = type B monoamine oxidase.

In contrast to the dopaminergic drugs, which act by multiple mechanisms, all of the anticholinergic agents share the same mechanism: blockade of muscarinic receptors in the striatum.

Clinical Guidelines

The American Academy of Neurology (AAN) has developed evidence-based guidelines for the treatment of Parkinson's disease. These guidelines were published in *Neurology* as six separate articles, released in 2002, 2006, and 2010. Their titles and release years are as follows:

- Initiation and Treatment for Parkinson Disease (Updated), 2002
- Diagnosis and Prognosis for New Onset Parkinson Disease, 2006
- Neuroprotective Strategies and Alternative Therapies for New Onset Parkinson Disease, 2006
- Evaluation and Treatment of Depression, Psychosis and Dementia in Parkinson Disease, 2006
- Medical and Surgical Treatment of Parkinson Disease with Motor Fluctuations and Dyskinesia, 2006
- Treatment of Nonmotor Symptoms of Parkinson Disease, 2010

The entire set is available free online at www.neurology.org. The recommendations below are based on these guidelines.

Drug Selection

Initial Treatment. For patients with mild symptoms, treatment can begin with selegiline, an MAO-B inhibitor that confers mild, symptomatic benefit. Rasagiline, an MAO-B

inhibitor that was not available when the guidelines were published, would probably work just as well.

For patients with more severe symptoms, treatment should begin with either levodopa (combined with carbidopa) or a dopamine agonist. Levodopa is more effective than the dopamine agonists, but long-term use carries a higher risk of disabling dyskinesias. Hence, the choice must be tailored to the patient: If improving motor function is the primary objective, then levodopa is preferred. However, if drug-induced dyskinesias are a primary concern, then a dopamine agonist would be preferred.

Management of Motor Fluctuations. Long-term treatment with levodopa or dopamine agonists is associated with two types of motor fluctuations: “off” times (loss of symptom relief) and *drug-induced dyskinesias* (involuntary movements). “Off” times can be reduced with three types of drugs: dopamine agonists, COMT inhibitors, and MAO-B inhibitors. Evidence of efficacy is strongest for entacapone (a COMT inhibitor) and rasagiline (an MAO-B inhibitor). The only drug recommended for dyskinesias is amantadine.

Neuroprotection. To date, there is no definitive proof that any drug can protect dopaminergic neurons from progressive degeneration. According to the 2006 guidelines, there is insufficient evidence to support or refute the use of riluzole, coenzyme Q-10, pramipexole, ropinirole, rasagiline, or amantadine for neuroprotection. As for vitamin E, there is good evidence that the compound does *not* confer protection, and hence should not be taken for this purpose. Early treatment with two MAO-B inhibitors—rasagiline and selegiline—can delay *symptom* progression. However, we

don't know if the delay is the result of protecting dopaminergic neurons, or simply the result of preventing dopamine destruction.

PHARMACOLOGY OF THE DRUGS USED FOR MOTOR SYMPTOMS

Levodopa

Levodopa was introduced in the 1960s, and has been a cornerstone of PD treatment ever since. Unfortunately, although the drug is highly effective, beneficial effects diminish over time. The most troubling adverse effects are dyskinesias. To enhance effects, levodopa is always combined with carbidopa as discussed in the following section.

Use in Parkinson's Disease

Beneficial Effects. Levodopa is the most effective drug for PD. At the beginning of treatment, about 75% of patients experience a 50% reduction in symptom severity. Levodopa is so effective, in fact, that a diagnosis of PD should be questioned if the patient fails to respond.

Full therapeutic responses may take several months to develop. Consequently, although the effects of levodopa can be significant, patients should not expect immediate improvement. Rather, they should be informed that beneficial effects are likely to increase steadily over the first few months.

In contrast to the dramatic improvements seen during initial therapy, long-term therapy with levodopa has been disappointing. Although symptoms may be well controlled during the first 2 years of treatment, by the end of year 5 ability to function may deteriorate to pretreatment levels. This probably reflects disease progression and not development of tolerance to levodopa.

Acute Loss of Effect. Acute loss of effect occurs in two patterns: gradual loss and abrupt loss. Gradual loss—"wearing off"—develops near the end of the dosing interval, and simply indicates that drug levels have declined to a subtherapeutic value. Wearing off can be minimized in three ways: (1) shortening the dosing interval, (2) giving a drug that prolongs levodopa's plasma half-life (eg, entacapone), and (3) giving a direct-acting dopamine agonist.

Abrupt loss of effect, often referred to as the "on-off" phenomenon, can occur at any time during the dosing interval—even while drug levels are high. "Off" times may last from minutes to hours. Over the course of treatment, "off" periods are likely to increase in both intensity and frequency. Drugs that can help reduce "off" times are listed in Table 21-2. As discussed below, avoiding high-protein meals may also help.

Mechanism of Action

Levodopa reduces symptoms by increasing synthesis of dopamine in the striatum (Fig. 21-2). Levodopa enters the brain via an active transport system that carries it across the blood-brain barrier. Once in the brain, the drug undergoes uptake into the few dopaminergic nerve terminals that remain in the striatum. Following uptake, levodopa, which has no direct effects of its own, is converted to dopamine, its active form. As dopamine, levodopa helps restore a proper balance between dopamine and ACh.

Conversion of levodopa to dopamine is depicted in Figure 21-3. As indicated, the enzyme that catalyzes the reaction is called a *decarboxylase* (because it removes a carboxyl group

TABLE 21-2 • Drugs for Motor Complications of Levodopa Therapy

Drug	Drug Class
Drugs for "Off" Times	
Definitely Effective	
Entacapone	COMT inhibitor
Rasagiline	MAO-B inhibitor
Probably Effective	
Pramipexole	DA agonist
Ropinirole	DA agonist
Tolcapone	COMT inhibitor
Possibly Effective	
Apomorphine	DA agonist
Cabergoline	DA agonist
Selegiline	MAO-B inhibitor
Drug for Levodopa-Induced Dyskinesias	
Amantadine	DA-releasing agent

COMT = catechol-*O*-methyltransferase, DA = dopamine, MAO-B = type B monoamine oxidase.

from levodopa). The activity of decarboxylases is enhanced by *pyridoxine* (vitamin B₆).

Why is PD treated with levodopa and not with dopamine itself? There are two reasons. First, dopamine cannot cross the blood-brain barrier (see Fig. 21-2). As noted, levodopa crosses the barrier by means of an active transport system, a system that does not transport dopamine itself. Second, dopamine has such a short half-life in the blood that it would be impractical to use even if it could cross the blood-brain barrier.

Pharmacokinetics

Levodopa is administered orally and undergoes rapid absorption from the small intestine. Food delays absorption by slowing gastric emptying. Furthermore, since neutral amino acids compete with levodopa for intestinal absorption (and for transport across the blood-brain barrier as well), high-protein foods will reduce therapeutic effects.

Only a small fraction of each dose reaches the brain. The majority is metabolized in the periphery, primarily by *decarboxylase enzymes* and to a lesser extent by COMT. Peripheral decarboxylases convert levodopa into dopamine, an active metabolite. In contrast, COMT converts levodopa into an inactive metabolite. Like the enzymes that decarboxylate levodopa within the brain, peripheral decarboxylases work faster in the presence of pyridoxine. Because of peripheral metabolism, less than 2% of each dose enters the brain.

Adverse Effects

Most side effects of levodopa are dose dependent. The elderly, who are the primary users of levodopa, are especially sensitive to adverse effects.

Nausea and Vomiting. Most patients experience nausea and vomiting early in treatment. The cause is activation of dopamine receptors in the chemoreceptor trigger zone (CTZ) of the medulla. Nausea and vomiting can be reduced by administering levodopa in low initial doses and with meals. (Food retards levodopa absorption, causing a de-

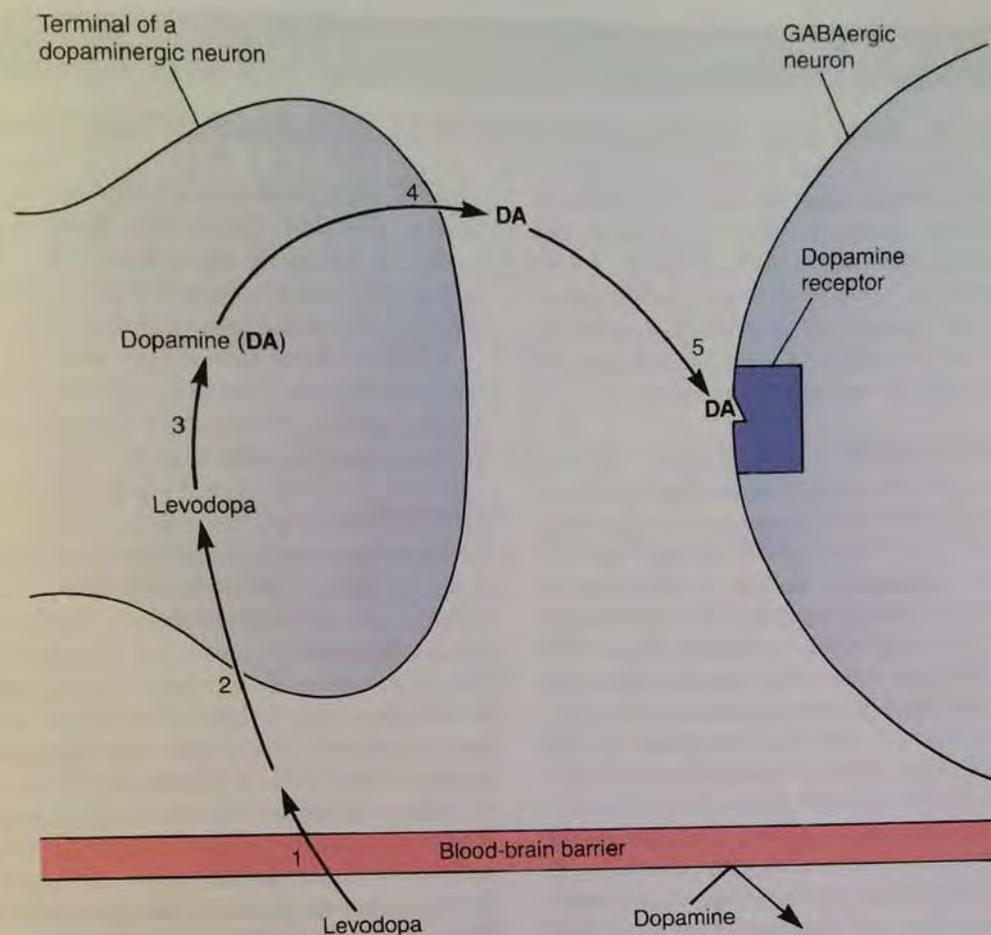


Figure 21-2 • Steps leading to alteration of CNS function by levodopa.

To produce its beneficial effects in PD, levodopa must be (1) transported across the blood-brain barrier; (2) taken up by dopaminergic nerve terminals in the striatum; (3) converted into dopamine; (4) released into the synaptic space; and (5) bound to dopamine receptors on striatal GABAergic neurons, causing them to fire at a slower rate. Note that dopamine itself is unable to cross the blood-brain barrier, and hence cannot be used to treat PD.

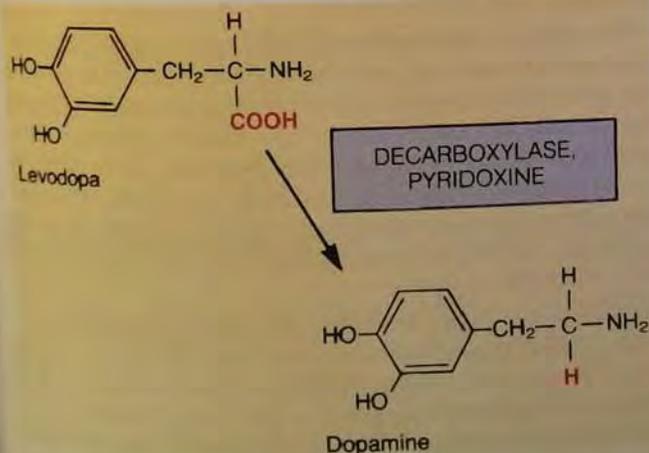


Figure 21-3 • Conversion of levodopa to dopamine.

Decarboxylases present in the brain, liver, and intestine convert levodopa into dopamine. Pyridoxine (vitamin B₆) accelerates the reaction.

crease in peak plasma drug levels and a corresponding decrease in stimulation of the CTZ.) However, since administration with food can reduce therapeutic effects (by decreasing levodopa absorption), administration with meals should be avoided if possible. Giving additional carbidopa

(without levodopa) can help reduce nausea and vomiting. Why carbidopa helps is unknown.

Dyskinesias. Ironically, levodopa, which is given to alleviate movement disorders, actually causes movement disorders in many patients. About 80% develop involuntary movements within the first year. Some dyskinesias are just annoying (eg, head bobbing, tics, grimacing), whereas others can be disabling (eg, ballismus, choreoathetosis). These dyskinesias develop just before or soon after optimal levodopa dosage has been achieved. Dyskinesias can be managed in three ways. First, the dosage of levodopa can be reduced. However, dosage reduction may allow PD symptoms to re-emerge. Second, we can give amantadine (see below), which can reduce dyskinesias in some patients. If these measures fail, the only remaining options are surgery and electrical stimulation (see Box 21-1).

Cardiovascular Effects. Postural hypotension is common early in treatment. The underlying mechanism is unknown. Hypotension can be reduced by increasing intake of salt and water. An alpha-adrenergic agonist can help too.

Conversion of levodopa to dopamine in the periphery can produce excessive activation of beta₁ receptors in the heart. *Dysrhythmias* can result, especially in patients with heart disease.

Psychosis. Psychosis develops in about 20% of patients. Prominent symptoms are visual hallucinations, vivid dreams

SURGICAL AND ELECTRICAL TREATMENTS FOR PARKINSON'S DISEASE

For patients with advanced Parkinson's disease (PD), levodopa therapy is far from ideal. Over time, the drug becomes less and less effective. Patients typically experience "off" times as well as drug-induced dyskinesias. For these patients, nondrug therapies may help. Potential options are deep brain stimulation, pallidotomy, and cell implants. Brain stimulation and pallidotomy have been very successful; cell implants have not.

Deep Brain Stimulation (DBS)

Electrical stimulation of specific brain areas can improve motor symptoms in patients with PD. Three areas have been targeted: the subthalamic nucleus (STN), the globus pallidus internus (GPI), and the ventralis intermedius nucleus of the thalamus. Stimulation of the STN and GPI have produced the best results. Compared with pallidotomy, electrical stimulation has several advantages: it's reversible and adjustable, and, because brain tissue is not permanently damaged, it can be done bilaterally with low risk. On the other hand, electrical stimulation is very expensive. Several studies on electrical stimulation have been conducted. A study on STN stimulation is described below.

In 1998, researchers reported that continuous, long-term electrical stimulation of the STN can improve symptoms in patients with advanced PD. This work was based on animal models of PD in which (1) motor symptoms were associated with abnormal neuronal activity in the STN and (2) electrical stimulation of the STN improved the symptoms. In patients with PD, electrodes were implanted *bilaterally* in the STN and then connected by a subcutaneous lead to a pulse generator implanted in the subclavicular region, much like a cardiac pacemaker. The pulse generator was then programmed by telemetry to adjust stimulation parameters (eg, voltage, frequency). All patients in the study had advanced PD and all were experiencing "off" periods with levodopa.

Electrical stimulation produced substantial benefits during "off" times but only modest benefits during "on" times. During "off" times, there was a 60% improvement in motor function (bradykinesia, rigidity, tremor, and gait). During "on" times, improvement was only 10%. Stimulation allowed all patients to become independent in most activities of daily living. On average, stimulation permitted a 50% reduction in levodopa dosage. Subsequent studies have confirmed these results.

Adverse effects were generally mild, but serious sequelae of the neurosurgery are possible. Of the 20 patients in this study, 8 experienced transient CNS effects, including confusion, hallucinations, temporospatial disorientation, and abulia (lack of will; inability to make decisions). All symptoms resolved within 2 weeks of the surgery. Of much greater concern, the procedure carries a 2% to 8% risk of cerebral hemorrhage. Surgical site infection and pain may also occur. Device-related complications include electrode migration, electrode failure, and pulse generator failure. Stimulation also carries an increased risk of falls, gait disturbance, balance disorder, depression, and dystonia (muscle contraction and spasm). Because of these risks, DBS should be reserved for patients with advanced PD who are otherwise good candidates for surgery.

How does STN stimulation improve PD symptoms? The answer is unclear. One theory, based on animal studies, suggests that electrical stimulation may *inhibit* overactivity of neurons in the STN. The net result would be to *increase* excitatory input to the cerebral cortex.

Electrical stimulation is expensive. The cost of surgery and the stimulation device may be \$50,000 or more. And every 3 to 5 years, additional costs arise when the batteries in the pulse generator must be replaced.

Pallidotomy

Posteroventral medial pallidotomy, or simply pallidotomy, is a neurosurgical procedure for destroying a region of the globus pallidus. As indicated in Figure 21-1, the globus pallidus, which helps regulate movement, receives input from the striatum. In patients with PD, striatal input to the globus pallidus is disrupted, causing the globus pallidus itself to malfunction. It has been argued that altered output from the globus pallidus underlies many of the symptoms of PD, including tremor, rigidity, and bradykinesia. The results of pallidotomy support this argument: For many patients with PD, *unilateral* destruction of the posteroventral medial region of the globus pallidus produces a substantial improvement in symptoms. The most consistent benefit is a reduction in levodopa-induced dyskinesias. Motor control during levodopa "off" times also improves. In contrast, very little improvement is seen during levodopa "on" times. Following pallidotomy, about 50% of patients who previously needed help with activities of daily living are able to live independently. Pallidotomy may also permit a temporary reduction in levodopa dosage. Although complications of the procedure are generally mild, intracerebral hemorrhage is a potential and serious risk.

Because pallidotomy is irreversible, and because complications can be serious, the procedure should be limited to patients with intractable levodopa-induced dyskinesias and to patients who are disabled by levodopa "off" times. Furthermore, because brain tissue is permanently destroyed, pallidotomy is usually performed *unilaterally*—thereby leaving the other side of the brain intact, just in case something goes wrong.

Cell Implants

The objective with cell implants is to replace degenerated dopaminergic neurons. Implants have been tried with human adrenal cells and with fetal brain cells from humans and pigs. Human brain cells work best, and even then benefits are modest.

In 1995, researchers finally obtained definitive proof that transplanting fetal dopaminergic neurons into the brain can benefit a patient with PD. In this case study, the patient had severe parkinsonism that would no longer respond to drug therapy. Following the transplant, symptoms steadily improved over 3 months, eventually allowing the patient to perform all activities of daily living without assistance. The improvements were sustained for 15 months, at which time the patient died of a massive pulmonary embolism unrelated to the transplant. Autopsy revealed that the grafts not only took but had become seamlessly integrated into the surrounding tissue. This was the

BOX 21-1 ■ SPECIAL INTEREST TOPIC—cont'd

first clear demonstration of a correlation between graft survival and improvement of symptoms.

In 1999, a study done with 40 patients showed that fetal tissue transplants are only moderately effective, and then only in patients who are relatively young. In this study, 20 patients received bilateral implants of dopamine-producing cells and 20 control patients received sham implants. Twelve months

later, brain scans indicated cell survival in 60% of the treated patients, regardless of age. However, *functional* improvement was modest (30%) and occurred only in patients under 60 years old. In patients over 60, there was no motor improvement despite survival of the implants. Furthermore, although motor function improved in some younger patients, it was not enough to permit a reduction in levodopa dosage.

or nightmares, and paranoid ideation (fears of personal endangerment, sense of persecution, feelings of being followed or spied on). Activation of dopamine receptors is in some way involved. Symptoms can be reduced by lowering levodopa dosage, but this will reduce beneficial effects too.

Treatment of levodopa-induced psychosis with first-generation antipsychotics is problematic. Yes, these agents can decrease psychologic symptoms. However, they will also *intensify* symptoms of PD. Why? Because they block receptors for dopamine in the striatum. In fact, when first-generation antipsychotic agents are used for schizophrenia, the biggest problem is parkinsonian side effects, referred to as extrapyramidal symptoms (EPS).

Two second-generation antipsychotics—*clozapine* and *quetiapine*—have been used successfully to manage levodopa-induced psychosis. Unlike the first-generation antipsychotic drugs, clozapine and quetiapine cause little or no blockade of dopamine receptors in the striatum, and hence do not cause EPS. In patients taking levodopa, these drugs can reduce psychotic symptoms without intensifying symptoms of PD. Interestingly, the dosage of clozapine is only 25 mg/day, about 20 times lower than the dosage used for schizophrenia. Clozapine and quetiapine are discussed at length in Chapter 31.

Other Adverse Effects. Levodopa may *darken sweat and urine*; patients should be informed about this harmless effect. The drug can *activate malignant melanoma* and conse-

quently should be avoided in patients with undiagnosed skin lesions.

Drug Interactions

Interactions between levodopa and other drugs can (1) increase beneficial effects of levodopa, (2) decrease beneficial effects of levodopa, and (3) increase toxicity from levodopa. Major interactions are summarized in Table 21-3. Several interactions are discussed immediately below; others are discussed later on.

First-Generation Antipsychotic Drugs. All of the first-generation antipsychotic drugs (eg, chlorpromazine, haloperidol) block receptors for dopamine in the striatum. As a result, they can decrease therapeutic effects of levodopa. Accordingly, concurrent use of levodopa and these drugs should be avoided. As discussed above, two second-generation agents—clozapine and quetiapine—do not block dopamine receptors in the striatum, and hence can be used safely in patients with PD.

Monoamine Oxidase Inhibitors. Levodopa can cause a hypertensive crisis if administered to an individual taking a *nonselective* inhibitor of monoamine oxidase (MAO). The mechanism is as follows: (1) Levodopa elevates neuronal stores of dopamine and norepinephrine (NE) by promoting synthesis of both transmitters. (2) Because intraneuronal MAO serves to inactivate dopamine and NE, inhibition of MAO allows elevated neuronal stores of these transmitters to

TABLE 21-3 ■ Major Drug Interactions of Levodopa

Drug Category	Drug	Mechanism of Interaction
Drugs that increase beneficial effects of levodopa	Carbidopa	Inhibits peripheral decarboxylation of levodopa
	Entacapone, tolecapone	Inhibit destruction of levodopa by COMT in the intestine and peripheral tissues
	Apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole	Stimulate dopamine receptors directly, and thereby add to the effects of dopamine derived from levodopa
	Amantadine	Promotes release of dopamine
Drugs that decrease beneficial effects of levodopa	Anticholinergic drugs	Block cholinergic receptors in the CNS, and thereby help restore the balance between dopamine and ACh
	Antipsychotic drugs*	Block dopamine receptors in the striatum
Drugs that increase levodopa toxicity	MAO inhibitors (especially <i>nonselective</i> MAO inhibitors)	Inhibition of MAO increases the risk of severe levodopa-induced hypertension

ACh = acetylcholine, CNS = central nervous system, COMT = catechol-*O*-methyltransferase, MAO = monoamine oxidase.

*First-generation antipsychotic agents block dopamine receptors in the striatum and can thereby nullify the therapeutic effects of levodopa. Two second-generation antipsychotics—clozapine [Clozaril] and quetiapine [Seroquel]—do not block dopamine receptors in the striatum, and hence do not nullify the therapeutic effects of levodopa.

grow even larger. (3) Because both dopamine and NE promote vasoconstriction, release of these agents in supranormal amounts can lead to massive vasoconstriction, thereby causing blood pressure to rise dangerously high. To avoid hypertensive crisis, nonselective MAO inhibitors should be withdrawn at least 2 weeks prior to giving levodopa.

Anticholinergic Drugs. As discussed above, excessive stimulation of cholinergic receptors contributes to the dyskinesias of PD. Therefore, by blocking these receptors, anticholinergic agents can enhance responses to levodopa.

Pyridoxine. Pyridoxine (vitamin B₆) stimulates decarboxylase activity. By accelerating decarboxylation of levodopa in the periphery, pyridoxine can decrease the amount of levodopa available to reach the central nervous system (CNS). As a result, therapeutic effects of levodopa can be reduced. However, since levodopa is now always combined with carbidopa, a drug that suppresses decarboxylase activity, this potential interaction is no longer a clinical concern.

Food Interactions

Meals with a high protein content can reduce therapeutic responses to levodopa. Why? Because neutral amino acids compete with levodopa for absorption from the intestine and for transport across the blood-brain barrier. Hence, a high-protein meal can significantly reduce both the amount of levodopa absorbed and the amount transported into the brain. It has been suggested that a high-protein meal could trigger an abrupt loss of effect (ie, an "off" episode). Accordingly, patients should be advised to spread their protein consumption evenly throughout the day.

Preparations

Until recently, levodopa, by itself, was available in capsules and tablets sold as *Dopar* and *Larodopa*. However, these single-drug preparations have been withdrawn. As a result, levodopa is now available only in combination preparations, either levodopa/carbidopa or levodopa/carbidopa/entacapone. These combination preparations are discussed below.

Levodopa/Carbidopa

The combination of levodopa plus carbidopa is our most effective therapy for PD—much more effective than levodopa alone. Levodopa plus carbidopa is available under two trade names: *Sinemet* and *Parcopa*.

Mechanism of Action

Carbidopa is used to enhance the effects of levodopa. Carbidopa has no therapeutic effects of its own, and therefore is always used in conjunction with levodopa. Carbidopa inhibits decarboxylation of levodopa in the intestine and peripheral tissues, thereby making more levodopa available to the CNS. Carbidopa does not prevent the conversion of levodopa to dopamine by decarboxylases in the brain. Why? Because carbidopa is unable to cross the blood-brain barrier.

The impact of carbidopa is shown schematically in Figure 21-4, which compares the fate of levodopa in the presence and absence of carbidopa. In the absence of carbidopa, about 98% of levodopa is lost in the periphery, leaving only 2% available to the brain. Why is levodopa lost? Primarily because decarboxylases in the GI tract and peripheral tissues convert it to dopamine. When these decarboxylases are inhibited by carbidopa, only 90% of levodopa is lost in the periphery, leaving 10% for actions in the brain.

Advantages of Carbidopa

The combination of carbidopa plus levodopa is superior to levodopa alone in three ways:

- By increasing the fraction of levodopa available for actions in the CNS, carbidopa allows the dosage of levodopa to be reduced by about 75%. In the example in Figure 21-4, in order to provide 10 mg of dopamine to the brain, we must administer 500 mg of levodopa if carbidopa is absent, but only 100 mg if carbidopa is present.
- By reducing production of dopamine in the periphery, carbidopa reduces cardiovascular responses to levodopa as well as nausea and vomiting.
- By causing direct inhibition of decarboxylase, carbidopa eliminates concerns about decreasing the effects of levodopa by taking a vitamin preparation that contains pyridoxine.

Disadvantages of Carbidopa

Carbidopa has no adverse effects of its own. Accordingly, any adverse responses from carbidopa/levodopa are the result of potentiating the effects of levodopa. When levodopa is combined with carbidopa, abnormal movements and psychiatric disturbances can occur sooner and be more intense than with levodopa alone.

Preparations, Dosage, and Administration

The combination of levodopa plus carbidopa is available under two trade names: *Sinemet* and *Parcopa*. A triple combination product—levodopa/carbidopa/entacapone—is discussed later. As noted, levodopa without carbidopa is no longer available.

Levodopa/Carbidopa: *Sinemet*. The *Sinemet* brand of levodopa/carbidopa is available in immediate-release (IR) and sustained-release (SR) tablets. The IR tablets are available in three strengths: (1) 10 mg carbidopa/100 mg levodopa, (2) 25 mg carbidopa/100 mg levodopa, and (3) 25 mg carbidopa/250 mg levodopa. The SR tablets [*Sinemet CR*] are available in two strengths: 25 mg carbidopa/100 mg levodopa, and 50 mg carbidopa/200 mg levodopa. With either the IR or SR formulation, dosage is low initially and then gradually increased. The usual maximum is 800 mg of levodopa a day, administered in divided doses.

Levodopa/Carbidopa: *Parcopa*. The *Parcopa* brand of levodopa/carbidopa was introduced in 2005. *Parcopa* products differ from *Sinemet* products in that *Parcopa* products are formulated to dissolve on the tongue and then be swallowed with saliva—a potential advantage for patients who, because of their PD, have difficulty swallowing tablets intact. Orally disintegrating *Parcopa* tablets are available in the same strengths as IR *Sinemet* tablets: 10 mg carbidopa/100 mg levodopa, 25 mg carbidopa/100 mg levodopa, and 25 mg carbidopa/250 mg levodopa. Dosage is the same as with *Sinemet*.

Carbidopa Alone. Carbidopa without levodopa, sold as *Lodospin*, is available by special request. When carbidopa is added to levodopa/carbidopa, carbidopa can reduce levodopa-induced nausea and vomiting.

Dopamine Agonists

Dopamine agonists are first-line drugs for PD. Beneficial effects result from direct activation of dopamine receptors in the striatum. For patients with mild or moderate symptoms, dopamine agonists are drugs of first choice. Although dopamine agonists are less effective than levodopa, they still have advantages. Specifically, in contrast to levodopa, they aren't dependent on enzymatic conversion to become active, aren't converted to potentially toxic metabolites, and don't compete with dietary proteins for uptake from the intestine or transport across the blood-brain barrier. In addition, when used long term, dopamine agonists have a lower incidence of response failures and are less likely to cause disabling dyskinesias. However, dopamine agonists do cause more serious side effects—especially hallucinations, day-

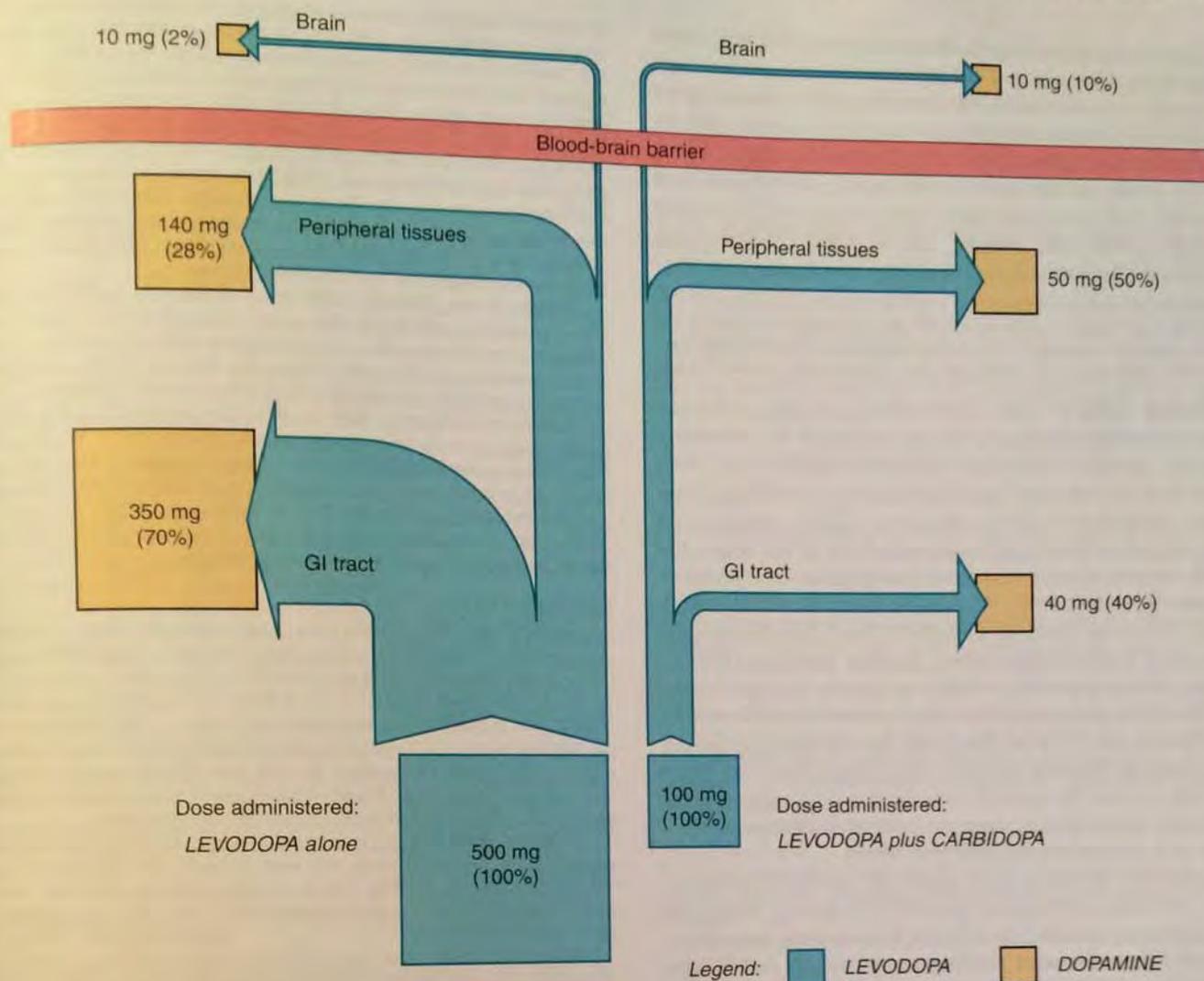


Figure 21-4 ■ Fate of levodopa in the presence and absence of carbidopa.

In the absence of carbidopa, 98% of an administered dose of levodopa is metabolized in intestinal and peripheral tissues—either by decarboxylases or COMT—leaving only 2% for actions in the brain. Hence, in order to deliver 10 mg of levodopa to the brain, the dose of levodopa must be large (500 mg). By inhibiting intestinal and peripheral decarboxylases, carbidopa increases the percentage of levodopa available to the brain. Hence, the dose needed to deliver 10 mg is greatly reduced (to 100 mg in this example). Since carbidopa cannot cross the blood-brain barrier, it does not suppress conversion of levodopa to dopamine in the brain. Furthermore, since carbidopa reduces peripheral production of dopamine (from 140 mg to 50 mg in this example), peripheral toxicity (nausea, cardiovascular effects) is greatly reduced. (Data in the figure are extrapolated from Nutt JG, Fellman JH: Pharmacokinetics of levodopa. *Clin Neuropharmacol* 7:35, 1984.)

time sleepiness, and postural hypotension. As a result, these drugs are usually reserved for younger patients, who tolerate their side effects better than do the elderly.

The dopamine agonists fall into two groups: derivatives of ergot (an alkaloid found in plants) and nonergot derivatives. The nonergot derivatives—*pramipexole*, *ropinirole*, and *apomorphine*—are highly selective for dopamine receptors. In contrast, the ergot derivatives—*bromocriptine* and *cabergoline*—are less selective: In addition activating dopamine receptors, these drugs cause mild *blockage* of serotonergic and alpha-adrenergic receptors. Because of their selectivity, the nonergot derivatives cause fewer side effects than the ergot derivatives, and hence are preferred.

Pramipexole

Actions and Uses. Pramipexole [Mirapex] is a nonergot dopamine receptor agonist. The drug is used alone in early-stage PD, and combined with levodopa in advanced-stage PD. Pramipexole binds selectively to dopamine D₂ and D₃ receptor subtypes. Binding to D₂ receptors underlies therapeutic effects. The significance of D₃ binding is unknown. When used as monotherapy in early PD, pramipexole can produce significant improvement in motor performance. When combined with levodopa in advanced PD, the drug can reduce fluctuations in motor control and may permit a reduction in levodopa dosage. In both cases, maximal benefits take several weeks to develop. Compared with levodopa, pramipexole is

less effective at controlling motor symptoms of PD, but is also less likely to cause motor fluctuations.

In addition to its use in PD, pramipexole is approved for patients with moderate to severe *restless legs syndrome* (RLS), a sensorimotor disorder characterized by unpleasant leg sensations that create an urge to move the legs in an effort to ease discomfort. Symptoms are usually more intense in the evening and often disrupt sleep. People with severe RLS experience sleep loss, daytime exhaustion, and diminished quality of life.

Pharmacokinetics. Pramipexole is rapidly absorbed, and plasma levels peak in 1 to 2 hours. Food reduces the speed of absorption but not the extent. Pramipexole undergoes wide distribution, and achieves a high concentration in red blood cells. The drug is eliminated unchanged in the urine.

Adverse Effects and Interactions. Pramipexole can produce a variety of adverse effects, primarily by activating dopamine receptors. The most common effects seen when pramipexole is used *alone* are nausea (28%), dizziness (25%), daytime somnolence (22%), insomnia (17%), constipation (14%), weakness (14%), and hallucinations (9%). When the drug is *combined with levodopa*, many patients experience orthostatic hypotension (54%) and dyskinesias (47%), which are not seen when the drug is used by itself. In addition, the incidence of hallucinations nearly doubles, rising to 17%.

A few patients have reported *sleep attacks* (overwhelming and irresistible sleepiness that comes on without warning). Sleep attacks can be a real danger for people who are driving (and a potential blessing for those in faculty meetings). Sleep attacks should not be equated with the normal sleepiness that occurs with dopaminergic agents. Patients who experience a sleep attack should inform their prescriber.

Pramipexole has been associated with *impulse control disorders*, including compulsive gambling, shopping, binge eating, and hypersexuality. These behaviors are dose related, begin about 9 months after starting pramipexole, and reverse when the drug is discontinued. Risk factors include relative youth, a family or personal history of alcohol abuse, and a personality trait called novelty seeking, characterized by impulsivity, a quick temper, and a low threshold for boredom. Before prescribing pramipexole, clinicians should screen patients for compulsive behaviors.

Cimetidine (a drug for peptic ulcer disease) can inhibit renal excretion of pramipexole, thereby increasing its blood level.

Preparations, Dosage, and Administration. Pramipexole is available in immediate-release (IR) tablets (0.125, 0.25, 0.5, 0.75, 1, and 1.5 mg) sold as *Mirapex*, and in extended-release (ER) tablets (0.375, 0.75, 1.5, 3, and 4.5 mg) sold as *Mirapex XR*. Dosing may be done with food to reduce nausea. To minimize adverse effects, dosage should be low initially and then gradually increased.

Parkinson's Disease. With the IR tablets, dosage is 0.125 mg 3 times/day initially, and then increased over 7 weeks to a maximum of 1.5 mg 3 times/day. With the ER tablets, dosage is 0.375 mg once daily initially, and then gradually increased to a maximum of 4.5 mg once daily. With both formulations, dosage should be reduced in patients with significant renal impairment.

Restless Legs Syndrome. Dosing is done once daily, 2 to 3 hours before bedtime, using the IR tablets. The daily dosage is 0.125 mg initially, and can be gradually increased to a maximum of 0.5 mg.

Ropinirole

Actions, Uses, and Adverse Effects. Ropinirole [Requip], a nonergot dopamine agonist, is similar to pramipexole with respect to receptor specificity, mechanism of action, indications, and adverse effects. Like pramipexole, ropinirole is highly selective for D₂ and D₃ receptors, and both drugs share the same indications: PD and RLS. In patients with PD, ropinirole can be used as

monotherapy (in early PD) and as an adjunct to levodopa (in advanced PD). In contrast to pramipexole, which is eliminated entirely by renal excretion, ropinirole is eliminated by hepatic metabolism. Some adverse effects are more common than with pramipexole. When ropinirole is used alone, the most common effects are nausea (60%), dizziness (40%), somnolence (40%), and hallucinations (5%). Rarely, sleep attacks occur. When ropinirole is combined with levodopa, the most important side effects are dyskinesias (34%), hallucinations (10%), and postural hypotension (2%). Note that these occur less frequently than when pramipexole is combined with levodopa. Like pramipexole, ropinirole can promote compulsive gambling, shopping, eating, and hypersexuality. Animal tests indicate that ropinirole can harm the developing fetus. Accordingly, the drug should not be used during pregnancy.

Preparations, Dosage, and Administration. Ropinirole is available in immediate-release (IR) film-coated tablets (0.25, 0.5, 1, 2, 3, 4, and 5 mg), sold as *Requip*, and in extended-release (ER) tablets (2, 4, 6, 8, and 12 mg), marketed as *Requip XL*. Dosing may be done with food to decrease nausea. Dosage should be low initially and then gradually increased.

Parkinson's Disease. With the IR tablets, dosing is begun at 0.25 mg 3 times a day, and can be increased over several months to a maximum of 8 mg 3 times a day. With the ER tablets, dosing is begun at 2 mg once a day, and can be increased over several months to a maximum of 24 mg once a day.

Restless Legs Syndrome. Dosing is done once daily, 1 to 3 hours before bedtime, using the IR tablets. The daily dosage is 0.25 mg initially, and can be gradually increased to a maximum of 4 mg.

Apomorphine

Actions and Therapeutic Use. Apomorphine [Apokyn] is a nonergot dopamine agonist approved for acute, subQ treatment of hypomobility during "off" episodes in patients with advanced PD. Unlike other dopamine agonists, the drug is not given PO, and is not indicated for routine PD management. When tested in patients experiencing at least 2 hours of "off" time a day, apomorphine produced a 62% improvement in PD rating scores, compared with no improvement in patients receiving placebo. Benefits were sustained during 4 weeks of use. Apomorphine is a derivative of morphine, but is devoid of typical opioid effects (eg, analgesia, euphoria, respiratory depression).

Pharmacokinetics. Apomorphine is highly lipophilic but undergoes extensive first-pass metabolism, and hence is ineffective when taken orally. After subQ injection, the drug undergoes rapid, complete absorption. Effects begin in 10 to 20 minutes and persist about 1 hour. The drug's half-life is about 40 minutes.

Adverse Effects. The most common adverse effects are injection-site reactions (26%), hallucinations (14%), yawning (8%), drowsiness (7%), dyskinesias (7%), rhinorrhea (4%), and nausea and vomiting (4%). During clinical trials, there was a 4% incidence of serious cardiovascular events: angina, myocardial infarction, cardiac arrest, and/or sudden death. Postural hypotension and fainting occurred in 2% of patients. Like other dopamine agonists, apomorphine poses a risk of daytime sleep attacks. In addition, apomorphine can promote hypersexuality and enhanced erections (the drug is used in Europe to treat erectile dysfunction). Rarely, apomorphine causes priapism (sustained, painful erection), possibly requiring surgical intervention.

Combined Use with an Antiemetic. To prevent nausea and vomiting during clinical trials, nearly all patients were treated with an antiemetic, starting 3 days before the first dose of apomorphine. The antiemetic chosen was trimethobenzamide [Tigan, others]. Two classes of antiemetics *cannot* be used: serotonin receptor agonists (eg, ondansetron [Zofran]) and dopamine receptor antagonists (eg, prochlorperazine [Compazine]). Why? Because serotonin receptor agonists will increase the risk of postural hypotension, while having no effect on the nausea and dopamine receptor antagonists will decrease the effectiveness of apomorphine and most other drugs for PD. About half the trial participants discontinued the antiemetic at some point, but continued taking apomorphine.

Preparations, Dosage, and Administration. Apomorphine [Apokyn] is available in 2-mL ampules and 3-mL cartridges, at a concentration of 10 mg/mL. Doses are given subQ. The 3-mL cartridges are used with the multidose injector pen provided. Only one dose is given for each "off" episode. In clinical trials, patients received an average of three doses a day. Doses should be low initially (1 to 2 mg) and then gradually increased (to a 6-mg maximum).

To control nausea and vomiting, package labeling states that all patients should take an antiemetic (eg, trimethobenzamide, 300 mg 3 times a day), starting 3 days before the first apomorphine dose. However, many patients find the antiemetic unnecessary, and discontinue it within a few days.

Ergot Derivatives: Bromocriptine and Cabergoline

Two ergot derivatives—bromocriptine and cabergoline—are employed for PD. Bromocriptine is approved for PD; cabergoline is not. Compared with the nonergot dopamine agonists, these drugs are much less well tolerated.

hence their use is limited. Of particular concern, the ergot derivatives have been associated with valvular heart injury. Because of this serious complication, a third ergot derivative—*pergolide* [Permax]—has been withdrawn. The side effect profile of the ergot derivatives differs from that of the nonergot agents because, in addition to activating dopamine receptors, the ergot drugs cause mild blockade of serotonergic and alpha-adrenergic receptors.

Bromocriptine. Bromocriptine [Parlodel], a derivative of ergot, is a direct-acting dopamine agonist. Beneficial effects derive from activating dopamine receptors in the striatum. Responses are equivalent to those seen with pramipexole and ropinirole. Bromocriptine is used alone in early PD and in combination with levodopa in advanced PD. When combined with levodopa, bromocriptine can prolong therapeutic responses and reduce motor fluctuations. In addition, since bromocriptine allows the dosage of levodopa to be reduced, the incidence of levodopa-induced dyskinesias may be reduced too.

Adverse effects are dose dependent and seen in 30% to 50% of patients. Nausea is most common, with an incidence of 50%. The most common dose-limiting effects are psychologic reactions (confusion, nightmares, agitation, hallucinations, paranoid delusions). These occur in about 30% of patients and are most likely when the dosage is high. Like levodopa, bromocriptine can cause dyskinesias and postural hypotension. Rarely, bromocriptine causes retroperitoneal fibrosis, pulmonary infiltrates, a Raynaud-like phenomenon, and erythromelalgia (vasodilation in the feet, and sometimes hands, resulting in swelling, redness, warmth, and burning pain). In addition, the ergot derivatives have been associated with valvular heart disease. The probable cause is activation of serotonin receptors on heart valves.

Bromocriptine is available in 5-mg capsules [Parlodel] and 2.5-mg tablets [Parlodel SnapTabs]. The initial dosage is 1.25 mg twice daily, administered with meals. Dosage is gradually increased until the desired response has been achieved, or until side effects become intolerable. Maintenance dosages range from 30 to 100 mg/day.

Cabergoline. Cabergoline, formerly available as *Dostinex*, is used occasionally in PD, although it is not approved by the Food and Drug Administration for this disorder. According to the 2006 AAN guidelines, the drug is "possibly effective" for improving "off" times during levodopa therapy. The pharmacology of cabergoline, as well as its use in hyperprolactinemia, are discussed in Chapter 63 (Drug Therapy of Infertility).

COMT Inhibitors

Two COMT inhibitors are available: entacapone and tolcapone. With both drugs, benefits derive from inhibiting metabolism of levodopa in the periphery; these drugs have no direct therapeutic effects of their own. Entacapone is safer and more effective than tolcapone, and hence is preferred.

Entacapone

Actions and Therapeutic Use. Entacapone [Comtan] is a selective, reversible inhibitor of COMT indicated only for use with levodopa. Like carbidopa, entacapone inhibits metabolism of levodopa in the intestine and peripheral tissues. However, the drugs inhibit different enzymes: carbidopa inhibits decarboxylases, whereas entacapone inhibits COMT. By inhibiting COMT, entacapone prolongs the half-life of levodopa in blood, and thereby prolongs the time that levodopa is available to the brain. In addition, entacapone increases levodopa availability by a second mechanism: By inhibiting COMT, entacapone decreases production of levodopa metabolites that compete with levodopa for transport across the blood-brain barrier. In clinical trials, entacapone increased the half-life of levodopa by 50% to 75%, and thereby caused levodopa blood levels to be smoother and more sustained. As a result, "wearing off" was delayed and "on" times were extended. Entacapone may also permit a reduction in levodopa dosage.

Pharmacokinetics. Entacapone is rapidly absorbed and reaches peak levels in 2 hours. Elimination is by hepatic metabolism followed by excretion in the feces and urine. The plasma half-life is 1.5 to 3.5 hours.

Adverse Effects. Most adverse effects result from increasing levodopa levels, and some are caused by entacapone

itself. By increasing levodopa levels, entacapone can cause dyskinesias, orthostatic hypotension, nausea, hallucinations, sleep disturbances, and impulse control disorders (see *Pramipexole*). These can be managed by decreasing levodopa dosage. Entacapone itself can cause vomiting, diarrhea, constipation, and yellow-orange discoloration of the urine.

Drug Interactions. Because it inhibits COMT, entacapone can, in theory, increase levels of drugs metabolized by COMT. In addition to levodopa, these include methyl dopa (an antihypertensive agent), dobutamine (an adrenergic agonist), and isoproterenol (a beta-adrenergic agonist). If entacapone is combined with these drugs, a reduction in their dosages may be needed.

Preparations, Dosage, and Administration. Entacapone [Comtan], by itself, is available in 200-mg tablets. The recommended dosage is 200 mg taken with each dose of levodopa/carbidopa—to a maximum of 8 doses (1600 mg) a day.

As discussed below, entacapone is also available in fixed-dose combinations with levodopa/carbidopa, under the trade name *Stalevo*.

Tolcapone

Actions and Therapeutic Use. Tolcapone [Tasmar] is a COMT inhibitor used only in conjunction with levodopa—and only if safer agents are ineffective or inappropriate. As with entacapone, benefits derive from inhibiting levodopa metabolism in the periphery, which prolongs levodopa availability. When given to patients taking levodopa, tolcapone improves motor function and may allow a reduction in levodopa dosage. For many patients, the drug reduces the "wearing-off" effect that can occur with levodopa, thereby extending levodopa "on" times by as much as 2.9 hours a day. Unfortunately, although tolcapone is effective, it is also dangerous. Deaths from liver failure have occurred. Because it carries a serious risk, tolcapone should be reserved for patients who cannot be treated with safer drugs. Also, when tolcapone is used, treatment should be limited to 3 weeks in the absence of a beneficial response.

Pharmacokinetics. Tolcapone is well absorbed following oral dosing. Plasma levels peak in 2 hours. In the blood, tolcapone is highly bound (over 99.9%) to plasma proteins, primarily albumin. The drug undergoes extensive hepatic metabolism followed by renal excretion. The plasma half-life is 2 to 3 hours.

Adverse Effects. Liver Failure. Tolcapone can cause severe hepatocellular injury. At least three patients have died from acute, fulminant liver failure. Prior to treatment, patients should be fully apprised of the risks. Patients with pre-existing liver dysfunction should not take the drug. Patients taking tolcapone should be informed about signs of emergent liver dysfunction (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine) and instructed to report these immediately. If liver injury is diagnosed, tolcapone should be discontinued and never used again.

Laboratory monitoring of liver enzymes is required. Tests for serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be conducted prior to treatment and then throughout treatment as follows: every 2 weeks for the first year, every 4 weeks for the next 6 months, and every 8 weeks thereafter. If ALT or AST levels exceed the upper limit of normal, tolcapone should be discontinued. Monitoring may not prevent liver injury, but early detection and immediate drug withdrawal can minimize harm.

Other Adverse Effects. By increasing the availability of levodopa, tolcapone can intensify levodopa-related effects, especially dyskinesias, orthostatic hypotension, nausea, hallucinations, sleep disturbances, and impulse control disorders (see *Pramipexole*); a reduction in levodopa dosage may be required. Tolcapone itself can cause diarrhea, hematuria, and yellow-orange discoloration of the urine. Abrupt withdrawal of tolcapone can produce symptoms that resemble neuroleptic malignant syndrome (fever, muscular rigidity, altered consciousness). In rats, large doses have caused renal tubular necrosis and tumors of the kidneys and uterus.

Preparations, Dosage, and Administration. Tolcapone [Tasmar] is available in 100- and 200-mg tablets for dosing with or without food. The usual dosage is 100 mg 3 times a day. The first dose should be administered in the morning along with levodopa/carbidopa. The next two doses are taken 6 and 12 hours later. If necessary, the dosage can be increased to 200 mg 3 times a day. However, elevations in ALT are more likely at the higher dosage.

Levodopa/Carbidopa/Entacapone

Levodopa, carbidopa, and entacapone are now available in fixed-dose combinations sold as *Stalevo*. As discussed above, both carbidopa and entacapone inhibit the enzymatic degradation of levodopa, and thereby enhance thera-

peptic effects. The triple combination is more convenient than taking levodopa/carbidopa and entacapone separately, and costs a little less too. Unfortunately, Stalevo is available only in immediate-release tablets and only in the following strengths:

- *Stalevo 50*—50 mg levodopa, 12.5 mg carbidopa, and 200 mg entacapone
- *Stalevo 75*—75 mg levodopa, 18.75 mg carbidopa, and 200 mg entacapone
- *Stalevo 100*—100 mg levodopa, 25 mg carbidopa, and 200 mg entacapone
- *Stalevo 125*—125 mg levodopa, 31.25 mg carbidopa, and 200 mg entacapone
- *Stalevo 150*—150 mg levodopa, 37.5 mg carbidopa, and 200 mg entacapone
- *Stalevo 200*—200 mg levodopa, 50 mg carbidopa, and 200 mg entacapone

Patients who need more flexibility in their regimen cannot be treated with Stalevo, nor can patients who require a sustained-release formulation. For each dose of Stalevo, only 1 tablet is taken. Also, since each tablet contains 200 mg of entacapone, and since patients should take no more than 1600 mg of entacapone a day, the daily limit for Stalevo is 8 tablets.

MAO-B Inhibitors

The MAO-B inhibitors—selegiline and rasagiline—are considered first-line drugs for PD even though benefits are modest. When combined with levodopa, they can reduce the “wearing-off” effect.

Selegiline

Selegiline [Eldepryl, Zelapar], also known as *deprenyl*, was the first MAO inhibitor approved for PD. The drug may be used alone or in combination with levodopa. In both cases, improvement of motor function is modest. There is some evidence suggesting that selegiline may delay neurodegeneration, and hence may delay disease progression. However, conclusive proof of neuroprotection is lacking. Nonetheless, current guidelines suggest trying selegiline in newly diagnosed patients, just in case the drug *does* confer some protection.

Actions and Use. Selegiline causes *selective, irreversible* inhibition of type B monoamine oxidase (MAO-B), the enzyme that inactivates dopamine in the striatum. Another form of MAO, known as MAO-A, inactivates NE and serotonin. As discussed in Chapter 32, nonselective inhibitors of MAO (ie, drugs that inhibit MAO-A and MAO-B) are used to treat depression—and pose a risk of hypertensive crisis as a side effect. Because selegiline is a selective inhibitor of MAO-B, the drug is not an antidepressant and, *at recommended doses*, poses little or no risk of hypertensive crisis.

Selegiline appears to benefit patients with PD in two ways. First, when used as an adjunct to levodopa, selegiline can suppress destruction of dopamine derived from levodopa. The mechanism is inhibition of MAO-B. By helping preserve dopamine, selegiline can prolong the effects of levodopa, and can thereby decrease fluctuations in motor control. Unfortunately, these benefits decline dramatically within 12 to 24 months.

In addition to preserving dopamine, there is some hope that selegiline may delay the progression of PD. When used early in the disease, selegiline can delay the need for levodopa. This may reflect a delay in the progression of the disease, or it may simply reflect direct symptomatic relief from selegiline itself.

If selegiline does slow the progression of PD, what might be the mechanism? In experimental animals, selegiline can prevent development of parkinsonism following exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that causes selective degeneration of dopaminergic neurons. (Humans accidentally exposed to MPTP develop severe parkinsonism.) Neuronal degeneration is not caused by MPTP itself, but rather by a toxic metabolite. Formation of this metabolite is catalyzed by MAO-B. By inhibiting MAO-B, selegiline prevents formation of the toxic metabolite, and thereby protects against neuronal injury. If selegiline does retard progression of PD, this mechanism could explain the effect. That is, just as selegiline protects animals by suppressing formation

of a neurotoxic metabolite of MPTP, the drug may retard progression of PD by suppressing formation of a neurotoxic metabolite of an as-yet unidentified compound.

Pharmacokinetics. For treatment of PD, selegiline is available in oral formulations (tablets and capsules) and in orally disintegrating tablets (ODTs).

Tablets and Capsules. Selegiline in tablets [generic only] and capsules [Eldepryl] undergoes rapid GI absorption, travels to the brain, and quickly penetrates the blood-brain barrier. Irreversible inhibition of MAO-B follows. Selegiline undergoes hepatic metabolism followed by renal excretion. Two metabolites—1-*amphetamine* and 1-*methamphetamine*—are CNS stimulants. These metabolites, which do not appear to have therapeutic effects, can be harmful. Because selegiline causes irreversible inhibition of MAO-B, effects persist until more MAO-B can be synthesized.

Orally Disintegrating Tablets. Unlike selegiline in tablets and capsules, which is absorbed from the GI tract, selegiline in ODTs [Zelapar] is absorbed through the oral mucosa. As a result, bioavailability is higher than with tablets and capsules, and hence doses can be lower. Otherwise, the pharmacokinetics of selegiline in ODTs, tablets, and capsules are identical.

Adverse Effects. When selegiline is used alone, the principal adverse effect is *insomnia*, presumably because of CNS excitation by amphetamine and methamphetamine. Insomnia can be minimized by administering the last daily dose no later than noon. Other adverse effects include orthostatic hypotension, dizziness, and GI symptoms. About 10% of patients taking selegiline ODTs experience irritation of the buccal mucosa.

Hypertensive Crisis. Although selegiline is selective for MAO-B, high doses can inhibit MAO-A, and hence there is a risk of hypertensive crisis. As discussed in Chapter 32, when a patient is taking an MAO inhibitor, hypertensive crisis can be triggered by ingesting foods that contain tyramine and by taking certain drugs, including sympathomimetics. Accordingly, patients should be instructed to avoid these foods and drugs, both while taking selegiline and for 2 weeks after stopping it. For a full list of foods and drugs to avoid, see Chapter 32.

Drug Interactions. Levodopa. When used with levodopa, selegiline can intensify adverse responses to levodopa-derived dopamine. These reactions—orthostatic hypotension, dyskinesias, and psychologic disturbances (hallucinations, confusion)—can be reduced by decreasing the dosage of levodopa.

Meperidine. Like the nonselective MAO inhibitors, selegiline can cause a dangerous interaction with meperidine [Demerol]. Symptoms include stupor, rigidity, agitation, and hyperthermia. The combination should be avoided.

Fluoxetine. Selegiline should not be combined with fluoxetine [Prozac]. The combination of a nonselective MAO inhibitor plus fluoxetine has been fatal. Although this interaction has not been reported with selegiline, prudence dictates caution. Accordingly, fluoxetine should be withdrawn at least 5 weeks before giving selegiline.

Preparations, Dosage, and Administration. Tablets and Capsules. Selegiline is available in 5-mg tablets [generic only] and capsules sold as *Eldepryl*. For treatment of PD, the usual dosage is 5 mg taken with breakfast and lunch, for a total of 10 mg a day. This dosage produces complete inhibition of MAO-B, and hence larger doses are unnecessary.

Orally Disintegrating Tablets. Selegiline is available in 1.25-mg ODTs sold as *Zelapar*. For patients with PD, treatment begins with 1.25 mg once a day for 6 weeks. If needed and tolerated, the dosage can then be raised to 2.5 mg once a day. Note that the maximum daily dose (2.5 mg) is 4 times lower than the maximum daily dose with tablets and capsules. Dosing should be done in the morning before breakfast, without liquid. Tablets are placed on the tongue, where they dissolve in seconds. Selegiline is then absorbed through the oral mucosa.

Transdermal System. Selegiline is available in a transdermal system marketed as *Emsam*, for treatment of major depressive disorder (see Chapter 32). Transdermal selegiline is not used for PD.

Rasagiline

Actions and Therapeutic Use. Rasagiline [Azilect] was approved in 2006, making it the second MAO-B inhibitor for PD. Like selegiline, rasagiline is a selective, irreversible inhibitor of MAO-B. Benefits derive from preserving dopamine in the brain. The drug is approved for initial monotherapy of PD and for combined use with levodopa. As with selegiline, benefits are modest. Rasagiline is similar to selegiline in most regards. The drug

difier primarily in that rasagiline is not converted to amphetamine or methamphetamine.

Pharmacokinetics. Rasagiline is rapidly absorbed, with a bioavailability of 36%. In the liver, the drug undergoes nearly complete metabolism by CYP1A2 (the 1A2 isozyme of cytochrome P450). Hepatic impairment and drugs that inhibit CYP1A2 will delay metabolism of rasagiline, causing blood levels of the drug to rise. In contrast to selegiline, rasagiline is not metabolized to amphetamine derivatives. Excretion is via the urine (62%) and feces (7%). The plasma half-life is 3 hours. However, because rasagiline causes irreversible inhibition of MAO-B, clinical effects persist until new MAO-B is synthesized.

Adverse Effects. When used as monotherapy, rasagiline is generally well tolerated. The most common side effects are headache (14%), arthralgia (7%), dyspepsia (7%), depression (5%), flu-like symptoms (5%), and falls (5%). Unlike selegiline, rasagiline does not cause insomnia.

When rasagiline is combined with levodopa, side effects increase. The most common reactions are dyskinesias (18%), accidental injury (12%), nausea (17%), headache (11%), orthostatic hypotension (9%), constipation (9%), weight loss (9%), arthralgia (8%), and hallucinations (4%).

Like selegiline, rasagiline may pose a risk of hypertensive crisis (owing to inhibition of MAO-A), and hence patients should be instructed to avoid tyramine-containing foods and certain drugs, including sympathomimetic agents.

Rasagiline may increase the risk of malignant melanoma, a deadly cancer of the skin. Periodic monitoring is recommended.

Drug and Food Interactions. Rasagiline has the potential to interact adversely with multiple drugs. Drugs that should be used with *caution* include:

- **Levodopa**—Like selegiline, rasagiline can intensify adverse responses to levodopa-derived dopamine.

- **CYP1A2 Inhibitors**—Blood levels of rasagiline can be raised by ciprofloxacin and other drugs that inhibit CYP1A2, the hepatic enzyme that inactivates rasagiline.

Drugs and foods that are *contraindicated* include:

- **MAO Inhibitors**—Combining rasagiline with another MAO inhibitor increases the risk of hypertensive crisis. At least 2 weeks should separate use of these drugs.

- **Sympathomimetics**—Sympathomimetics (eg, amphetamines, ephedrine, phenylephrine, pseudoephedrine) increase the risk of hypertensive crisis and must be avoided.

- **Tyramine-Containing Foods**—These agents increase the risk of hypertensive crisis and must be avoided.

- **Antidepressants**—Combining rasagiline with mirtazapine, selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors, and tricyclic antidepressants may pose a risk of hyperpyrexia and death. These drugs should be discontinued at least 2 weeks before starting rasagiline. Fluoxetine (an SSRI) should be discontinued at least 5 weeks before starting rasagiline.

- **Analgesics**—Combining rasagiline with meperidine, methadone, propoxyphene,* or tramadol may pose a risk of serious reactions, including coma, respiratory depression, convulsions, hypertension, hypotension, and even death. At least 2 weeks should separate use of these drugs.

- **Dextromethorphan**—Combining rasagiline with dextromethorphan may pose a risk of brief episodes of psychosis and bizarre behavior.

- **Cyclobenzaprine**—This drug is structurally related to the tricyclic antidepressants, and hence should be avoided.

Preparations, Dosage, and Administration. Rasagiline [Azilect] is available in 0.5- and 1-mg tablets.

For *monotherapy*, the usual dosage is 1 mg once a day, taken with or without food. For patients taking ciprofloxacin and other drugs that inhibit CYP1A2, the daily dosage should be reduced to 0.5 mg. For patients with mild hepatic impairment, the daily dosage should be reduced to 0.5 mg. Patients with moderate to severe hepatic impairment should not use the drug.

For *adjunctive therapy* with levodopa, the dosage is 0.5 mg once a day usually, and may be increased to 1 mg once a day if needed. If the patient develops dopaminergic side effects, including dyskinesias or hallucinations, decreasing the dosage of levodopa—not rasagiline—should be considered.

Amantadine

Actions and Uses. Amantadine [Symmetrel] was developed as an antiviral agent (see Chapter 93), and was later found effective in PD. Possible

*Propoxyphene [Darvon] is no longer available in the United States.

mechanisms include inhibition of dopamine uptake, stimulation of dopamine release, blockade of cholinergic receptors, and blockade of glutamate receptors. Responses develop rapidly—often within 2 to 3 days—but are much less profound than with levodopa or the dopamine agonists. Furthermore, responses may begin to diminish within 3 to 6 months. Accordingly, amantadine is not considered a first-line agent. However, the drug may be helpful for managing dyskinesias caused by levodopa.

Adverse Effects. Amantadine can cause adverse CNS effects (confusion, lightheadedness, anxiety) and peripheral effects that are thought to result from muscarinic blockade (blurred vision, urinary retention, dry mouth, constipation). All of these are generally mild when amantadine is used alone. However, if amantadine is combined with an anticholinergic agent, both the CNS and peripheral responses will be intensified.

Patients taking amantadine for 1 month or longer often develop *livedo reticularis*, a condition characterized by mottled discoloration of the skin. Livedo reticularis is benign and gradually subsides following amantadine withdrawal.

Preparations, Dosage, and Administration. Amantadine [Symmetrel] is supplied in 100-mg tablets and capsules and in a syrup (10 mg/mL). The usual dosage is 100 mg twice daily. Because amantadine is eliminated primarily by the kidneys, dosage must be reduced in patients with renal impairment.

Amantadine often loses effectiveness after several months. If effects diminish, they can be restored by increasing the dosage or by interrupting treatment for several weeks.

Amantadine can enhance responses to levodopa and anticholinergic agents. When combined with these drugs, amantadine is administered in the same doses employed when taken alone.

Centrally Acting Anticholinergic Drugs

Anticholinergic drugs have been used in PD since 1867, making them the oldest medicines for this disease. These drugs alleviate symptoms by blocking muscarinic receptors in the striatum, thereby improving the functional imbalance between dopamine and ACh. Anticholinergic drugs can reduce tremor and possibly rigidity, but not bradykinesia. These drugs are less effective than levodopa or the dopamine agonists, but better tolerated. Today, anticholinergics are used as second-line therapy for tremor. They are most appropriate for younger patients with mild symptoms. Anticholinergics are generally avoided in the elderly, who are intolerant of CNS side effects (sedation, confusion, delusions, and hallucinations).

Although the anticholinergic drugs used today are somewhat selective for cholinergic receptors in the CNS, they can also block cholinergic receptors in the periphery. As a result, they can cause dry mouth, blurred vision, photophobia, urinary retention, constipation, and tachycardia. These effects are usually dose limiting. Blockade of cholinergic receptors in the eye may precipitate or aggravate glaucoma. Accordingly, intraocular pressure should be measured periodically. Peripheral anticholinergic effects are discussed fully in Chapter 14.

The anticholinergic agents used most often are *benztropine* [Cogentin] and *trihexyphenidyl*, formerly available as *Artane*. Doses are low initially and then gradually increased, until the desired response is achieved or until side effects become intolerable. For trihexyphenidyl, the initial dosage is 1 mg once a day, and the maximum dosage is 2 mg 3 times a day. For benztropine, the initial dosage is 0.5 mg twice a day, and the maximum dosage is 2 mg twice a day. If anticholinergic drugs are discontinued abruptly, symptoms of parkinsonism may be intensified.

NONMOTOR SYMPTOMS AND THEIR MANAGEMENT

In addition to experiencing characteristic motor symptoms, about 90% of patients with PD develop nonmotor symptoms, notably autonomic disturbances, sleep disturbances, depression, dementia, and psychosis. Management is addressed in two evidence-based guidelines: *Practice Parameter: Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease*, issued in 2006, and *Practice Parameter: Treatment of Nonmotor Symptoms of Parkinson Disease*, issued in 2010. These guidelines, issued by the American Academy of Neurology, are available free online at www.neurology.org.

Autonomic Symptoms. Disruption of autonomic function can produce a variety of symptoms, including constipation, urinary incontinence, drooling, orthostatic hypotension, cold intolerance, and erectile dysfunction. The intensity of these symptoms increases in parallel with the intensity of motor symptoms. Erectile function can be managed with sildenafil [Viagra] and other inhibitors of type 5 phosphodiesterase (see Chapter 66). Orthostatic

differs primarily in that rasagiline is not converted to amphetamine or methamphetamine.

Pharmacokinetics. Rasagiline is rapidly absorbed, with a bioavailability of 36%. In the liver, the drug undergoes nearly complete metabolism by CYP1A2 (the 1A2 isozyme of cytochrome P450). Hepatic impairment and drugs that inhibit CYP1A2 will delay metabolism of rasagiline, causing blood levels of the drug to rise. In contrast to selegiline, rasagiline is not metabolized to amphetamine derivatives. Excretion is via the urine (62%) and feces (7%). The plasma half-life is 3 hours. However, because rasagiline causes irreversible inhibition of MAO-B, clinical effects persist until new MAO-B is synthesized.

Adverse Effects. When used as monotherapy, rasagiline is generally well tolerated. The most common side effects are headache (14%), arthralgia (7%), dyspepsia (7%), depression (5%), flu-like symptoms (5%), and falls (5%). Unlike selegiline, rasagiline does not cause insomnia.

When rasagiline is combined with levodopa, side effects increase. The most common reactions are dyskinesias (18%), accidental injury (12%), nausea (12%), headache (11%), orthostatic hypotension (9%), constipation (9%), weight loss (9%), arthralgia (8%), and hallucinations (4%).

Like selegiline, rasagiline may pose a risk of hypertensive crisis (owing to inhibition of MAO-A), and hence patients should be instructed to avoid tyramine-containing foods and certain drugs, including sympathomimetic agents.

Rasagiline may increase the risk of malignant melanoma, a deadly cancer of the skin. Periodic monitoring is recommended.

Drug and Food Interactions. Rasagiline has the potential to interact adversely with multiple drugs. Drugs that should be used with caution include:

- **Levodopa**—Like selegiline, rasagiline can intensify adverse responses to levodopa-derived dopamine.
- **CYP1A2 Inhibitors**—Blood levels of rasagiline can be raised by ciprofloxacin and other drugs that inhibit CYP1A2, the hepatic enzyme that inactivates rasagiline.
Drugs and foods that are *contraindicated* include:
- **MAO Inhibitors**—Combining rasagiline with another MAO inhibitor increases the risk of hypertensive crisis. At least 2 weeks should separate use of these drugs.
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- **Antidepressants**—Combining rasagiline with mirtazapine, selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors, and tricyclic antidepressants may pose a risk of hyperpyrexia and death. These drugs should be discontinued at least 2 weeks before starting rasagiline. Fluoxetine (an SSRI) should be discontinued at least 5 weeks before starting rasagiline.
- **Analgesics**—Combining rasagiline with meperidine, methadone, propoxyphene,* or tramadol may pose a risk of serious reactions, including coma, respiratory depression, convulsions, hypertension, hypotension, and even death. At least 2 weeks should separate use of these drugs.
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Like selegiline, rasagiline may pose a risk of hypertensive crisis (owing to inhibition of MAO-A), and hence patients should be instructed to avoid tyramine-containing foods and certain drugs, including sympathomimetic agents.

Rasagiline may increase the risk of malignant melanoma, a deadly cancer of the skin. Periodic monitoring is recommended.

Drug and Food Interactions. Rasagiline has the potential to interact adversely with multiple drugs. Drugs that should be used with *caution* include:

- **Levodopa**—Like selegiline, rasagiline can intensify adverse responses to levodopa-derived dopamine.
 - **CYP1A2 Inhibitors**—Blood levels of rasagiline can be raised by ciprofloxacin and other drugs that inhibit CYP1A2, the hepatic enzyme that inactivates rasagiline.
- Drugs and foods that are *contraindicated* include:
- **MAO Inhibitors**—Combining rasagiline with another MAO inhibitor increases the risk of hypertensive crisis. At least 2 weeks should separate use of these drugs.
 - **Sympathomimetics**—Sympathomimetics (eg, amphetamines, ephedrine, phenylephrine, pseudoephedrine) increase the risk of hypertensive crisis and must be avoided.
 - **Tyramine-Containing Foods**—These agents increase the risk of hypertensive crisis and must be avoided.
 - **Antidepressants**—Combining rasagiline with mirtazapine, selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors, and tricyclic antidepressants may pose a risk of hyperpyrexia and death. These drugs should be discontinued at least 2 weeks before starting rasagiline. Fluoxetine (an SSRI) should be discontinued at least 5 weeks before starting rasagiline.
 - **Analgesics**—Combining rasagiline with meperidine, methadone, propoxyphene,* or tramadol may pose a risk of serious reactions, including coma, respiratory depression, convulsions, hypertension, hypotension, and even death. At least 2 weeks should separate use of these drugs.
 - **Dextromethorphan**—Combining rasagiline with dextromethorphan may pose a risk of brief episodes of psychosis and bizarre behavior.
 - **Cyclobenzaprine**—This drug is structurally related to the tricyclic antidepressants, and hence should be avoided.

Preparations, Dosage, and Administration. Rasagiline [Azilect] is available in 0.5- and 1-mg tablets.

For *monotherapy*, the usual dosage is 1 mg once a day, taken with or without food. For patients taking ciprofloxacin and other drugs that inhibit CYP1A2, the daily dosage should be reduced to 0.5 mg. For patients with mild hepatic impairment, the daily dosage should be reduced to 0.5 mg. Patients with moderate to severe hepatic impairment should not use the drug.

For *adjunctive therapy* with levodopa, the dosage is 0.5 mg once a day initially, and may be increased to 1 mg once a day if needed. If the patient develops dopaminergic side effects, including dyskinesias or hallucinations, reducing the dosage of levodopa—not rasagiline—should be considered.

Amantadine

Actions and Uses. Amantadine [Symmetrel] was developed as an antiviral agent (see Chapter 93), and was later found effective in PD. Possible

*Propoxyphene [Darvon] is no longer available in the United States.

mechanisms include inhibition of dopamine uptake, stimulation of dopamine release, blockade of cholinergic receptors, and blockade of glutamate receptors. Responses develop rapidly—often within 2 to 3 days—but are much less profound than with levodopa or the dopamine agonists. Furthermore, responses may begin to diminish within 3 to 6 months. Accordingly, amantadine is not considered a first-line agent. However, the drug may be helpful for managing dyskinesias caused by levodopa.

Adverse Effects. Amantadine can cause adverse CNS effects (confusion, lightheadedness, anxiety) and peripheral effects that are thought to result from muscarinic blockade (blurred vision, urinary retention, dry mouth, constipation). All of these are generally mild when amantadine is used alone. However, if amantadine is combined with an anticholinergic agent, both the CNS and peripheral responses will be intensified.

Patients taking amantadine for 1 month or longer often develop *livedo reticularis*, a condition characterized by mottled discoloration of the skin. Livedo reticularis is benign and gradually subsides following amantadine withdrawal.

Preparations, Dosage, and Administration. Amantadine [Symmetrel] is supplied in 100-mg tablets and capsules and in a syrup (10 mg/mL). The usual dosage is 100 mg twice daily. Because amantadine is eliminated primarily by the kidneys, dosage must be reduced in patients with renal impairment.

Amantadine often loses effectiveness after several months. If effects diminish, they can be restored by increasing the dosage or by interrupting treatment for several weeks.

Amantadine can enhance responses to levodopa and anticholinergic agents. When combined with these drugs, amantadine is administered in the same doses employed when taken alone.

Centrally Acting Anticholinergic Drugs

Anticholinergic drugs have been used in PD since 1867, making them the oldest medicines for this disease. These drugs alleviate symptoms by blocking muscarinic receptors in the striatum, thereby improving the functional imbalance between dopamine and ACh. Anticholinergic drugs can reduce tremor and possibly rigidity, but not bradykinesia. These drugs are less effective than levodopa or the dopamine agonists, but better tolerated. Today, anticholinergics are used as second-line therapy for tremor. They are most appropriate for younger patients with mild symptoms. Anticholinergics are generally avoided in the elderly, who are intolerant of CNS side effects (sedation, confusion, delusions, and hallucinations).

Although the anticholinergic drugs used today are somewhat selective for cholinergic receptors in the CNS, they can also block cholinergic receptors in the periphery. As a result, they can cause dry mouth, blurred vision, photophobia, urinary retention, constipation, and tachycardia. These effects are usually dose limiting. Blockade of cholinergic receptors in the eye may precipitate or aggravate glaucoma. Accordingly, intraocular pressure should be measured periodically. Peripheral anticholinergic effects are discussed fully in Chapter 14.

The anticholinergic agents used most often are *benztropine* [Cogentin] and *trihexyphenidyl*, formerly available as *Artane*. Doses are low initially and then gradually increased, until the desired response is achieved or until side effects become intolerable. For trihexyphenidyl, the initial dosage is 1 mg once a day, and the maximum dosage is 2 mg 3 times a day. For benztropine, the initial dosage is 0.5 mg twice a day, and the maximum dosage is 2 mg twice a day. If anticholinergic drugs are discontinued abruptly, symptoms of parkinsonism may be intensified.

NONMOTOR SYMPTOMS AND THEIR MANAGEMENT

In addition to experiencing characteristic motor symptoms, about 90% of patients with PD develop nonmotor symptoms, notably autonomic disturbances, sleep disturbances, depression, dementia, and psychosis. Management is addressed in two evidence-based guidelines: *Practice Parameter: Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease*, issued in 2006, and *Practice Parameter: Treatment of Nonmotor Symptoms of Parkinson Disease*, issued in 2010. These guidelines, issued by the American Academy of Neurology, are available free online at www.neurology.org.

Autonomic Symptoms. Disruption of autonomic function can produce a variety of symptoms, including constipation, urinary incontinence, drooling, orthostatic hypotension, cold intolerance, and erectile dysfunction. The intensity of these symptoms increases in parallel with the intensity of motor symptoms. Erectile function can be managed with sildenafil [Viagra] and other inhibitors of type 5 phosphodiesterase (see Chapter 66). Orthostatic

hypotension can be improved by increasing intake of salt and fluid, and possibly by taking fludrocortisone, a mineralocorticoid (see Chapter 60). Urinary incontinence may improve with oxybutynin and other peripherally acting anticholinergic drugs (see Chapter 14). Constipation can be managed by getting regular exercise and maintaining adequate intake of fluid and fiber. Polyethylene glycol (an osmotic laxative) or a stool softener (eg, docusate) may also be tried (see Chapter 79).

Sleep Disturbances. Parkinson's disease is associated with *excessive daytime sleepiness* (EDS), *periodic limb movements of sleep* (PLMS), and *insomnia* (difficulty falling asleep and staying asleep). EDS may respond to modafinil [Provigil, Alertec[®]], a nonamphetamine CNS stimulant (see Chapter 36). For PLMS, levodopa/carbidopa should be considered; the nonergot dopamine agonists—pramipexole and ropinirole—may also help. Insomnia may be improved by levodopa/carbidopa and melatonin (see Chapter 34). Levodopa/carbidopa helps by reducing motor symptoms that can impair sleep. Melatonin helps by making people *feel* they are sleeping better, even though objective measures of sleep quality may not improve.

Depression. About 50% of PD patients develop depression, partly in reaction to having a debilitating disease, and partly due to the disease process itself. According to the 2006 AAN guidelines, only one drug—*amitriptyline*—has been proved effective in these patients. Unfortunately, amitriptyline, a tricyclic antidepressant, has anticholinergic effects that can exacerbate dementia, and antiadrenergic effects that can exacerbate orthostatic hypotension. Data for

other antidepressants, including selective serotonin reuptake inhibitors and bupropion, are insufficient to prove or disprove efficacy in PD.

Dementia. Dementia occurs in 40% of PD patients. The AAN guidelines recommend considering treatment with two drugs: *donepezil* and *rivastigmine*. Both drugs are cholinesterase inhibitors developed for Alzheimer's disease (Chapter 22). In patients with PD, these drugs can produce a modest improvement in cognitive function, without causing significant worsening of motor symptoms, even though these drugs increase availability of acetylcholine at central synapses.

Psychosis. In patients with PD, psychosis is usually caused by the drugs taken to control motor symptoms. Most of these drugs—levodopa, dopamine agonists, amantadine, and anticholinergic drugs—can cause hallucinations. Therefore, if psychosis develops, dopamine agonists, amantadine, and anticholinergic drugs should be withdrawn, and the dosage of levodopa should be reduced to the lowest effective amount. If antipsychotic medication is needed, *first-generation* antipsychotics should be *avoided*. Why? Because all of these drugs block receptors for dopamine, and hence can intensify motor symptoms. Accordingly, the AAN guidelines recommend considering two *second-generation* antipsychotics: *clozapine* and *quetiapine*. Since clozapine can cause agranulocytosis, many clinicians prefer quetiapine. The guidelines recommend against routine use of olanzapine, another second-generation agent. The antipsychotic drugs are discussed in Chapter 31.

KEY POINTS

- Parkinson's disease is a neurodegenerative disorder that produces characteristic motor symptoms: tremor at rest, rigidity, postural instability, and bradykinesia.
- In addition to motor symptoms, PD can cause nonmotor symptoms, including autonomic dysfunction, sleep disturbances, depression, psychosis, and dementia.
- The primary pathology in PD is degeneration of neurons in the substantia nigra that supply dopamine to the striatum. The result is an imbalance between dopamine and ACh.
- Motor symptoms are treated primarily with drugs that directly or indirectly activate dopamine receptors. Drugs that block cholinergic receptors can also be used.
- Levodopa (combined with carbidopa) is the most effective treatment for motor symptoms.
- Levodopa relieves motor symptoms by undergoing conversion to dopamine in surviving nerve terminals in the striatum.
- The enzyme that converts levodopa to dopamine is called a decarboxylase.
- Acute loss of response to levodopa occurs in two patterns: gradual "wearing off," which develops at the end of the dosing interval, and abrupt loss of effect ("on-off" phenomenon), which can occur at any time during the dosing interval.
- The principal adverse effects of levodopa are nausea, dyskinesias, hypotension, and psychosis.
- First-generation antipsychotic drugs block dopamine receptors in the striatum, and can thereby negate the effects of levodopa. Two second-generation antipsychotics—clozapine and quetiapine—do not block dopamine receptors in the striatum, and hence can be used safely to treat levodopa-induced psychosis.
- Combining levodopa with a nonselective MAO inhibitor can result in hypertensive crisis.
- Because amino acids compete with levodopa for absorption from the intestine and for transport across the blood-brain barrier, high-protein meals can reduce therapeutic effects.
- Carbidopa enhances the effects of levodopa by preventing decarboxylation of levodopa in the intestine and peripheral tissues. Since carbidopa cannot cross the blood-brain barrier, it does not prevent conversion of levodopa to dopamine in the brain.
- Pramipexole, an oral nonergot dopamine agonist, is a first-line drug for motor symptoms. It can be used alone in early PD and combined with levodopa in advanced PD.
- Pramipexole and other dopamine agonists relieve motor symptoms by causing direct activation of dopamine receptors in the striatum.
- The major adverse effects of pramipexole—nausea, dyskinesia, postural hypotension, and hallucinations—result from excessive activation of dopamine receptors.
- Entacapone, a COMT inhibitor, is combined with levodopa to enhance levodopa's effects. The drug inhibits metabolism of levodopa by COMT in the intestine and peripheral tissues, thereby making more levodopa available to the brain.
- Selegiline and rasagiline enhance responses to levodopa by inhibiting MAO-B, the brain enzyme that inactivates dopamine.
- Anticholinergic drugs relieve symptoms of PD by blocking cholinergic receptors in the striatum.

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Summary of Major Nursing Implications*

LEVODOPA/CARBIDOPA [SINEMET, PARCOPA]

Preadministration Assessment

Therapeutic Goal

The goal of treatment is to improve the patient's ability to carry out activities of daily living. Levodopa does not cure PD or delay its progression.

Baseline Data

Assess motor symptoms—bradykinesia, akinesia, postural instability, tremor, rigidity—and the extent to which they interfere with activities of daily living (ability to work, dress, bathe, walk, etc.).

Identifying High-Risk Patients

Levodopa is *contraindicated* for patients with malignant melanoma (it can activate this neoplasm) and for patients taking nonselective MAO inhibitors.

Exercise *caution* in patients with cardiac disease and psychiatric disorders and in patients taking selective MAO-B inhibitors.

Implementation: Administration

Route

Oral

Administration

Motor symptoms may render self-medication impossible. Assist the patient with dosing when needed. If appropriate, involve family members in medicating outpatients. Inform patients that levodopa may be taken with food to reduce nausea and vomiting. However, high-protein meals should be avoided.

So that expectations may be realistic, inform patients that benefits of levodopa may be delayed for weeks to months. This knowledge will facilitate adherence.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects
Evaluate for improvements in activities of daily living and for reductions in bradykinesia, postural instability, tremor, and rigidity.

Managing Acute Loss of Effect

"Off" times can be reduced by combining levodopa/carbidopa with a dopamine agonist (eg, pramipexole), a COMT inhibitor (eg, entacapone), or an MAO-B inhibitor (eg, rasagiline). Forewarn patients about possible abrupt loss of therapeutic effects and instruct them to notify the prescriber if this occurs. Avoiding high-protein meals may help.

Minimizing Adverse Effects

Nausea and Vomiting. Inform patients that nausea and vomiting can be reduced by taking levodopa with food. Instruct patients to notify the prescriber if nausea and vomiting persist or become severe.

Dyskinesias. Inform patients about possible levodopa-induced movement disorders (tremor, dystonic movements, twitching) and instruct them to notify the prescriber if these develop. Giving amantadine may help.

If the hospitalized patient develops dyskinesias, withhold levodopa and consult the prescriber about a possible reduction in dosage.

Dysrhythmias. Inform patients about signs of excessive cardiac stimulation (palpitations, tachycardia, irregular heartbeat) and instruct them to notify the prescriber if these occur.

Orthostatic Hypotension. Inform patients about symptoms of hypotension (dizziness, lightheadedness) and advise them to sit or lie down if these occur. Advise patients to move slowly when assuming an erect posture.

Psychosis. Inform patients about possible levodopa-induced psychosis (visual hallucinations, vivid dreams, paranoia) and instruct them to notify the prescriber if these develop. Treatment with clozapine or quetiapine can help.

Minimizing Adverse Interactions

First-Generation Antipsychotic Drugs. These can block responses to levodopa and should be avoided. Two second-generation antipsychotics—clozapine and quetiapine—can be used safely.

MAO Inhibitors. Concurrent use of levodopa and a nonselective MAO inhibitor can produce severe hypertension. Withdraw nonselective MAO inhibitors at least 2 weeks before initiating levodopa.

Anticholinergic Drugs. These can enhance therapeutic responses to levodopa, but they also increase the risk of adverse psychiatric effects.

High-Protein Meals. Amino acids compete with levodopa for absorption from the intestine and for transport across the blood-brain barrier. Instruct patients not to take levodopa/carbidopa with a high-protein meal.

DOPAMINE AGONISTS

Apomorphine
Bromocriptine
Cabergoline
Pramipexole
Ropinirole

Preadministration Assessment

Therapeutic Goal

The goal of treatment is to improve the patient's ability to carry out activities of daily living. Dopamine agonists do not cure PD or delay its progression.

Apomorphine is reserved for rescue treatment of hypomobility during "off" episodes in patients with advanced PD.

Baseline Data

Assess motor symptoms—bradykinesia, akinesia, postural instability, tremor, rigidity—and the extent to which these interfere with activities of daily living (ability to work, dress, bathe, walk, etc.).

Identifying High-Risk Patients
Use all dopamine agonists with *caution* in elderly patients and in patients with psychiatric disorders. Use pramipexole with *caution* in patients with kidney dysfunction. Avoid ropinirole during pregnancy. Use pramipexole and ropinirole with *caution* in patients prone to compulsive behavior.

Implementation: Administration

Route

Oral. Cabergoline, bromocriptine, pramipexole, ropinirole.

Subcutaneous. Apomorphine.

Administration

Parkinsonism may render self-medication impossible. Assist the patient with dosing when needed. If appropriate, involve family members in medicating outpatients.

Inform patients that oral dopamine agonists may be taken with food to reduce nausea and vomiting.

To minimize adverse effects, dosage should be low initially and then gradually increased.

Reduce dosage of pramipexole in patients with significant renal dysfunction.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Evaluate for improvements in activities of daily living and for reductions in bradykinesia, postural instability, tremor, and rigidity.

Minimizing Adverse Effects

Nausea and Vomiting. Inform patients that nausea and vomiting can be reduced by taking oral dopamine ago-

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

nists with food. Instruct patients to notify the prescriber if nausea and vomiting persist or become severe. Instruct patients taking apomorphine to pretreat with trimethoprima-mide (Tigan), an antiemetic.

Orthostatic Hypotension. Inform patients about symptoms of hypotension (dizziness, lightheadedness) and advise them to sit or lie down if these occur. Advise patients to move slowly when assuming an erect posture.

Dyskinesias. Inform patients about possible movement disorders (tremor, dystonic movements, twitching) and instruct them to notify the prescriber if these develop.

Hallucinations. Forewarn patients that dopamine agonists can cause hallucinations, especially in the elderly, and instruct them to notify the prescriber if these develop.

Sleep Attacks. Warn patients that pramipexole, ropinirole, and apomorphine may cause sleep attacks. Instruct patients that, if a sleep attack occurs, they should inform the prescriber and avoid potentially hazardous activities (eg, driving).

Fetal Injury. Inform women of child-bearing age that ropinirole may harm the developing fetus, and advise them to use effective birth control. If pregnancy occurs, switching to a different dopamine agonist is advised.

Impulse Control Disorders. Pramipexole and ropinirole may induce compulsive, self-rewarding behaviors, including compulsive gambling, eating, shopping, and hypersexuality. Risk factors include relative youth, a family or personal history of alcohol abuse, and a novelty-seeking personality. Before prescribing these drugs, clinicians should screen patient for compulsive behaviors.

Alzheimer's Disease

Pathophysiology

Risk Factors, Symptoms, Biomarkers, and Diagnosis Drugs for Cognitive Impairment

Cholinesterase Inhibitors

Memantine

Drugs for Neuropsychiatric Symptoms

Can We Prevent Alzheimer's Disease or Delay Cognitive Decline?

Alzheimer's disease (AD) is a devastating illness characterized by progressive memory loss, impaired thinking, neuropsychiatric symptoms (eg, hallucinations, delusions), and inability to perform routine tasks of daily living. AD affects about 5.3 million older Americans and kills about 100,000 each year, making it the fourth leading cause of death among adults, and the sixth leading cause overall. The annual cost of AD and other dementias—about \$172 billion—is exceeded only by the costs of heart disease and cancer. Major pathologic findings are cerebral atrophy, degeneration of cholinergic neurons, and the presence of neuritic plaques and neurofibrillary tangles—all of which begin to develop years before clinical symptoms appear. This neuronal damage is irreversible, and hence AD cannot be cured. Drugs in current use do little to relieve symptoms or prevent neuronal loss. Furthermore, there is no solid proof that any intervention can delay the onset of AD or cognitive decline.

PATHOPHYSIOLOGY

The underlying cause of AD is unknown. Scientists have discovered important pieces of the AD puzzle, but still don't know how they fit together. It may well be that AD results from a combination of factors, rather than from a single cause.

Degeneration of Neurons

Neuronal degeneration occurs in the hippocampus early in AD, followed later by degeneration of neurons in the cerebral cortex. The hippocampus serves an important role in memory. The cerebral cortex is central to speech, perception, reasoning, and other higher functions. As hippocampal neurons degenerate, short-term memory begins to fail. As cortical neurons degenerate, patients begin having difficulty with language. With advancing cortical degeneration, more severe symptoms appear. These include complete loss of speech, loss of bladder and bowel control, and complete inability for self-care. AD eventually destroys enough brain function to cause death. Because of neuronal degeneration, cerebral volume declines.

Reduced Cholinergic Transmission

In patients with advanced AD, levels of acetylcholine (ACh) are 90% below normal. This dramatic loss contrasts with the small loss that occurs normally with age. Loss of ACh is significant for two reasons. First, ACh is an important transmitter in the hippocampus and cerebral cortex, regions where neuronal degeneration occurs. Second, ACh is critical to forming memories, and its decline has been linked to memory loss. However, although loss of cholinergic function is clearly important, it cannot be the whole story. Why? Because in 1999, researchers reported that, in patients with *mild* AD, markers for cholinergic transmission are essentially normal. Hence, loss of cholinergic function cannot explain the cognitive deficits that occur early in the disease process.

Beta-Amyloid and Neuritic Plaques

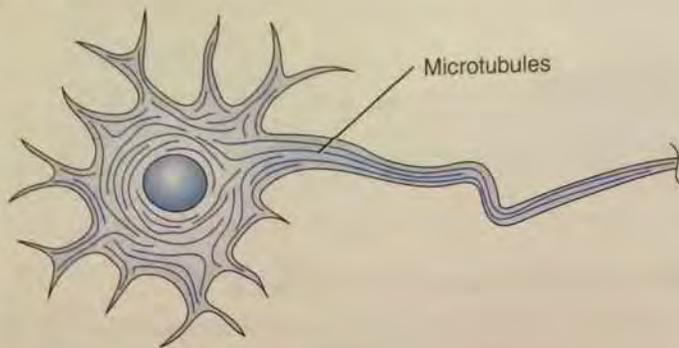
Neuritic plaques, which form outside of neurons, are a hallmark of AD. These spherical bodies are composed of a central core of *beta-amyloid* (a protein fragment) surrounded by remnants of axons and dendrites. Neuritic plaques are seen mainly in the hippocampus and cerebral cortex. The relationship of neuritic plaques to the disease process is unknown.

In patients with AD, beta-amyloid is present in high levels and may contribute to neuronal injury. Several lines of evidence support this possibility: beta-amyloid can kill hippocampal cells grown in culture; it can release free radicals, which injure cells; it can disrupt potassium channels; and it may form channels in the cell membrane that promote excessive entry of calcium. Also, low doses of beta-amyloid cause vasoconstriction, and high doses cause permanent blood vessel injury (secondary to release of oxygen free radicals). By disrupting blood vessels, beta-amyloid could slowly starve neurons to death. Perhaps the strongest evidence linking beta-amyloid to AD is the observation that injection of the compound directly into the brains of rhesus monkeys produces pathology essentially identical to that of AD. Interestingly, beta-amyloid is harmful only to old monkeys; young monkeys are not affected. This may indicate that, as the brain ages, it produces substances that act in concert with beta-amyloid to permit neurotoxic effects. Of note, accumulation of beta-amyloid begins early in the disease process, perhaps 10 to 20 years before the first symptoms of AD appear. Because of the central role that beta-amyloid appears to play in AD, treatments directed against beta-amyloid are in development.

Neurofibrillary Tangles and Tau

Like neuritic plaques, neurofibrillary tangles are a prominent feature of AD. These tangles, which form inside of neurons, result when the orderly arrangement of microtubules becomes disrupted (Fig. 22-1). The underlying cause

A Normal



B Alzheimer's Disease

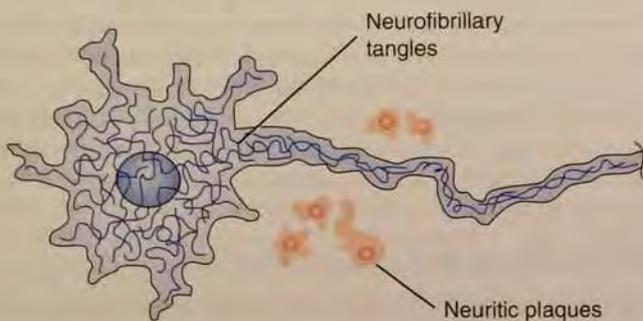


Figure 22-1 ■ Histologic changes in Alzheimer's disease. A, Healthy neuron. B, Neuron affected by Alzheimer's disease, showing characteristic intracellular neurofibrillary tangles. Note also extracellular neuritic plaques.

is production of an abnormal form of tau, a protein that, in healthy neurons, forms cross-bridges between microtubules, and thereby keeps their configuration stable. In patients with AD, tau twists into paired helical filaments. As a result, the orderly arrangement of microtubules transforms into neurofibrillary tangles.

Apolipoprotein E4

Apolipoprotein E (apoE), long known for its role in cholesterol transport, may also contribute to AD. Like some other proteins, apoE has more than one form. In fact, it has three forms, named apoE2, apoE3, and apoE4. (Don't ask what happened to apoE1.) Only one form—apoE4—is associated with AD. Genetic research has shown that individuals with one or two copies of the gene that codes for apoE4 are at increased risk for AD. In contrast, apoE2 seems protective.

What does apoE4 do? One possibility is that it promotes formation of neuritic plaques. ApoE4 binds quickly and tightly to beta-amyloid, causing this normally soluble substance to become insoluble, which could promote deposition of beta-amyloid in plaque.

It is important to note that apoE4 is neither necessary nor sufficient to cause AD. There are many people with AD who do not have the gene for apoE4. Conversely, in one study involving people who were 90 years old and homozygous for apoE4, 50% had not developed AD.

Endoplasmic Reticulum–Associated Binding Protein

The discovery of endoplasmic reticulum–associated binding protein (ERAB) adds another piece to the AD puzzle. Involvement of ERAB in AD is supported by several observations: ERAB is present in high concentration in the brains of patients with AD; ERAB is found in association with beta-amyloid, a compound with neurotoxic effects; high concentrations of ERAB enhance the neurotoxic effects of beta-amyloid; and the neurotoxic effects of beta-amyloid can be blocked by blocking the actions of ERAB.

Homocysteine

Elevated plasma levels of homocysteine are associated with an increased risk of AD. (Homocysteine is an amino acid formed from dietary methionine.) An elevation of 5 mmol/L appears to increase the risk by 40%; an elevation of 14 mmol/L appears to double the risk. How might homocysteine promote AD? One possibility is reduced blood flow secondary to blockage of cerebral blood vessels. Another possibility is direct injury to nerve cells. Fortunately, even if homocysteine really does promote AD, the risk can be easily reduced: Levels of homocysteine can be lowered by eating foods rich in folic acid and vitamins B₆ and B₁₂, or by taking dietary supplements that contain these compounds.

RISK FACTORS, SYMPTOMS, BIOMARKERS, AND DIAGNOSIS

Risk Factors

The major known risk factor for AD is advancing age. In 90% of patients, the age of onset is 65 years or older. After age 65, the risk of AD increases exponentially, doubling every 10 years until age 85 to 90, after which the risk of getting AD levels off or declines. The only other known risk factor is a family history of AD. Being female *may* be a risk factor. However, the higher incidence of AD in women may occur simply because women live longer than men. Other possible risk factors include head injury, low educational level, production of apoE4, high levels of homocysteine, low levels of folic acid, estrogen/progestin therapy, sedentary lifestyle, and nicotine in cigarette smoke.

Symptoms

Alzheimer's is a disease in which symptoms progress relentlessly from mild to moderate to severe (Table 22-1). Symptoms typically begin after age 65, but may appear in people as young as 40. Early in the disease, patients begin to experience memory loss and confusion. They may be disoriented and get lost in familiar surroundings. Judgment becomes impaired and personality may change. As the disease progresses, patients have increasing difficulty with self-care. Between 70% and 90% eventually develop behavior problems (wandering, pacing, agitation, screaming). Symptoms may intensify in the evening, a phenomenon known as "sundowning." In the final stages of AD, the patient is unable to recognize close family members or communicate in any way. All sense of identity is lost and the individual is completely dependent on others for survival. The time from onset of symptoms to death may be 20 years or longer, but is usually 4 to 8 years. Although there is no clearly effective therapy for *core symptoms*, other symp-

TABLE 22-1 • Symptoms of Alzheimer's Disease

Mild Symptoms

Confusion and memory loss
Disorientation; getting lost in familiar surroundings
Problems with routine tasks
Changes in personality and judgment

Moderate Symptoms

Difficulty with activities of daily living, such as feeding and bathing
Anxiety, suspiciousness, agitation
Sleep disturbances
Wandering, pacing
Difficulty recognizing family and friends

Severe Symptoms

Loss of speech
Loss of appetite; weight loss
Loss of bladder and bowel control
Total dependence on caregiver

toms (eg, incontinence, depression) can be treated. In addition, resources are available to help families cope with AD and prepare for future caregiving needs.

Biomarkers

Biomarkers are biochemical, anatomic, or physiologic parameters—measured *in vivo*—that reflect a pathophysiologic process. The biomarkers of AD fall into two major groups: (1) biomarkers of beta-amyloid accumulation and (2) biomarkers of neuronal degeneration or injury.

To detect *beta-amyloid accumulation*, two tests are used most widely:

- *Positron emission tomography (PET)*. The test uses a radiolabeled compound—usually florbetapir or Pittsburgh Compound B—that binds with beta-amyloid, and thereby renders beta-amyloid visible in the scan.
- *Measurement of beta-amyloid₄₂ in cerebrospinal fluid (CSF)*. A low level of beta-amyloid₄₂ in CSF indicates a high level of beta-amyloid in the brain.

Because beta-amyloid accumulation begins early in the disease process, measurement of these biomarkers can detect possible disease onset years before symptoms appear.

To detect *neuronal degeneration or injury*, three principal tests are employed:

- *Measurement of tau in CSF*. A high level of tau suggests neuronal injury.
- *PET scan showing fluorodeoxyglucose uptake*. Synaptic dysfunction of AD is suggested by reduced fluorodeoxyglucose uptake at specific sites in the temporoparietal cortex.
- *Structural magnetic resonance imaging (sMRI)*. Neuronal degeneration of AD is indicated by a specific pattern of atrophy involving the medial, basal, and lateral temporal lobes, as well as the medial and lateral parietal cortices.

Unlike the biomarkers for beta-amyloid accumulation, which can be detected very early in the disease process, biomarkers for neuronal degeneration don't appear until just before symptom onset.

It is important to note that, at this time, biomarkers have only limited clinical utility. Why? Because interpreting test results can be difficult. It is true that, in many cases, test results will be clearly abnormal or clearly normal, and hence can help confirm or exclude a diagnosis of AD. However, in many other cases, results may be ambiguous, and hence will not allow a clear assessment of disease status. Furthermore, since tests for biomarkers are relatively new, universal standards for quantifying these tests have not been developed. Accordingly, although testing for biomarkers can be very helpful in a research setting (see below), testing is much less helpful for routine patient management.

Diagnosis

In 2011, the National Institute on Aging and the Alzheimer's Association issued revised diagnostic criteria for AD. The new criteria update those issued in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA), now the Alzheimer's Association. Under the revised criteria, AD is divided into an asymptomatic preclinical phase and two symptomatic clinical phases: (1) mild cognitive impairment (MCI) due to AD, and (2) probable dementia due to AD. Diagnosis of the preclinical phase is based solely on biomarkers. For the two clinical phases, diagnosis is routinely based on the clinical evaluation. However, although biomarkers are not *required* for these diagnoses, biomarkers *can* be used to compliment the clinical evaluation. The new guidelines are available online at www.alz.org.

Preclinical AD. The preclinical phase of AD begins years before patients develop any memory loss or problems with thinking. Because there are no symptoms at this stage, diagnosis is based entirely on the presence of biomarkers, indicating beta-amyloid accumulation and/or neuronal degeneration. If the diagnosis is correct, cognitive symptoms will develop long after the evidence for beta-amyloid accumulation was obtained. Similarly, biomarkers for neuronal degeneration should appear long after the biomarkers for beta-amyloid were first evident.

At this time, a diagnosis of preclinical AD is useful only for selecting subjects for research, not for routine patient care. For studies on drug development, application of these criteria will greatly increase the likelihood that subjects actually have AD, even though cognitive impairment is mild or completely absent. Without using biomarkers to diagnose preclinical AD, we couldn't tell if minimal cognitive impairment was an early sign of AD, some other pathology, or no pathology at all—and hence study results would be difficult to interpret. What about clinical practice? At this time, we have no treatments that can alter the course of AD. Accordingly, even if we could establish a definitive early diagnosis, there's not much we can do to help. In the future, when we do have drugs that can delay AD onset or slow disease progression, then a definitive early diagnosis will have great benefit, allowing us to implement effective therapy at the earliest possible time.

Probable Dementia Due to AD. Diagnostic criteria for *all-cause dementia* and *probable dementia of AD* are summarized in Table 22-2. As indicated, dementia of any cause is defined by deficits in two or more cognitive areas—memory, decision making, language, personality, visuospatial function—that are severe enough to interfere with function at work or in usual

TABLE 22-2 ■ Diagnostic Criteria for All-Cause Dementia, Probable Dementia Due to Alzheimer's Disease, and Mild Cognitive Impairment Due to Alzheimer's Disease

All-Cause Dementia

Dementia is diagnosed when there are cognitive or behavioral symptoms that:

1. Interfere with the ability to function at work or at usual activities
2. Represent a decline from previous levels of functioning and performing
3. Are not explained by delirium or a major psychiatric disorder
4. Involve at least two of the following domains:
 - *Impaired ability to acquire and remember new information*—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
 - *Impaired reasoning and handling of complex tasks, poor judgment*—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
 - *Impaired visuospatial abilities*—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
 - *Impaired language functions (speaking, reading, writing)*—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
 - *Changes in personality, behavior, or comportment*—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

Probable Dementia Due to Alzheimer's Disease

Probable AD dementia is diagnosed when there are cognitive or behavioral symptoms that meet the criteria for all-cause dementia, and:

- There is a clear-cut history of worsening of cognition
- Cognitive decline developed gradually over months to years, not suddenly over hours or days
- Symptoms cannot be explained by a systemic illness, neurologic illness (eg, stroke, dementia with Lewy bodies, frontotemporal dementia), or use of drugs that can significantly impair cognition

Mild Cognitive Impairment (MCI) Due to AD

Diagnostic criteria for MCI of AD are the same as for probable dementia of AD—except that symptoms in MCI of AD are not severe enough to cause significant interference with performance at work or in usual daily activities.

Source: McKhann GM, Knopman DS, Chertokow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimer's Association*, 2011. Available online at www.alz.org/research/diagnostic_criteria/; accessed August 9, 2011.

daily activities. In addition, these deficits must represent a decline from a previous level of functioning, and they must not be due to delirium or a major psychiatric disorder.

To make a diagnosis of *probable dementia of AD*, symptoms must meet the criteria for all-cause dementia, and they must have a clear history of gradual decline (over months to years), and must not be explainable by a systemic illness, stroke, neurologic illness, or use of drugs that can significantly impair cognition. Note that, by these criteria, diagnosis of *probable AD dementia* is based entirely on the clinical evaluation, not on measurement of biomarkers. However, although information on biomarkers is not *required* for a diagnosis, this information *can* be used to increase the certainty the underlying cause of dementia is the AD pathophysiologic process.

Mild Cognitive Impairment Due to AD. This phase of AD precedes the development of dementia. As with diagnosis of AD dementia, diagnosis of MCI due to AD is based entirely on the clinical evaluation. Biomarkers are not required. Diagnostic criteria for MCI of AD are much like those for dementia of AD. In fact, the only difference is that cognitive and behavioral deficits must be sufficiently mild such that they don't interfere significantly with performance at work or in usual daily activities. As with diagnosis of AD dementia, biomarkers can be used to help identify the pathophysiologic process underlying the clinical deficit. In addition,

biomarkers can help predict whether progression to AD dementia is likely to occur soon.

DRUGS FOR COGNITIVE IMPAIRMENT

Ideally, the goal of treatment is to improve symptoms and reverse cognitive decline. Unfortunately, available drugs can't do this. At best, drugs may retard loss of memory and cognition, and prolong independent function. However, for many patients, even these modest goals are elusive.

Five drugs are approved for treating Alzheimer's dementia, and none of them is very effective. Four of the drugs—donepezil, galantamine, rivastigmine, and tacrine—are cholinesterase inhibitors. The fifth drug—memantine—blocks neuronal receptors for *N*-methyl-D-aspartate (NMDA). In 2008, the American College of Physicians and the American Academy of Family Physicians reviewed published research on these drugs and released their findings in a clinical guideline: *Effectiveness of Cholinesterase Inhibitors and Memantine for Treating Dementia*. Their major conclusion? Treatment of dementia with these drugs can yield improvement that is statistically significant but clinically marginal. As one expert put it, benefits of these drugs are equivalent to losing half a pound after taking a weight loss drug for 6 months: The loss may be statistically significant, but it lacks clinical sig-

TABLE 22-3 • Drugs for Cognitive Impairment

Drug	Indication (AD Severity)	Dosing Schedule	Major Mode of Elimination	Comments
Cholinesterase Inhibitors*				
Donepezil [Aricept]	Mild to severe	Once daily at bedtime	Metabolized by hepatic cytochrome P450	
Rivastigmine [Exelon]	Mild to moderate	<i>Oral:</i> Twice daily, with AM and PM meal <i>Patch:</i> Once daily	Metabolized by cholinesterase	Causes "irreversible" inhibition of cholinesterase. The patch is well tolerated because peak blood levels are low. The patch may be good for patients with difficulty swallowing.
Galantamine [Razadyne, Reminyl ⁺]	Mild to moderate	<i>Immediate-release tablets and oral solution:</i> Twice daily, with AM and PM meal <i>Extended-release capsules:</i> Once daily	Metabolized by hepatic cytochrome P450 and excreted by the kidneys	Reduce dosage in patients with moderate hepatic or renal impairment, and discontinue in patients with severe hepatic or renal impairment.
NMDA Antagonist				
Memantine [Namenda, Ebixa ⁺]	Moderate to severe	See text	Excreted by the kidneys	Reduce dosage in patients with moderate renal impairment and discontinue in patients with severe renal impairment.

AD = Alzheimer's disease, NMDA = *N*-methyl-D-aspartate.

*Only three cholinesterase inhibitors are listed. A fourth agent—tacrine [Cognex]—is available, but used rarely owing to hepatotoxicity and inconvenient dosing.

nificance. Given the modest benefits of these drugs, the guidelines do not recommend that all patients receive one, leaving the decision to the patient, family, and prescriber. The guidelines also conclude there is no proof that any of the five drugs is more effective than the others, and hence selection among them should be based on tolerability, ease of use, and cost. As for how long treatment should last, the guidelines note a lack of information on optimal treatment duration, as well as information that might guide treatment cessation. Properties of the cholinesterase inhibitors and memantine are summarized in Table 22-3.

Cholinesterase Inhibitors

The cholinesterase inhibitors were the first drugs approved by the Food and Drug Administration (FDA) to treat AD. In clinical trials, these drugs produced modest improvements in cognition, behavior, and function, and slightly delayed disease progression. Four cholinesterase inhibitors are currently available. However, only three are recommended: donepezil, galantamine, and rivastigmine. The fourth—tacrine—carries a significant risk of liver damage, and should be avoided.

Group Properties

Mechanism of Action. Cholinesterase inhibitors prevent the breakdown of ACh by acetylcholinesterase (AChE), and thereby increase the availability of ACh at cholinergic synapses. In patients with AD, the result is enhanced transmission by central cholinergic neurons that have not yet been de-

stroyed. Cholinesterase inhibitors do not cure AD, and they do not stop disease progression—although they may slow progression by a few months.

Therapeutic Effect. All cholinesterase inhibitors are approved for patients with *mild to moderate* symptoms, and one agent—donepezil—is also approved for those with *severe* symptoms. Unfortunately, treatment only benefits 1 in 12 patients. Among those who do benefit, improvements are seen in quality of life and cognitive functions (eg, memory, thought, reasoning). However, these improvements are modest and short lasting. There is no convincing evidence of marked improvement or significant delay of disease progression. Nonetheless, although improvements are neither universal, dramatic, nor long lasting, and although side effects are common (see below), the benefits may still be worth the risks for some patients.

Adverse Effects. By elevating ACh in the periphery, all cholinesterase inhibitors can cause typical cholinergic side effects. Gastrointestinal effects—*nausea, vomiting, dyspepsia, diarrhea*—occur often. *Dizziness* and *headache* are also common. Elevation of ACh at synapses in the lungs can cause *bronchoconstriction*. Accordingly, cholinesterase inhibitors should be used with caution in patients with asthma or chronic obstructive pulmonary disease (COPD). One drug—tacrine—carries a high risk of *liver injury*, and hence is used rarely.

Cardiovascular effects, although uncommon, are a serious concern. Increased activation of cholinergic receptors in the heart can cause symptomatic bradycardia, leading to fainting,

falls, fall-related fractures, and pacemaker placement. If a patient is experiencing bradycardia, fainting, or falls, drug withdrawal may be indicated, especially if cognitive benefits are lacking.

Drug Interactions. Drugs that block cholinergic receptors (eg, first-generation antihistamines, tricyclic antidepressants, conventional antipsychotics) can reduce therapeutic effects, and should be avoided.

Dosage and Duration of Treatment. Dosage should be carefully titrated, and treatment should continue as long as clinically indicated. The highest doses produce the greatest benefits—but also the most intense side effects. Accordingly, dosage should be low initially and then gradually increased to the highest tolerable amount. Treatment can continue indefinitely, or until side effects become intolerable or benefits are lost.

Properties of Individual Cholinesterase Inhibitors

Of the four cholinesterase inhibitors with FDA approval, only three—donepezil, galantamine, and rivastigmine—are widely used. These three drugs have not been directly compared with one another for efficacy. However, they appear to offer equivalent benefits. Accordingly, selection among them is based on side effects, ease of dosing, and cost.

Tacrine. Tacrine [Cognex], introduced in 1993, was the first cholinesterase inhibitor approved for AD. The drug causes reversible inhibition of AChE. Benefits derive from increasing ACh concentrations at cholinergic synapses in the brain. Tacrine has two major drawbacks: (1) it can damage the liver and (2) dosing must be done 4 times a day. Because of these drawbacks, and because safer, more convenient drugs are available, tacrine is rarely used. For more information on tacrine, refer to earlier editions of this book.

Donepezil. Donepezil [Aricept, Aricept ODT], approved in 1996, is indicated for mild, moderate, or severe AD. The drug causes reversible inhibition of AChE—but is more selective for the form of AChE found in the brain than that found in the periphery. Like other cholinesterase inhibitors, donepezil does not affect the underlying disease process.

Donepezil is well absorbed following oral administration and undergoes metabolism by hepatic cytochrome P450 enzymes. Elimination is mainly in the urine and partly in the bile. Donepezil has a prolonged plasma half-life (about 60 hours), and hence can be administered just once a day.

Although donepezil is somewhat selective for brain cholinesterase, it can still cause peripheral cholinergic effects; nausea (11%) and diarrhea (10%) are most common. Like other drugs in this class, donepezil can cause bradycardia, fainting, falls, and fall-related fractures. Unlike tacrine, donepezil is not hepatotoxic.

Donepezil is available in two oral formulations: standard tablets (5, 10, and 23 mg) and orally disintegrating tablets (5 and 10 mg). With both formulations, dosing is done late in the evening, with or without food. To minimize side effects, dosage should be slowly titrated. The initial dosage is 5 mg once daily. After 4 to 6 weeks, dosage may be increased to 10 mg once daily. For patients with moderate or severe AD who have taken 10 mg daily for at least 3 months, dosage may be increased to 23 mg once daily. However, at this dosage, the likelihood of side effects is greatly increased.

Rivastigmine. Rivastigmine [Exelon], released in 2000, is approved for AD and for dementia of Parkinson's disease. Unlike donepezil, which causes reversible inhibition of AChE, rivastigmine causes irreversible inhibition. As with other cholinesterase inhibitors, benefits in AD are modest.

Rivastigmine is available in tablets and solution for oral dosing and a "patch" for transdermal dosing. Oral rivastigmine is well absorbed from the GI tract, especially in the presence of food. With the patch, blood levels are lower and more steady than with oral therapy. In contrast to other cholinesterase inhibitors, rivastigmine is converted to inactive metabolites by AChE, and not by cytochrome P450 enzymes in the liver. The half-life is short—about 1.5 hours.

Like other cholinesterase inhibitors, rivastigmine can cause peripheral cholinergic side effects. With oral dosing, the most common cholinergic effects are nausea (47%), vomiting (31%), diarrhea (19%), abdominal pain (13%), and anorexia (17%). Significant weight loss (7% of initial weight) occurs in 18% to 26% of patients. By enhancing cholinergic transmission,

rivastigmine can intensify symptoms in patients with peptic ulcer disease, bradycardia, sick sinus syndrome, urinary obstruction, and lung disease. Transdermal dosing is advised. Like other drugs in this class, rivastigmine can cause bradycardia, fainting, falls, and fall-related fractures. Blood levels are lower with transdermal dosing than with oral dosing, and hence the intensity of side effects is lower as well. In contrast to tacrine, rivastigmine is not hepatotoxic. Rivastigmine has no significant drug interactions, probably because it does not interact with hepatic drug-metabolizing enzymes.

Rivastigmine for oral dosing is available in tablets (1.5, 3, 4.5, and 6 mg) and solution (2 mg/mL). The initial dosage is 1.5 mg twice daily. The maximum dosage is 6 mg twice daily. All doses should be administered with food to enhance absorption and reduce GI effects.

Rivastigmine patches for transdermal dosing are available in two strengths, delivering 4.6 mg/24 hr and 9.5 mg/24 hr. A single patch is applied once daily to the chest, upper arm, upper back, or lower back. The site should be changed daily, and not repeated for at least 14 days. Before a new patch is applied, the old one must be removed. If not, toxicity can result. (About 50% of the starting dose remains in the patch after 24 hours.) Bathing should not affect treatment. Patients should begin treatment with the 4.6-mg patch and, after 4 weeks, change to the 9.5-mg patch for maintenance. For patients transitioning from oral therapy, the first patch should be applied on the day after the last oral dose. These patients should start with the 4.6-mg patch (if their oral dose was below 6 mg a day) or the 9.5-mg patch (if their oral dose was 6 to 12 mg/day).

Galantamine. Galantamine [Razadyne, Reminyl[®]], approved in 2001, is a reversible cholinesterase inhibitor indicated for mild to moderate AD. The drug is prepared by extraction from daffodil bulbs. In clinical trials, galantamine improved cognitive function, behavioral symptoms, quality of life, and ability to perform activities of daily living. However, as with other cholinesterase inhibitors, benefits were modest and short lasting.

Galantamine is rapidly and completely absorbed following oral administration. Protein binding in plasma is low. Elimination is by hepatic metabolism and renal excretion. Moderate to severe hepatic or renal impairment delays elimination and increases blood levels. In healthy adults, the half-life is about 7 hours.

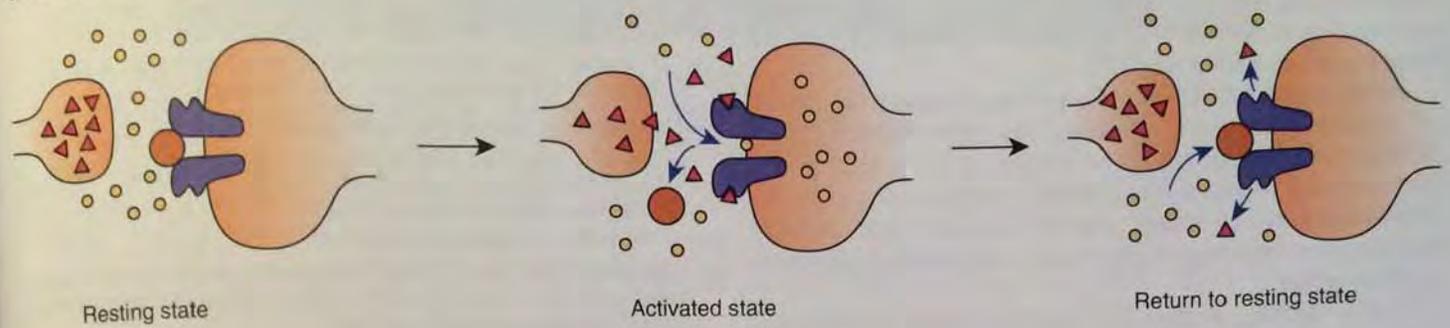
The most common adverse effects are nausea (13% to 17%), vomiting (6% to 10%), diarrhea (6% to 12%), anorexia (7% to 9%), and weight loss (5%). Nausea and other GI complaints are greater than with donepezil, but less than with oral rivastigmine. By increasing cholinergic stimulation in the heart, galantamine can cause bradycardia, fainting, falls, and fall-related fractures. Like other cholinesterase inhibitors, galantamine can cause bronchoconstriction, and hence must be used with caution in patients with asthma or COPD. Unlike tacrine, galantamine is not hepatotoxic. Drugs that block cholinergic receptors (eg, first-generation antihistamines, tricyclic antidepressants, conventional antipsychotics) can reduce therapeutic effects, and should be avoided.

Galantamine is available in immediate-release (IR) tablets (4, 8, and 12 mg), extended-release (ER) capsules (8, 16, and 24 mg), and solution (4 mg/mL). With all formulations, dosage should be gradually titrated to minimize GI complaints. For the solution and IR tablets, dosing is begun at 4 mg twice daily (taken with the morning and evening meals); after a minimum of 4 weeks, dosage may be increased to 8 mg twice daily; and 4 weeks later, dosage may be increased again to 12 mg twice daily. For the ER capsules, dosing is begun at 8 mg once daily; after a minimum of 4 weeks, dosage may be increased to 16 mg once daily; and 4 weeks later, dosage may be increased to 24 mg once daily. With all formulations, dosage must be adjusted in patients with hepatic or renal impairment as follows: For those with moderate hepatic or renal impairment, the maximum dosage is 16 mg/day; for those with severe hepatic or renal impairment, galantamine should be avoided.

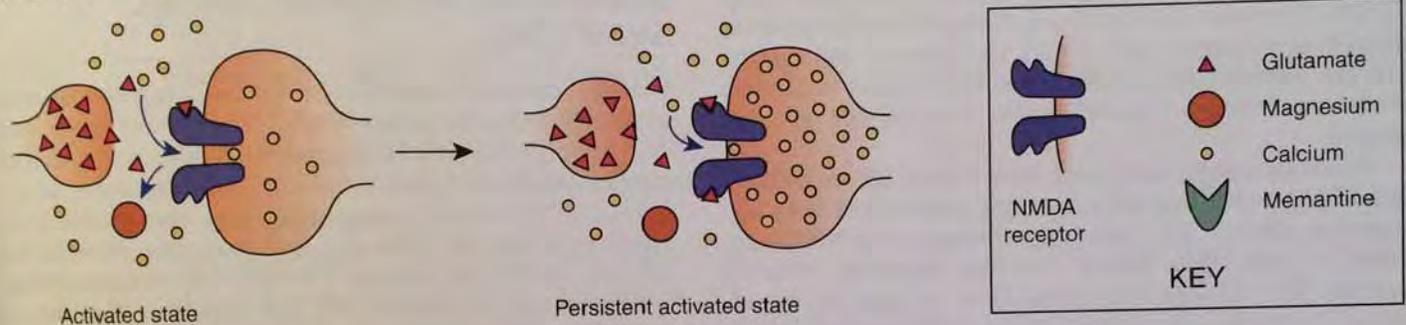
Memantine

Memantine [Namenda, Namenda XR, Ebixa[®]] is a first-in-class NMDA (*N*-methyl-D-aspartate) receptor antagonist. Unlike the cholinesterase inhibitors, which can be used for mild AD, memantine is indicated only for moderate or severe AD. We don't yet know if memantine is more effective than the cholinesterase inhibitors, but we do know it's better tolerated. Although memantine helps treat symptoms of AD, there is no evidence that it modifies the underlying disease process. Memantine was approved by the FDA in 2003, but has been used in Germany since 1982.

A Normal Physiology



B Pathophysiology



C Effect of Memantine

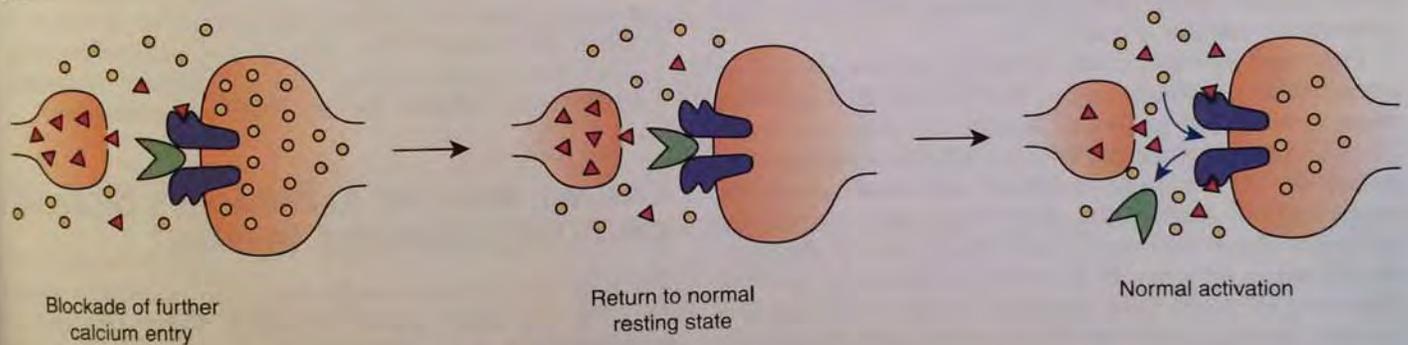


Figure 22-2 • Memantine mechanism of action.

A, Normal physiology. In the resting postsynaptic neuron, magnesium occupies the NMDA receptor channel, blocking calcium entry. Binding of glutamate to the receptor displaces magnesium, allowing calcium to enter. When glutamate dissociates from the receptor, magnesium returns to the channel and blocks further calcium inflow. The brief period of calcium entry constitutes a "signal" in the learning and memory process. **B, Pathophysiology.** Slow but steady leakage of glutamate from the presynaptic neuron keeps the NMDA receptor in a constantly activated state, thereby allowing excessive calcium influx, which can impair memory and learning, and can eventually cause neuronal death. **C, Effect of memantine.** Memantine blocks calcium entry when extracellular glutamate is low, and thereby stops further calcium entry, which allows intracellular calcium levels to normalize. When a burst of glutamate is released in response to an action potential, the resulting high level of glutamate is able to displace memantine, causing a brief period of calcium entry. Not shown: When glutamate diffuses away, memantine reblocks the channel, and thereby stops further calcium entry, despite continuing low levels of glutamate in the synapse.

Therapeutic Effects. In patients with moderate to severe AD, memantine appears to confer modest benefits. For many patients, the drug can slow the decline in function, and, in some cases, it may actually cause symptoms to improve. In one study, patients taking memantine for 28 weeks scored higher on tests of cognitive function and day-to-day function than did those

taking placebo, suggesting that memantine slowed functional decline. In another study, treatment with memantine plus donepezil (a cholinesterase inhibitor) was compared with donepezil alone. The result? After 24 weeks, those taking the combination showed less decline in cognitive and day-to-day function than those taking donepezil alone, suggesting that either (1) the two

agents confer independent benefits or (2) they act synergistically to enhance each other's effects. Of note, although memantine can benefit patients with moderate to severe AD, it does not benefit patients with mild AD.

Mechanism of Action. Memantine modulates the effects of glutamate (the major excitatory transmitter in the CNS) at NMDA receptors, which are believed to play a critical role in learning and memory. The NMDA receptor—a transmembrane protein with a central channel—regulates calcium entry into neurons. Binding of glutamate to the receptor promotes calcium influx.

Under healthy conditions, an action potential releases a burst of glutamate into the synaptic space. Glutamate then binds with the NMDA receptor, displaces magnesium from the receptor channel, and thereby permits calcium entry (Fig. 22-2A). Glutamate then quickly dissociates from the receptor, permitting magnesium to reblock the channel, and thereby prevents further calcium influx. The brief period of calcium entry constitutes a “signal” in the learning and memory process.

Under pathologic conditions, there is slow but steady leakage of glutamate from the presynaptic neuron, and from surrounding glia too. As a result, the channel in the NMDA receptor is kept open, thereby allowing excessive influx of calcium (Fig. 22-2B). High intracellular calcium has two effects: (1) impaired learning and memory (because the “noise” created by excessive calcium overpowers the “signal” created when calcium enters in response to glutamate released by a nerve impulse); and (2) neurodegeneration (because too much intracellular calcium is toxic).

How does memantine help? It blocks calcium influx when extracellular glutamate is low, but permits calcium influx when extracellular glutamate is high. As shown in Figure 22-2C, when the glutamate level is low, memantine is able to occupy the NMDA receptor channel, and thereby block the steady entry of calcium. As a result, the level of intracellular calcium is able to normalize. Then, when a burst of glutamate is released in response to an action potential, the resulting high level of extracellular glutamate is able to displace memantine, causing a brief period of calcium entry. Because intracellular calcium is now low, normal signaling can occur. When glutamate diffuses away from the receptor, memantine reblocks the channel, and thereby stops further calcium entry, despite continuing low levels of glutamate in the synapse.

Pharmacokinetics. Memantine is well absorbed following oral dosing, both in the presence and absence of food. Plasma levels peak in 3 to 7 hours. The drug undergoes little metabolism, and is excreted largely unchanged in the urine. The half-life is long—60 to 80 hours. Clearance is reduced in patients with renal impairment.

Adverse Effects. Memantine is well tolerated. The most common side effects are dizziness (7%), headache (6%), confusion (6%), and constipation (5%). In clinical trials, the incidence of these effects was about the same as in patients taking placebo.

Drug Interactions. In theory, combining memantine with another NMDA antagonist, such as amantadine [Symmetrel] or ketamine [Ketalar], could have an undesirable additive effect. Accordingly, such combinations should be used with caution.

Sodium bicarbonate and other drugs that alkalinize the urine can greatly decrease the renal excretion of memantine. Accumulation of the drug to toxic levels might result.

Dosage and Administration. Memantine is available in three oral formulations: immediate-release tablets (5 and 10 mg), sold as *Namenda*; extended-release capsules (7, 14, 21, and 28 mg), sold as *Namenda XR*; and a solution (2 mg/mL), sold as *Namenda*. With all three, dosing may be done with or without food. Dosage must be titrated as described below.

Immediate-release tablets and oral solution:

- 5 mg/day (5 mg once a day), for 1 week or more
- 10 mg/day (5 mg twice a day), for 1 week or more
- 15 mg/day (5 mg and 10 mg in separate doses), for 1 week or more
- 20 mg/day (10 mg twice a day), for maintenance

Extended-release capsules:

- 7 mg once daily for 1 week or more
- 14 mg once daily for 1 week or more
- 21 mg once daily for 1 week or more
- 21 mg once daily for maintenance

In patients with moderate renal impairment, a dosage reduction may be needed, regardless of the formulation used. In patients with severe renal impairment, memantine should be avoided.

DRUGS FOR NEUROPSYCHIATRIC SYMPTOMS

Neuropsychiatric symptoms (eg, agitation, aggression, delusions, hallucinations) occur in more than 80% of people with AD. Although multiple drug classes—antipsychotics, cholinesterase inhibitors, mood stabilizers, antidepressants, anxiolytics, NMDA receptor antagonists—have been tried as treatment, very few are effective, and even then benefits are limited. There is convincing evidence that neuropsychiatric symptoms can be reduced with two atypical antipsychotics: *risperidone* [Risperdal] and *olanzapine* [Zyprexa]. However, benefits are modest, and these drugs slightly increase mortality, mainly from cardiovascular events and infection. Cholinesterase inhibitors may offer modest help. There is little or no evidence for a benefit from conventional antipsychotics (eg, haloperidol, chlorpromazine), mood stabilizers (valproate, carbamazepine, lithium), antidepressants, or memantine.

CAN WE PREVENT ALZHEIMER'S DISEASE OR DELAY COGNITIVE DECLINE?

Probably not—at least with the interventions available today. In 2010, an expert panel released a report—*Preventing Alzheimer's Disease and Cognitive Decline*—which stated that we have no good evidence supporting the association of any modifiable factor—diet, exercise, social interaction, economic status, nutritional supplements, medications, environmental toxins—with reduced risk of AD. However, this discouraging conclusion does not mean that all available interventions have been proved not to work. Rather, it means that the evidence is too meager to prove that some interventions might work. For example, studies have shown that cognitive training and exercise may help protect against AD and cognitive decline, but the quality of these studies is poor. Similarly, low-quality studies have shown possible protection from adopting a Mediterranean diet and consuming alcohol in moderation. Conversely, there is fairly good evidence that two supplements—*Ginkgo biloba* and vitamin E—do not confer protection. Likewise, there is fairly good evidence that the cholinesterase inhibitors neither prevent development of AD nor prevent cognitive decline. For one possible intervention—use of estrogen/progestin therapy—there is fairly good evidence of increased risk. Table 22-4 summarizes the panel's conclusions regarding certain interventions, indicating the effect of the intervention and the quality of the research involved.

TABLE 22-4 ■ Interventions to Delay the Onset of Alzheimer's Disease or Slow Cognitive Decline

Intervention	Effect	Quality of Evidence
POTENTIAL INTERVENTIONS TO DELAY ONSET OF ALZHEIMER'S DISEASE		
Nutrition		
Mediterranean diet	Possible benefit	Low
Light to moderate alcohol intake	Possible benefit	Low
Folic acid	Possible benefit	Low
<i>Ginkgo biloba</i>	No benefit	High
Vitamin E	No benefit	Moderate
Homocysteine	No benefit	Low
Vitamin B ₁₂	No benefit	Low
Vitamin C	No benefit	Low
Omega-3 fatty acids	No benefit	Low
Beta-carotene	No benefit	Low
Medications		
Statins	Possible benefit	Low
Cholinesterase inhibitors	No benefit	Moderate
Antihypertensives	No benefit	Low
Celecoxib, rofecoxib, naproxen	Increased risk	Low
Estrogen alone	No benefit	Low
Estrogen plus progestin	Increased risk	Moderate
Social and Behavioral Factors		
Cognitive training	Small protective effect	Low
Physical activity	Small protective effect	Low
POTENTIAL INTERVENTIONS TO IMPROVE OR MAINTAIN COGNITIVE FUNCTION		
Nutrition		
Vitamin E	No effect or no consistent effect across trials	High
Vitamin B ₆	No effect or no consistent effect across trials	Moderate
Vitamin B ₁₂	No effect or no consistent effect across trials	Moderate
Folic acid	No effect or no consistent effect across trials	Moderate
Medications		
Cholinesterase inhibitors	No benefit	Moderate
Statins	No benefit	High
Estrogen	No benefit	High
Antihypertensives	No benefit	Low
NSAIDs	No benefit or increased risk	Low
Social and Behavioral Factors		
Cognitive training	Small protective effect	High
Physical activity	Small protective effect	Low
Noncognitive, nonphysical leisure activity	Small protective effect	Low

Modified from Williams JW, Plassman BL, Burke J, Holsinger T, Benjamin S. Preventing Alzheimer's Disease and Cognitive Decline: Evidence Report/Technology Assessment No. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHS 290-2007-10066-1.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality, April 2010.

KEY POINTS

- Alzheimer's disease (AD) is a relentless illness characterized by progressive memory loss, impaired thinking, neuropsychiatric symptoms, and inability to perform routine tasks of daily living.
- The histopathology of AD is characterized by neuritic plaques, neurofibrillary tangles, and degeneration of cholinergic neurons in the hippocampus and cerebral cortex.
- Neuritic plaques are spherical, extracellular bodies that consist of a beta-amyloid core surrounded by remnants of axons and dendrites.
- In patients with AD, beta-amyloid is present in high levels and may contribute to neuronal injury.
- Neurofibrillary tangles result from production of a faulty form of tau, a protein that in healthy neurons serves to maintain the orderly arrangement of neurotubules.
- The major known risk factor for AD is advancing age.
- New tests for AD biomarkers can indicate the presence of beta-amyloid accumulation as well as neuronal degeneration and dysfunction.
- According to revised diagnostic criteria issued in 2011, AD has three phases: an asymptomatic preclinical phase, and two symptomatic clinical phases, called mild cognitive impairment due to AD and dementia due to AD.
- Preclinical AD is diagnosed entirely on the basis of biomarkers
- AD dementia and MCI are routinely diagnosed on the basis of clinical status, although biomarkers can be used to complement the evaluation.
- AD dementia can be treated with cholinesterase inhibitors or memantine. Although these drugs produced statistically significant symptomatic improvement in clinical trials, benefits in most patients are marginal.
- Cholinesterase inhibitors (eg, donepezil) increase the availability of acetylcholine at cholinergic synapses, and thereby enhance transmission by cholinergic neurons that have not yet been destroyed by AD.
- Cholinesterase inhibitors produce modest improvements in cognition, behavior, and function in 1 out of 12 AD patients.
- Cholinesterase inhibitors do not cure AD, and they do not stop disease progression.
- The efficacy of all cholinesterase inhibitors appears equal.
- By elevating ACh in the periphery, all cholinesterase inhibitors can cause typical cholinergic side effects. Gastrointestinal effects—nausea, vomiting, dyspepsia, diarrhea—are most common. Of greater concern, by increasing ACh in the heart, these drugs can cause bradycardia, leading to fainting, falls, fall-related fractures, and pacemaker placement.
- Drugs that block cholinergic receptors (eg, first-generation antihistamines, tricyclic antidepressants, conventional antipsychotics) can reduce responses to cholinesterase inhibitors.
- Memantine is the first representative of a new class of drugs for AD, the NMDA receptor antagonists. Benefits derive from modulating the effects of glutamate at NMDA receptors.
- Unlike cholinesterase inhibitors, all of which can be used for mild AD, memantine is approved only for moderate to severe AD.
- Like the cholinesterase inhibitors, memantine has only modest beneficial effects.
- Memantine appears devoid of significant adverse effects.
- There is no solid evidence that drugs, nutrients, supplements, exercise, cognitive training, or any other intervention can prevent AD or delay cognitive decline.

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Drugs for Multiple Sclerosis

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Drugs Used to Manage MS Symptoms

Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune disorder that damages the myelin sheath of neurons in the central nervous system (CNS), causing a wide variety of sensory, motor, and cognitive deficits. Initially, most patients experience periods of acute clinical exacerbations (relapses) alternating with periods of complete or partial recovery (remissions). Over time, symptoms usually grow progressively worse—although the course of the disease is unpredictable and highly variable. Among young adults, MS causes more disability than any other neurologic disease. Nonetheless, most patients manage to lead fairly normal lives, and life expectancy is only slightly reduced. Multiple sclerosis affects about 400,000 people in the United States and 2.5 million worldwide.

Drug therapy of MS changed dramatically in 1993, the year the first disease-modifying agent was approved. Prior to this time, treatment was purely symptomatic. We had no drugs that could alter the disease process. By using disease-modifying drugs, we can now slow the progression of MS, decrease the frequency and intensity of relapses, and delay permanent neurologic loss. As a result, we can significantly improve prognosis, especially if treatment is started early.

OVERVIEW OF MS AND ITS TREATMENT

Pathophysiology

What's the Primary Pathology of MS? The pathologic hallmark of MS is the presence of multifocal regions of inflammation and myelin destruction in the CNS (brain, spinal cord, and optic nerve). Because of demyelination, axonal conduction is slowed or blocked, giving rise to a host of neuro-

logic signs and symptoms. As inflammation subsides, damaged tissue is replaced by astrocyte-derived filaments, forming scars known as *scleroses*, hence the disease name. It is important to note that, in addition to stripping off myelin, inflammation may injure the underlying axon, and may also damage oligodendrocytes, the cells that produce CNS myelin. Axon injury can also occur in the *absence* of inflammation, and can be seen early in the course of the disease.

How Does Inflammation Occur? The mechanism appears to be autoimmune: Cells of the immune system mistakenly identify components of myelin as being foreign, and hence mount an attack against them. For the attack to occur, circulating lymphocytes (T cells) and monocytes (macrophages) must adhere to the endothelium of CNS blood vessels, migrate across the vessel wall, and then initiate the inflammatory process. The end result is an inflammatory cascade that destroys myelin and may also injure the axonal membrane and nearby oligodendrocytes.

What Initiates the Autoimmune Process? No one knows. The most likely candidates are genetics, environmental factors, and microbial pathogens. We suspect a *genetic link* for two reasons. First, the risk of MS for first-degree relatives of someone with the disease is 10 to 20 times higher than the risk for people in the general population. Second, the risk of MS differs for members of different races. For example, the incidence is highest among Caucasians (especially those of northern European descent), much lower among Asians, and nearly zero among Inuits (the indigenous people of the Arctic). We suspect *environmental factors* because the risk is not the same in all places: In the United States, MS is more common in northern states than in southern states; around the globe, MS is most common in countries that have a moderately cool climate, whether in the northern or southern hemisphere; and, as we move from the equator toward the poles, the incidence of MS increases. *Microbial pathogens* suspected of initiating autoimmunity include Epstein-Barr virus, human herpesvirus 6, and *Chlamydia pneumoniae*. The bottom line? *Multiple sclerosis appears to be a disease that develops in genetically vulnerable people following exposure to an environmental or microbial factor that initiates autoimmune activity.*

What Happens When an Acute Attack Is Over? When inflammation subsides, some degree of recovery occurs, at least in the early stages of the disease. Three mechanisms are involved: (1) partial remyelination, (2) functional axonal compensation (axons redistribute their sodium channels from the nodes of Ranvier to the entire region of demyelination), and (3) development of alternative neuronal circuits that bypass the damaged region. Unfortunately, with recurrent episodes of demyelination, recovery becomes less and less complete. Possible reasons include mounting astrocytic scarring, irreversible axonal injury, and the death of neurons and oligodendrocytes.

Does MS Injure the Myelin Sheath of Peripheral Neurons? No. Myelin in the periphery is made by Schwann cells, whereas myelin in the CNS is made by oligodendrocytes. Although myelin produced by these two cell types is very similar, it is not identical. Because peripheral myelin differs somewhat from CNS myelin, the immune system does not identify peripheral myelin as foreign, and hence this myelin is spared.

Signs and Symptoms

People with MS can experience a wide variety of signs and symptoms. Depending on where CNS demyelination occurs, a patient may experience paresthesias (numbness, tingling, pins and needles), muscle or motor problems (weakness, clumsiness, ataxia, spasms, spasticity, tremors, cramps), visual impairment (blurred vision, double vision, blindness), bladder and bowel symptoms (incontinence, urinary urgency, urinary hesitancy, constipation), sexual dysfunction, disabling fatigue, emotional lability, depression, cognitive impairment, slurred speech, dysphagia, dizziness, vertigo, neuropathic pain, and more. The intensity of these symptoms is determined by the size of the region of demyelination. To quantify the impact of MS symptoms, most clinicians employ the Kurtzke Expanded Disability Status Scale (EDSS), an instrument that measures the impact of MS on nine different functional systems (eg, visual, sensory, cerebellar). The results are tabulated and reported on a scale from 0 to 10, with 0 representing no disability and 10 representing death. An EDSS of 4 or greater indicates difficulties with ambulation. Symptoms of MS are discussed further under *Drugs Used to Manage MS Symptoms*.

MS Subtypes

There are four subtypes of MS—relapsing-remitting, secondary progressive, primary progressive, and progressive-relapsing—defined by the clinical course the disease follows. Symptom patterns that characterize the MS subtypes are depicted in Figure 23-1.

Relapsing-Remitting MS. This subtype is characterized by recurrent, clearly defined episodes of neurologic dysfunction (relapses) separated by periods of partial or full recovery (remissions). Between 85% and 90% of patients have this form initially. Symptoms develop over several days, and then typically resolve within weeks. The average patient has two relapses every 3 years. Specific signs and symptoms during an attack depend on the size and location of CNS lesions, and hence vary from one attack to the next, and from one patient to another. The disease usually begins in the second or third decade of life, and affects twice as many women as men.

Secondary Progressive MS. This subtype occurs when a patient with relapsing-remitting MS develops steadily worsening dysfunction—with or without occasional plateaus, acute exacerbations, or minor remissions. Within 10 to 20 years of symptom onset, about 50% of patients with relapsing-remitting MS develop secondary progressive MS.

Primary Progressive MS. In this subtype, symptoms grow progressively more intense from the outset, although some patients may experience occasional plateaus or even temporary improvement. Clear remissions, however, do not occur. Only 10% of patients have this form of MS.

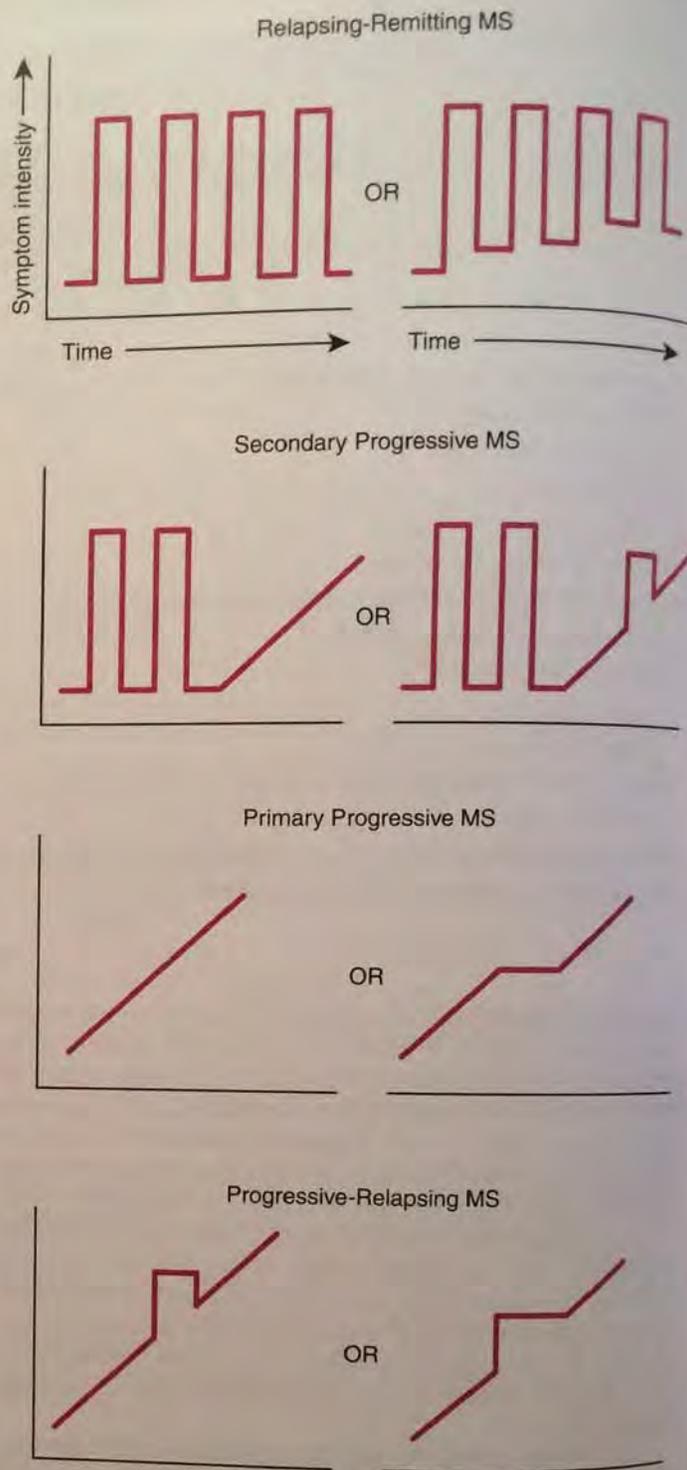


Figure 23-1 ■ Symptom patterns that define the four subtypes of MS.

Progressive-Relapsing MS. This subtype, which is rare, looks like primary progressive MS, but with acute exacerbations superimposed on the steady intensification of symptoms.

Diagnosis

Diagnosis of MS is based on clinical presentation supplemented with laboratory data. As a rule, we cannot diagnose MS on the basis of symptoms or signs or laboratory tests alone. Rather, for most patients, all three kinds of information are needed. In addition, because the signs, symptoms, and test results that suggest MS can also suggest other disorders, a

positive diagnosis cannot be made until all other possibilities have been ruled out. Diagnosis of MS is confounded by interpatient variability in symptoms and the course the disease follows.

In 1965, the following diagnostic criteria were introduced:

- There must be objective evidence of *two or more* clinical attacks lasting at least 24 hours each.
- The attacks must be *separated in time* by at least 1 month.
- The attacks must be *separated in space* (that is, the CNS damage underlying clinical symptoms must occur at different sites).
- There must be no better explanation for the attacks.

Since these criteria were introduced, additional diagnostic tools have become available. Important among these are magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) tests, and measurement of the visual evoked potential (VEP). All three tests can help *confirm* a suspected diagnosis of MS, but they cannot, by themselves, provide definitive proof of the disease. Properties of these tests are as follows:

- MRI is the most sensitive way to image the brain. Sensitivity can be made even greater with *gadolinium*, an IV contrast agent. MRI is especially good for detecting areas of demyelination. However, it is important to note that, in some patients who have clinically definite MS, an MRI scan may fail to detect any lesions. Hence, a negative scan does not necessarily rule out MS. Conversely, because other disorders can produce a positive scan, a positive

scan, by itself, does not prove the presence of MS, although it *can* help *confirm* a suspected case.

- Tests of CSF are used to assess immune activity within the CNS. Two tests are employed: measurement of immunoglobulin G (IgG) levels and measurement of oligoclonal IgG bands (OCBs), which indicate intrathecal production of antibodies. More than 90% of patients with MS have OCBs. However, as with MRI scans, other disorders can also produce positive test results—and negative results may be seen in some patients who *do* have MS. Accordingly, CSF analysis, by itself, can neither confirm nor rule out MS.
- The VEP test measures how quickly the brain responds to a visual stimulus, and hence indirectly measures conduction velocity in the optic nerve. In patients with MS, the VEP is delayed, indicating conduction velocity is slowed (owing to demyelination of the optic nerve). However, as with MRI scans and CSF tests, the VEP test is not specific for MS: Other disorders can produce positive results, and some patients with MS may get negative results.

Diagnostic criteria for MS were revised by the McDonald committee in 2001, revised again in 2005, and revised yet again in 2010 (Table 23–1). The latest criteria are still founded on the patient's clinical presentation, but also incorporate information from MRI scans and CSF tests. These criteria were adopted to permit the earliest possible diagnosis of MS, and hence permit the earliest possible implementation of disease-modifying therapy.

TABLE 23–1 • 2010 Revised McDonald Criteria for Diagnosis of MS

Number of Attacks	Clinical Evidence of Lesions	Additional Data Needed for a Diagnosis of MS
2 or more	Objective clinical evidence of 2 or more lesions <i>or</i> objective clinical evidence of 1 lesion with reasonable historic evidence of a prior attack	None: Clinical evidence alone will suffice.
2 or more	Objective clinical evidence of 1 lesion	Proof of <u>dissemination in space</u> shown by <i>either</i> MRI (ie, at least 2 lesions visible on the MRI in CNS regions typically affected by MS) <i>or</i> await another clinical attack implicating a different CNS site.
1	Objective clinical evidence of 2 or more lesions	Proof of <u>dissemination in time</u> shown by <i>either</i> MRI (eg, a new lesion is visible on a follow-up MRI) <i>or</i> await a second clinical attack
1	Objective clinical evidence of 1 lesion (clinically isolated syndrome)	Proof of <u>dissemination in space</u> shown by <i>either</i> MRI <i>or</i> await a second clinical attack implicating a different site <i>plus</i> Proof of <u>dissemination in time</u> shown by <i>either</i> MRI <i>or</i> await a second clinical attack
0 (Insidious neurologic progression suggestive of MS but with no clear clinical attack)		One year of disease progression (retrospectively or prospectively determined) <i>plus</i> Two out of three of the following: <ul style="list-style-type: none"> • Proof of <u>dissemination in space</u> in the <i>brain</i> as shown by MRI • Proof of <u>dissemination in space</u> in the <i>spinal cord</i> as shown by MRI • Positive CSF*

*CSF = cerebrospinal fluid. A positive CSF test shows either oligoclonal bands different from those in serum or a raised IgG index.

Adapted from Polman CH, Reingold SC, Banwell B, et al: Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald Criteria. *Ann Neurol* 69:292–302, 2011

Drug Therapy Overview

In patients with MS, drugs are employed to (1) modify the disease process, (2) treat an acute relapse, and (3) manage symptoms. We have no drugs that can cure MS.

Disease-Modifying Therapy

Disease-modifying drugs can decrease the frequency and severity of relapses, reduce development of brain lesions, decrease future disability, and help maintain quality of life. In addition, they may prevent permanent damage to axons. However, it is important to note that, although these drugs can slow disease progression, they do not cure MS. Also, they do not work for all patients. Those with relapsing-remitting MS benefit most.

There are two main groups of disease-modifying drugs: *immunomodulators* and *immunosuppressants* (Table 23-2). The immunomodulators—interferon beta, glatiramer acetate, natalizumab, and fingolimod—are safer than mitoxantrone (the major immunosuppressant in use), and hence are generally preferred.

Relapsing-Remitting MS. All patients with relapsing-remitting MS—regardless of age, frequency of attacks, or level of disability—should receive one of the immunomodulators:

- Interferon beta-1a [Avonex], for IM use
- Interferon beta-1a [Rebif], for subQ use
- Interferon beta-1b [Betaseron, Extavia], for subQ use
- Glatiramer acetate [Copaxone], for subQ use
- Natalizumab [Tysabri], for IV use
- Fingolimod [Gilenya], for PO use

Treatment should begin *as soon as possible* after relapsing-remitting MS has been diagnosed. Why? Because early treatment can help prevent axonal injury, and may thereby prevent permanent neurologic deficits.

Treatment should continue indefinitely. The principal reasons for stopping would be toxicity or a clear lack of effect. Unfortunately, if disease-modifying therapy is stopped, disease progression may return to the pretreatment rate.

If treatment with an immunomodulator fails to prevent severe relapses or disease progression, treatment with mitoxantrone (an immunosuppressant) should be considered. However, keep in mind that mitoxantrone can cause serious toxicity (eg, myelosuppression, heart damage), and hence should be reserved for patients who truly need it.

Secondary Progressive MS. Interferon beta can benefit certain patients with secondary progressive MS, specifically, those who still experience acute relapses. For these people, interferon beta can reduce the severity and frequency of attacks, and can reduce development of MRI-detectable brain lesions. Whether other disease-modifying drugs can help is unclear.

Mitoxantrone can decrease clinical attack rate, reduce development of new brain lesions, and slow progression of disability. However, although the drug is effective, cardiotoxicity precludes long-term use.

Progressive-Relapsing MS. Mitoxantrone is the only disease-modifying drug approved for this disorder. Unfortunately, benefits are generally modest.

Primary Progressive MS. No disease-modifying therapy has been shown effective against this form of MS. However, ongoing studies with immunosuppressants (eg, methotrexate, azathioprine, cyclophosphamide) are encouraging.

TABLE 23-2 ■ Disease-Modifying Drugs for MS

Generic Name	Trade Name	Route	Dose	Dosing Schedule	Annual Cost	Adverse Effects
IMMUNOMODULATORS						
Interferon Beta Preparations						
Interferon beta-1a	Avonex	IM	30 mcg	Once a week	\$35,600	<i>All three preparations:</i> • Flu-like symptoms • Liver injury • Myelosuppression • Injection-site reactions
Interferon beta-1a	Rebif	subQ	44 mcg	3 times a week	\$35,700	
Interferon beta-1b	Betaseron, Extavia	subQ	250 mcg	Every other day	\$35,400	
Other Immunomodulators						
Glatiramer acetate	Copaxone	subQ	20 mg	Once a day	\$43,000	• Injection-site reactions • Postinjection reaction • Progressive multifocal leukoencephalopathy • Liver injury • Allergic reactions • Bradycardia • Infections • Liver injury • Macular edema • Fetal harm
Natalizumab	Tysabri	IV	300 mg	Every 4 weeks	\$40,400	
Fingolimod	Gilenya	PO	0.5 mg	Once a day	\$48,000	
IMMUNOSUPPRESSANT						
Mitoxantrone	Novantrone	IV	12 mg/m ² *	Every 3 months	\$6,300	• Myelosuppression • Cardiotoxicity • Fetal harm

*Maximum lifetime dose is 140 mg/m² (because of cardiotoxicity).

Treating an Acute Episode (Relapse)

A short course of a *high-dose IV glucocorticoid* (eg, 500 mg to 1 gm of methylprednisolone daily for 3 to 5 days) is the preferred treatment of an acute relapse. Glucocorticoids suppress inflammation and can thereby reduce the severity and duration of a clinical attack. As discussed in Chapter 72, these drugs are very safe when used short term, elevation of blood glucose being the principal concern. By contrast, long-term exposure can cause osteoporosis and other serious adverse effects. Accordingly, frequent use (more than 3 times a year) or prolonged use (longer than 3 weeks at a time) should be avoided.

Acute relapse may also be treated with *IV gamma globulin*. This option can be especially helpful in patients intolerant of or unresponsive to glucocorticoids. Results have been good.

Drug Therapy of Symptoms

All four subtypes of MS share the same symptoms (eg, fatigue, spasticity, pain, bladder dysfunction, bowel dysfunction, sexual dysfunction). Accordingly, the drugs used for treatment are the same for all patients, regardless of MS subtype. Specific treatments are discussed below under *Drugs Used to Manage MS Symptoms*.

DISEASE-MODIFYING DRUGS I: IMMUNOMODULATORS

Seven immunomodulators are available: glatiramer acetate [Copaxone], natalizumab [Tysabri], fingolimod [Gilenya] and four preparations of interferon beta [Avonex, Rebif, Betaseron, Extavia]. With the exception of natalizumab, all of these drugs are recommended as first-line therapy for patients with relapsing-remitting MS and for patients with secondary progressive MS who still experience acute exacerbations. Natalizumab is reserved for patients with relapsing-remitting MS who have not responded to at least one of the other four drugs. Why? Because, very rarely, natalizumab has been associated with a potentially fatal infection of the brain.

All of the *first-line* immunomodulators—glatiramer, fingolimod, and the interferon beta preparations—have nearly equal efficacy, decreasing the relapse rate by about 30%. Because benefits are very similar, selection among these drugs is based primarily on patient and prescriber preference. If a particular drug is intolerable or ineffective, a different one should be tried. Natalizumab is more effective than the first-line drugs, decreasing the relapse rate by 68%, but is also more dangerous. As noted, although the immunomodulators can modify the course of MS, they do not cure the disease.

With the exception of fingolimod, all of the first-line immunomodulators are administered by self-injection (IM or SQ). Fingolimod is administered PO. Natalizumab, a second-line drug, is administered by IV infusion (at an approved infusion center). All seven drugs are expensive: One year of treatment costs between \$35,000 and \$48,000. Properties of these drugs are summarized in Table 23-2.

Interferon Beta Preparations

Description and Mechanism

Interferon beta is a naturally occurring glycoprotein with antiviral, antiproliferative, and immunomodulatory actions. Natural interferon beta is produced in response to viral invasion

and other biologic inducers. In patients with MS, it is believed to help in two ways. First, it inhibits the migration of proinflammatory leukocytes across the blood-brain barrier, thereby preventing these cells from reaching neurons of the CNS. Second, it suppresses T helper cell activity.

Two forms of interferon beta are used clinically: *interferon beta-1a* [Avonex, Rebif] and *interferon beta-1b* [Betaseron, Extavia]. Both forms are manufactured using recombinant DNA technology. Interferon beta-1a contains 166 amino acids plus glycoproteins, and is identical to natural human interferon beta with respect to amino acid content. Interferon beta-1b contains only 165 amino acids and has no glycoproteins, and hence differs somewhat from the natural compound. The two preparations of interferon beta-1a—Avonex and Rebif—differ slightly in their glycoprotein content, and are administered by different routes (see below). The two preparations of interferon beta-1b—Betaseron and Extavia—are identical. In fact, they are both manufactured in the same plant.

Therapeutic Use

All four interferon beta products are approved for relapsing forms of MS. These drugs can decrease the frequency and severity of attacks, reduce the number and size of MRI-detectable lesions, and delay the progression of disability. Benefits with Rebif, Betaseron, and Extavia may be somewhat greater than with Avonex, perhaps because Avonex is given less frequently and in lower dosage (see below).

In addition to its use in relapsing MS, interferon beta-1b [Betaseron] is approved for patients with secondary progressive MS.

Adverse Effects and Drug Interactions

Interferon beta is generally well tolerated, although side effects are common.

Flu-like Reactions. Flu-like reactions occur often. Symptoms include headache, fever, chills, malaise, muscle aches, and stiffness. Fortunately, these diminish over time, despite continued interferon beta use. Symptoms can be minimized by (1) starting with a low dose and then slowly titrating up to the full dose, and (2) giving an analgesic-antipyretic medication (ie, acetaminophen; ibuprofen or another nonsteroidal anti-inflammatory drug).

Hepatotoxicity. Interferon beta can injure the liver, typically causing an asymptomatic increase in circulating liver enzymes. Very rarely, patients develop hepatitis or even liver failure. To monitor for hepatotoxicity, liver function tests (LFTs) should be performed at baseline, 1 month later, then every 3 months for 1 year, and every 6 months thereafter. If LFTs indicate significant liver injury, a temporary reduction in dosage or interruption of treatment is indicated. When liver function returns to normal, treatment can resume, but careful monitoring is required. Interferon beta should be used with caution in patients who abuse alcohol, use hepatotoxic medications, or have active liver disease or a history of liver disease.

Myelosuppression. Interferon beta can suppress bone marrow function, thereby decreasing production of all blood cell types. To monitor for myelosuppression, complete blood counts should be obtained at baseline, every 3 months for 1 year, and every 6 months thereafter.

Injection-Site Reactions. Subcutaneous injection (of Rebif or Betaseron) can cause pain, erythema (redness), bumps,

and itching. Physical measures to reduce discomfort include rotating the injection site, applying ice (briefly) before and after the injection, and applying a warm, moist compress after the injection. Oral diphenhydramine [Benadryl] or topical hydrocortisone can reduce persistent itching and erythema. However, continuous use of topical hydrocortisone should be avoided, owing to a risk of skin damage. Very rarely, subQ injections (of Betaseron, Extavia, or Rebif) have caused local necrosis. Intramuscular injection (of Avonex) can cause discomfort and bruising.

Depression. It is unclear whether interferon beta promotes depression. Early studies showed an increased risk of depression, suicidal ideation, and suicide attempts. However, later studies have not confirmed these observations.

Neutralizing Antibodies. Like all other foreign proteins, interferon beta is immunogenic, and hence can stimulate production of antibodies against itself. If present in sufficiently high titers, these neutralizing antibodies can decrease clinical benefits.

Drug Interactions. Exercise caution when combining interferon beta with other drugs that can suppress the bone marrow or cause liver injury.

Preparations, Dosage, and Administration

Avonex (Interferon Beta-1a for IM Use). Avonex is available in pre-filled, single-use syringes (30 mcg/0.5 mL) and as a powder (30 mcg/0.5 mL when reconstituted with sterile water). The dosage is 30 mcg IM once a week. Store pre-filled syringes at 36°F to 46°F (2°C to 8°C). Store the powder at 36°F to 46°F (2°C to 8°C) or, if refrigeration is unavailable, store at or below 77°F (25°C) for up to 30 days. Injections are made late in the day so that flu-like symptoms occur during sleep.

Rebif (Interferon Beta-1a for SubQ Use). Rebif is available in pre-filled, single-use syringes containing either 8.8 mcg/0.2 mL, 22 mcg/0.5 mL, or 44 mcg/0.5 mL. Injections are made subQ 3 times a week, preferably in late afternoon or evening, at least 48 hours apart, and on the same days each week (eg, Monday, Wednesday, Friday). Dosage is titrated as follows: 8.8 mcg/dose for weeks 1 and 2; 22 mcg/dose for weeks 3 and 4; and 44 mcg/dose thereafter. Store Rebif refrigerated at 36°F to 46°F (2°C to 8°C) or, if refrigeration is unavailable, at or below 77°F (25°C) for up to 30 days.

Betaseron and Extavia (Interferon Beta-1b for SubQ Use). Betaseron and Extavia are supplied as a powder (300 mcg) in single-use vials. Just prior to use, the drug is reconstituted to form a 250-mcg/mL solution. Doses are given subQ every other day. Dosage is titrated as follows: 62.5 mcg/dose for weeks 1 and 2; 125 mcg/dose for weeks 3 and 4; 287.5 mcg/dose for weeks 4 and 5; and 250 mcg/dose thereafter. Store the powder at room temperature. Following reconstitution, the drug solution may be stored up to 3 hours refrigerated.

Glatiramer Acetate

Therapeutic Use. Glatiramer acetate [Copaxone], also known as *copolymer-1*, is used for long-term therapy of relapsing-remitting MS. Like interferon beta, glatiramer can reduce the frequency and severity of relapses, decrease MRI-detectable lesions, and delay the progression of disability. Glatiramer requires more frequent injections than interferon beta, and is less well tolerated.

Description and Mechanism. Glatiramer is a polypeptide composed of a random sequence of four amino acids: L-alanine, L-glutamate, L-lysine, and L-tyrosine. The drug is similar in structure to myelin basic protein, a component of the axonal myelin sheath. In patients with MS, the drug promotes a "T-cell shift." That is, it decreases production of pro-inflammatory TH1 cells and increases production of anti-inflammatory TH2 cells. The anti-inflammatory cells migrate

across the blood-brain barrier at sites of inflammation, and then suppress the inflammatory attack on myelin.

Adverse Effects and Drug Interactions. Glatiramer is generally well tolerated. Injection-site reactions—pain, erythema, pruritus (itching), induration (pitting)—are most common. Unlike interferon beta, glatiramer does not cause flu-like symptoms, myelosuppression, or liver toxicity. About 10% of patients experience a self-limited *postinjection reaction*—characterized by flushing, palpitations, severe chest pain, anxiety, laryngeal constriction, and urticaria—that typically lasts 15 to 20 minutes. No specific treatment is indicated. Safety in pregnancy and breast-feeding have not been established. No significant interactions with other MS drugs have been observed.

Preparations, Dosage, and Administration. Glatiramer acetate [Copaxone] is available in single-use, pre-filled syringes that contain 20 mg/mL glatiramer plus 40 mg of mannitol. The recommended dosage is 20 mg (1 mL) once a day, injected subQ into the arm, abdomen, hip, or thigh. Store under refrigeration at 36°F to 46°F (2°C to 8°C).

Natalizumab

Natalizumab [Tysabri], a recombinant monoclonal antibody, was introduced in 2004 and then withdrawn a few months later, in response to three reports of progressive multifocal leukoencephalopathy (PML), a severe infection of the brain. The drug was re-introduced in 2006, but with protective restrictions on who can prescribe, dispense, administer, and receive it.

Therapeutic Uses

Natalizumab is approved for two autoimmune diseases: multiple sclerosis and Crohn's disease (an inflammatory disorder of the bowel). Owing to the risk of PML, natalizumab is a second-line choice for both conditions.

Multiple Sclerosis. Natalizumab is approved only for *monotherapy of relapsing forms of MS*. In the AFFIRM trial, which compared natalizumab with placebo, natalizumab reduced the annualized rate of relapse by 68%, and reduced the number of new or enlarging brain lesions by 83%. These benefits are superior to those seen with interferon beta or glatiramer. However, owing to the risk of PML, natalizumab should be reserved for patients who have not responded to at least one of the first-line agents, and should not be combined with other disease-modifying drugs.

Crohn's Disease. Natalizumab is approved for induction and maintenance therapy of moderate to severe Crohn's disease in patients who have been unresponsive to or intolerant of other therapies, including inhibitors of tumor necrosis factor (TNF)-alpha. In clinical trials, benefits of the drug were modest. Natalizumab must not be combined with TNF-alpha inhibitors or with immunosuppressants (eg, cyclophosphamide, azathioprine, methotrexate). Crohn's disease and its treatment are discussed at length in Chapter 80.

Mechanism of Action

In patients with MS and Crohn's disease, natalizumab prevents circulating leukocytes (T cells and monocytes) from leaving the vasculature, and thereby prevents these cells from migrating to sites where they can do harm. In order to exit the vasculature, activated leukocytes must first adhere to the vascular endothelium, a process that requires the interaction of two types of molecules: (1) *integrins* (adhesion molecules)

expressed on the surface of leukocytes and (2) *integrin receptors* expressed on cells of the vascular epithelium. Natalizumab binds with integrin molecules on leukocytes, and thereby renders these cells unable to bind with integrin receptors on the capillary wall. As a result, the leukocytes cannot cross the capillary wall, and hence are unable to exit the vasculature to reach their sites of inflammatory action. In patients with MS, natalizumab prevents activated leukocytes from crossing the blood-brain barrier. In patients with Crohn's disease, the drug prevents leukocytes from crossing capillaries that deliver blood to cells of the GI tract.

Adverse Effects

Natalizumab is generally well tolerated. The most common reactions are headache and fatigue. Other common reactions include abdominal discomfort, arthralgia, depression, diarrhea, gastroenteritis, urinary tract infections, and lower respiratory tract infections. The most serious effects are PML, liver injury, and hypersensitivity reactions.

Progressive Multifocal Leukoencephalopathy.

Shortly after natalizumab was released, there were reports of PML, a serious, often fatal infection of the CNS caused by reactivation of the JC virus, an opportunistic pathogen resistant to all available drugs. Of the patients who survive PML, 80% to 90% are left highly disabled. As of May 2011, there had been 124 reported cases of PML among 83,300 natalizumab recipients worldwide, making the incidence 1.4 cases per 1000 patients. Risk for PML increases over time: The longer natalizumab is used, the higher the risk. Why does natalizumab promote PML? Because it suppresses immune function. Risk is increased by other immunosuppressant drugs, and by HIV/AIDS and other conditions that compromise cell-mediated immunity.

To reduce the risk of PML, natalizumab is available only through the *TOUCH Prescribing Program*. Patients, prescribers, infusion nurses, infusion centers, and pharmacies associated with infusion centers must all register with the program. In addition, prescribers and patients must understand the risks of natalizumab, including PML and other opportunistic infections—and patients must be screened for PML prior to each infusion. Also, patients should be informed about symptoms of PML—progressive weakness on one side of the body; clumsiness of the limbs; disturbed vision; changes in thinking, memory, or orientation—and instructed to report them immediately.

Hepatotoxicity. Like interferon beta, natalizumab can injure the liver. Patients should be informed about signs of liver injury—jaundice, nausea, vomiting, fatigue, anorexia, stomach pain, darkening of the urine—and instructed to report these immediately. If significant liver injury is diagnosed, natalizumab should be discontinued.

Hypersensitivity Reactions. Natalizumab can cause a variety of allergic reactions, manifesting as hives, itching, chest pain, dizziness, chills, rash, flushing, and hypotension. Severe reactions (eg, anaphylaxis) usually develop within 2 hours of infusion onset, but can also develop later. The risk of a severe reaction is increased by the presence of neutralizing antibodies. If a severe reaction develops, natalizumab should be discontinued and never used again.

Neutralizing Antibodies. Antibodies against natalizumab develop in about 6% of patients. These antibodies greatly decrease the efficacy of natalizumab and increase the risk of hypersensitivity and infusion reactions.

Drug Interactions

As noted, *immunosuppressants* (eg, mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate) increase the risk of PML and other opportunistic infections. Accordingly, these drugs should be discontinued at least 3 months before natalizumab is started.

Preparations, Dosage, and Administration

Natalizumab [Tysabri] is supplied in single-use vials (300 mg/15 mL) for dilution in 100 mL of 0.9% sodium chloride injection. Dosing is by IV infusion, done over a 1-hour span. The dosage for MS and Crohn's disease is 300 mg every 4 weeks. Patients should be observed during the infusion and for 1 hour after. If any signs of hypersensitivity develop, the infusion should be stopped immediately. Before natalizumab can be administered, everyone involved with the drug—patients, physicians, pharmacists, infusion nurses, and infusion centers—must be registered with the TOUCH Prescribing Program. Natalizumab vials should be stored cold (36°F to 46°F [2°C to 8°C]), but not frozen.

Fingolimod

Fingolimod [Gilenya] is a first-in-class *sphingosine 1-phosphate receptor modulator*, and the first *oral* disease-modifying agent for MS. The drug was approved in 2010 for reducing the frequency of MS exacerbations and delaying disability in patients with relapsing forms of the disease. In clinical trials, fingolimod was somewhat more effective than interferon beta. Unfortunately, although effective, fingolimod can cause significant adverse effects. Accordingly, it should be reserved for patients who cannot tolerate injections or have not responded well to other immunomodulators.

Pharmacokinetics

Fingolimod is administered PO and absorption is nearly complete (93%), both in the presence and absence of food. Plasma levels peak 12 to 16 hours after dosing. Protein binding in blood is high (99.7%). In the liver, some of the drug is converted to its active form—*fingolimod phosphate*—and some is converted to inactive metabolites, through the actions of several isozymes of cytochrome P450 (CYP). Most (81%) of the drug is eliminated in the urine in the form of inactive metabolites, and much less (2.5%) is eliminated in the feces as fingolimod itself or fingolimod phosphate. The drug has a long half-life (6 to 9 days), and hence it takes a long time (1 to 2 months) for plasma levels to reach plateau. Likewise, it takes a long time for blood levels to decline when treatment stops.

Mechanism of Action

Fingolimod, in the form of fingolimod phosphate, binds with high affinity to a class of molecules known as *sphingosine 1-phosphate (S1P) receptors*, which help regulate multiple processes. How does fingolimod help in MS? It binds with S1P receptors on lymphocytes, causing their sequestration in lymph nodes. As a result, there are fewer lymphocytes in peripheral blood, and hence fewer lymphocytes enter the brain. This reduction in lymphocytes reduces the inflammation that underlies neuronal injury.

Adverse Effects

Fingolimod can cause multiple adverse effects. The most common are headache (25%), diarrhea (12%), cough (10%), back pain (12%), influenza (13%), and elevation of liver enzymes (14%). The most serious are bradycardia, macular

edema, infection, fetal harm, and liver injury. Since S1P receptors help regulate multiple processes—including heart rate, vascular tone, airway resistance, neuronal excitability, neurogenesis, angiogenesis, and auditory and vestibular function—this variety of adverse effects should be no surprise.

Bradycardia. Fingolimod reduces heart rate. This effect is maximal within 6 hours after the first daily dose, and then diminishes following each subsequent dose over the next month. For most patients, bradycardia is asymptomatic, although some experience dizziness, fatigue, palpitations, or chest pain, all of which resolve within 24 hours. Owing to the risk of bradycardia, patients should be observed for 6 hours after their first dose, and for 6 hours after the first dose given following an interruption in treatment of 2 weeks or longer. If symptomatic bradycardia occurs, heart rate can be increased with atropine (a muscarinic antagonist) or with isoproterenol (a beta-adrenergic agonist).

Patients at risk for bradycardia include those with heart failure, ischemic heart disease, or pre-existing bradycardia, and those taking certain antidysrhythmic drugs, especially beta blockers and two calcium channel blockers: verapamil or diltiazem. An electrocardiogram (ECG) should be obtained for these patients (if a recent ECG is not available).

Macular Edema. Fingolimod can cause macular edema (swelling of the macula of the eye) owing to leakage and accumulation of fluid. In clinical trials, the incidence was 0.4%. Risk is increased by diabetes and uveitis. To monitor for macular edema, patients should undergo an ophthalmologic exam at baseline, 3 to 4 months after starting treatment, and whenever their vision changes. Patients should be instructed to inform the prescriber if they experience vision problems (blurriness, shadows, sensitivity to light, altered color vision, blind spot in the center of the visual field). Fortunately, macular edema generally resolves with or without stopping fingolimod, although some patients have visual deficits even after the edema is gone.

Liver Injury. Fingolimod can cause liver injury, manifesting as elevations in circulating liver transaminases. LFTs should be performed at baseline and whenever signs of liver injury appear. Patients should be informed about signs of liver injury (nausea, vomiting, anorexia, stomach pain, fatigue, dark urine, jaundice) and instructed to inform the prescriber if these develop. If LFTs confirm significant liver damage, fingolimod should be discontinued.

Infection. Fingolimod causes a 20% to 30% decrease in circulating lymphocytes, and thereby increases the risk of infection. Risk is increased during treatment and for 2 months after stopping. Live virus vaccines should not be used during this time. Patients with an active infection should not use the drug. Inform patients about signs of infection (fever, fatigue, chills, body aches) and instruct them to contact the prescriber if these develop. If a serious infection is diagnosed, interruption of treatment should be considered.

Patients who have not had chickenpox (varicella-zoster virus [VZV] infection) and have not received VZV vaccine should be tested for VZV antibodies before starting fingolimod. Antibody-negative patients should be given VZV vaccine, and fingolimod started 1 month later.

Fetal Harm. Fingolimod is teratogenic and embryolethal in animals—at doses equivalent to those used clinically. There are no well-controlled studies in pregnant women.

Women of child-bearing age should be informed about the risk of fetal harm, and advised to use two effective forms of contraception, both during treatment and for 2 months after stopping.

Use During Breast-feeding. Fingolimod is excreted in the milk of rats, and probably in the milk of humans. Given the drug's potential for harm, prudence dictates avoiding breast-feeding while using fingolimod, and for some time after stopping.

Reduced Lung Function. Fingolimod can cause a dose-dependent decrease in lung function. Patients should be advised to inform the prescriber if they experience new or worsening dyspnea (shortness of breath).

Drug Interactions

Ketoconazole. Ketoconazole, an antifungal drug, inhibits some CYP isozymes, and can thereby increase fingolimod levels (by as much as 70%). Patients should be monitored for fingolimod toxicity.

Cardiac Drugs. Drugs that slow heart rate (eg, beta blockers, verapamil, diltiazem) can intensify fingolimod-induced bradycardia. Owing to its effects on heart function, fingolimod may increase the risk of torsades de pointes (a potential fatal dysrhythmia) if combined with a class IA antidysrhythmic drug (eg, quinidine, procainamide, disopyramide) or a class III antidysrhythmic drug (amiodarone, sotalol). Patients using any of these combinations should be monitored.

Vaccines. Because fingolimod suppresses immune function, it can reduce the immune response to all vaccines, and can increase the risk of infection from live virus vaccines. Accordingly, vaccinations should not be attempted while using fingolimod or for 2 months after stopping it.

Drugs That Suppress Immune Function. Combining fingolimod with an immunosuppressant, certain anticancer drugs, or another immunomodulator will cause more immunosuppression than when fingolimod is used alone, thereby increasing the risk of infection.

Preparations, Dosage, and Administration

Fingolimod [Gilenya] is supplied in 0.5-mg hard gelatin capsules. The recommended dosage is 0.5 mg once daily, taken with or without food. Higher doses increase the risk of adverse effects, but do not increase benefits. Like other immunomodulators for MS, fingolimod is expensive, costing about \$48,000/year.

DISEASE-MODIFYING DRUGS II: IMMUNOSUPPRESSANTS

At this time, only one immunosuppressant—mitoxantrone—is approved by the Food and Drug Administration (FDA) for treating MS. Mitoxantrone, originally used for cancer, produces greater immunosuppression than the immunomodulators, but is also more toxic. In addition to mitoxantrone, several other anticancer/immunosuppressants are employed in MS, although they are not FDA approved for this use.

Mitoxantrone

Mitoxantrone [Novantrone] was developed to treat cancer (see Chapter 102), and then later approved for MS. The drug poses a significant risk of toxicity, and hence is generally reserved for patients who cannot be treated with safer agents.

Therapeutic Use

Mitoxantrone is approved for decreasing neurologic disability and clinical relapses in patients with

- Worsening relapsing-remitting MS
- Secondary progressive MS
- Progressive-relapsing MS

For these patients, the drug may delay the time to relapse and the time to disability progression. In addition, it may decrease the number of new MRI-detectable lesions. Mitoxantrone is *not* effective against primary progressive MS.

Mechanism of Action

Mitoxantrone is a cytotoxic drug that binds with DNA and inhibits topoisomerase II. These actions inhibit DNA and RNA synthesis, and promote cross-linking and breakage of DNA strands. In cell culture, mitoxantrone is toxic to all cells, whether dividing or not. However, in clinical practice, the drug appears especially toxic to tissues with a high percentage of actively dividing cells (bone marrow, hair follicles, GI mucosa). In patients with MS, mitoxantrone suppresses production of immune system cells (B lymphocytes, T lymphocytes, and macrophages), and thereby decreases autoimmune destruction of myelin. Additional protection may derive from reducing antigen presentation and reducing production of cytokines (eg, interleukin-2, TNF-alpha, interferon gamma) that participate in the immune response.

Pharmacokinetics

Following IV infusion, mitoxantrone undergoes rapid, widespread distribution. Elimination occurs slowly, primarily by hepatic metabolism and biliary excretion. In patients with liver dysfunction, clearance of the drug is delayed, thereby increasing the risk of toxicity. Accordingly, mitoxantrone should not be given to patients with liver disease. To assess liver status, LFTs should be performed at baseline and prior to each infusion. If LFTs are abnormal, the drug should be withheld.

Adverse Effects

Mitoxantrone can cause a variety of adverse effects. Myelosuppression, cardiotoxicity, and fetal injury are the greatest concerns.

Myelosuppression. Toxicity to the bone marrow cells (myelosuppression) can decrease production of platelets and all blood cells. Loss of neutrophils, which is maximal 10 to 14 days after dosing, increases the risk of *severe infection*. Patients should be advised to avoid contact with people who have infections, and should report signs of infection (fever, chills, cough, hoarseness) immediately. Also, patients should not be immunized with a live virus vaccine (because the vaccine itself could cause infection). To guide mitoxantrone use, complete blood counts should be obtained at baseline, before each infusion, 10 to 14 days after each infusion, and whenever signs of infection develop. Dosing should not be done if the neutrophil count is below 1500 cells/mm³.

Cardiotoxicity. Mitoxantrone can cause irreversible injury to the heart, manifesting as a reduced left ventricular ejection fraction (LVEF) or outright heart failure. Injury may become apparent during treatment, or months to years after drug use has ceased. Cardiotoxicity is directly related to the cumulative lifetime dose. Risk increases significantly if the cumulative dose exceeds 140 mg/m², and hence the total should not exceed this

amount. Mitoxantrone should not be given to patients with cardiac impairment. Accordingly, LVEF should be determined prior to the first dose, and, if the LVEF is less than 50%, mitoxantrone should be withheld. During treatment, LVEF should be measured before every dose and whenever signs of heart failure develop (eg, peripheral edema, fatigue, shortness of breath).

Fetal Harm. Mitoxantrone has the potential for fetal harm, and is classified in FDA Pregnancy Risk Category D. In animal studies, extremely low doses were associated with growth retardation and premature delivery. To date, teratogenicity of mitoxantrone has not been proved. However, since mitoxantrone has the same mechanism as known teratogens, its teratogenicity can be inferred. Women of child-bearing age should avoid becoming pregnant, and pregnancy should be ruled out before each dose. If pregnancy occurs, counseling about possible termination of pregnancy should be offered.

Other Adverse Effects. Because mitoxantrone is especially toxic to tissues with a high percentage of dividing cells, it can cause reversible hair loss and injury to the GI mucosa, resulting in stomatitis and GI distress. The drug can also cause nausea, vomiting, menstrual irregularities (eg, amenorrhea), and symptoms of allergy (itching, rash, hypotension, shortness of breath). In addition, mitoxantrone can impart a harmless, blue-green tint to the skin, sclera, and urine; patients should be forewarned. Very rarely, patients taking mitoxantrone for MS have developed acute myelogenous leukemia, although a causal relationship has not been established.

Monitoring Summary

To minimize risk, we need to

- Perform complete blood counts at baseline, before each dose, and 10 to 14 days after each dose.
- Perform LFTs at baseline and before each dose.
- Perform a pregnancy test before each dose.
- Determine LVEF before each dose and whenever signs of heart failure develop.

Preparations, Dosage, and Administration

Mitoxantrone [Novantrone] is available in solution (2 mg/mL) in 10-, 12.5-, and 15-mL multi-use vials. For patients with MS, the dosage is 12 mg/m² every 3 months, infused IV over 5 to 30 minutes. The maximum lifetime cumulative dose is 140 mg/m². Before infusing, dilute each dose with at least 50 mL of normal saline or 5% dextrose in water; then administer into a free-flowing IV line. Extravasation can cause severe local injury. Accordingly, if extravasation occurs, discontinue the infusion immediately and restart in a different vein. Don't mix mitoxantrone with other drugs.

DISEASE-MODIFYING DRUGS III: INVESTIGATIONAL AGENTS

New disease-modifying drugs for MS are in development. The goal is to create drugs that are more effective, safer, and convenient than the drugs in use today. Nearly all of these drugs disrupt the proliferation, activation, or migration of lymphocytes, and thereby suppress inflammation in the CNS. Like mitoxantrone, some of these drugs were originally developed to treat cancer (Table 23-3). Others are being developed specifically for MS. Although research on these drugs is promising, it's too soon to tell if any of them will represent a significant improvement over the drugs we have now.

DRUGS USED TO MANAGE MS SYMPTOMS

Multiple sclerosis is associated with an array of potentially debilitating symptoms. Accordingly, effective management is essential for maintaining productivity and quality of life. However, despite the importance of symptom management, the discussion below is brief. Why? Because all of the drugs

TABLE 23-3 ■ Investigational Disease-Modifying Drugs for MS

Drug	Route	Approved Use	Mechanism of Action	Benefits in Relapsing Forms of MS
ANTICANCER DRUGS				
Alemtuzumab [Campath]	IV	<ul style="list-style-type: none"> • B-cell chronic lymphocytic leukemia 	A monoclonal antibody that binds the CD52 antigen on B lymphocytes, thereby causing their immune destruction.	Reduces relapse rates and disability progression.
Cyclophosphamide	PO, IV	<ul style="list-style-type: none"> • Lymphomas • Breast cancer • Other cancers • Nephrotic syndrome 	Alkylates DNA and causes strand breaks. Decreases the number and activity of lymphocytes.	May reduce relapse rates, slow disease progression, and improve symptoms, but clinical trials have been inconclusive.
Methotrexate [Rheumatrex, Trexall]	PO, IV, IM	<ul style="list-style-type: none"> • Choriocarcinoma • Many other cancers • Rheumatoid arthritis • Psoriasis 	An antimetabolite that suppresses DNA synthesis and cell replication. Mechanism in MS is unclear.	Clinical trials have failed to show any clear benefits in MS.
Ofatumumab [Arzerra]	IV	<ul style="list-style-type: none"> • B-cell chronic lymphocytic leukemia 	A monoclonal antibody that binds with CD20 molecules on B lymphocytes, thereby causing their immune destruction.	Reduces development of new MRI-detectable lesions. Effects on relapse rates are unknown.
OTHER DRUGS				
Azathioprine [Imuran]	PO, IV	<ul style="list-style-type: none"> • Prevention of kidney transplant rejection • Rheumatoid arthritis 	Undergoes conversion to 6-mercaptopurine, which inhibits DNA synthesis, and thereby reduces the activation, proliferation, and differentiation of T and B lymphocytes.	May be as effective as interferon beta for reducing relapse rates and disability progression. Approved for MS in Germany, but not in the United States.
Dimethyl fumarate	PO	<ul style="list-style-type: none"> • No approved uses 	Promotes apoptosis (self-destruction) of activated T lymphocytes, and inhibits migration of lymphocytes into the CNS.	Reduces relapse rates and maintains or improves disability.
Fingertast	PO	<ul style="list-style-type: none"> • No approved uses 	Like natalizumab [Tysabri], fingertast is an integrin antagonist that prevents migration of leukocytes into the CNS.	Reduces development of new MRI-detectable lesions, and may reduce relapse rates. To date, there have been no reported cases of PML, the greatest concern with natalizumab.
Laquinimod	PO	<ul style="list-style-type: none"> • No approved uses 	Alters T helper lymphocyte function.	Produces a modest reduction in relapse rates, and an even more modest reduction in disability.
Ocrelizumab	IV	<ul style="list-style-type: none"> • No approved uses 	A monoclonal antibody that binds with CD20 molecules on B lymphocytes, thereby causing their immune destruction.	Reduces relapse rates and development of new MRI-detectable lesions.
Teriflunomide	PO	<ul style="list-style-type: none"> • No approved uses 	Inhibits DNA synthesis—by inhibiting dihydroorotate dehydrogenase, needed for <i>de novo</i> pyrimidine synthesis—and thereby reduces activity and proliferation of B and T lymphocytes.	Reduces relapse rates and disability progression when used alone, and augments clinical benefits when combined with interferon B or glatiramer.

PML = progressive multifocal leukoencephalopathy.

employed are discussed at length in other chapters. For more details on symptom management, the web site of the National Multiple Sclerosis Society—www.nationalmssociety.org—is a good resource.

Bladder Dysfunction

Bladder dysfunction is very common, occurring in up to 90% of patients. The underlying cause is disruption of nerve traffic in areas of the CNS that control the bladder detrusor muscle and bladder sphincter. (Recall that coordinated

contraction of the detrusor and relaxation of the sphincter are required for normal voiding.) Three types of bladder dysfunction may be seen: detrusor hyperreflexia, detrusor-sphincter dyssynergia, and flaccid bladder. All three can be successfully managed.

Detrusor hyperreflexia results from decreased inhibition of the bladder reflex and manifests as urinary frequency, urinary urgency, nocturia, and incontinence. Relief is accomplished with anticholinergic drugs, which relax the detrusor and thereby permit a normal volume of urine to accumulate be-

fore bladder emptying. Options include *tolterodine* [Detrol], *oxybutynin* [Ditropan, Oxytrol], *darifenacin* [Enablex], and *solfifenacin* [VESicare].

Detrusor-sphincter dyssynergia is characterized by a lack of synchronization between detrusor contraction and sphincter relaxation. The result is difficulty initiating or stopping urination, and incomplete bladder emptying. Some patients respond to *alpha-adrenergic blocking agents*, such as phenoxybenzamine [Dibenzylin], tamsulosin [Flomax], or terazosin [Hytrin], all of which promote sphincter relaxation. However, most patients require intermittent or continuous catheterization.

In patients with *flaccid bladder*, there is a loss of reflex detrusor contraction, resulting in impaired bladder emptying. In some cases, the condition responds to *bethanechol* [Urecholine], a muscarinic agonist that directly stimulates the detrusor. However, as with detrusor-sphincter dyssynergia, many patients require intermittent or continuous catheterization.

Bowel Dysfunction

Constipation is relatively common, whereas fecal incontinence is relatively rare. Constipation can be managed by increasing dietary fiber and fluids, taking fiber supplements, performing regular exercise, and, if needed, using a bulk-forming laxative, such as *psyllium* [Metamucil]. Rapid relief can be achieved by instilling a mini-enema, sold under the name Enemeez. The product consists of docusate sodium (a stool softener) in a soft-soap base composed of polyethylene glycol and glycerin. Fecal incontinence can be managed by establishing a regular bowel routine and, if needed, using a bulk-forming laxative (to improve stool consistency) and/or using an anticholinergic agent (eg, hyoscyamine) to reduce bowel motility. Be aware, however, that excessive slowing of bowel motility can produce constipation.

Fatigue

Fatigue develops in up to 90% of patients. The underlying cause is unknown. Regular exercise can help. The most common drug therapies are *amantadine* [Symmetrel] and *modafinil* [Provigil, Alertec]. Both are generally well tolerated. *Methylphenidate* [Ritalin] and *amphetamine mixture* [Adderall] are the next options. *Selective serotonin reuptake inhibitors* (SSRIs) can reduce fatigue, and hence are a good choice for patients who are also depressed.

Depression

Depression is seen in about 70% of MS patients. In these people, depression may be reactive—that is, it may be an emotional response to having a chronic, progressive, disabling disease—or it may be the result of MS-induced injury to neurons that help regulate mood. Depression can be induced by antidepressant drugs and with counseling. For drug therapy, treated with antidepressant drugs and with counseling. For drug therapy, the SSRIs, such as fluoxetine [Prozac] and sertraline [Zoloft], can elevate mood, but often seem to increase fatigue. In contrast, *bupropion* [Wellbutrin], which has stimulant properties, can relieve depression and may help fight fatigue. The *tricyclic antidepressants*, such as amitriptyline (formerly available as Elavil) and nortriptyline [Pamelor], can treat pain, sleep disturbances, and incontinence (owing to detrusor hyperreflexia) in addition to improving mood.

Sexual Dysfunction

Among MS patients, sexual dysfunction may affect as many as 91% of men and 72% of women. Among men, erectile dysfunction is the most common complaint. Among women, complaints include vaginal dryness, reduced libido, and decreased vaginal and clitoral sensation. Possible causes of sexual dysfunction include depression, side effects of drugs, and injury to neurons of the lower spinal cord. Erectile dysfunction can be treated with *sildenafil* [Viagra], *vardeafil* [Levitra], and other inhibitors of phosphodiesterase type 5 (see Chapter 66). Vaginal dryness can be managed with a water-soluble personal lubricant (eg, K-Y Jelly); petroleum jelly (Vaseline) should be avoided. There are no drugs proved to enhance vaginal sensation, clitoral sensation, or libido.

Neuropathic Pain

Neuropathic pain results from injury to neurons (in contrast to nociceptive pain, which results from injury to peripheral tissues.) Neuropathic pain responds poorly to traditional analgesics, but often does respond to certain antiepileptic drugs and antidepressants. The antiepileptic drugs employed include *carbamazepine* [Tegretol], *gabapentin* [Neurontin], and *oxcarbazepine* [Trileptal]. The antidepressants employed, all from the tricyclic family, include *nortriptyline* [Pamelor], *imipramine* [Tofranil], and *amitriptyline* (formerly available as Elavil). Please note that pain relief with antidepressants occurs even in patients who are not depressed, and hence is not simply the result of elevating mood.

Dalfampridine to Improve Walking

Actions and Uses. In 2010, the FDA approved oral dalfampridine [Ampyra] to improve walking in patients with MS, making dalfampridine the first and only drug approved specifically to manage an MS symptom. All other drugs approved for MS are used to decrease relapse rates, or to prevent accumulation of disability. In clinical trials, improvements in walking speed were modest: Only one-third of patients were able to walk faster, and the increase in speed was only 20%. Nonetheless, since impaired walking is one of the most common and debilitating sequelae of MS, any hope for improvement is welcome. How does dalfampridine work? The drug blocks potassium channels. Although the precise mechanism underlying clinical improvement is unclear, a good guess is that blockade of neuronal potassium channels reduces leakage of current from demyelinated axons, and thereby improves conduction.

Pharmacokinetics. Dalfampridine is absorbed rapidly and completely after oral dosing. With the extended-release formulation, plasma levels peak in 3 to 4 hours. Most of each dose is eliminated intact in the urine. Very little metabolism occurs. In patients with normal kidney function, or with mild renal impairment, the half-life is 6 hours. By contrast, in patients with severe renal impairment, the half-life increases to 19 hours.

Adverse Effects. The most common adverse effects are urinary tract infection (12%), insomnia (9%), headache (7%), dizziness (7%), weakness (7%), nausea (7%), balance disorder (5%), and back pain (5%). Much more troubling, high doses (20 mg twice daily) pose a risk of *seizures*. Accordingly, dosage must not exceed 20 mg/day. Renal impairment can raise blood levels of dalfampridine, and can thereby increase the risk of seizures.

Preparations, Dosage, and Administration. Dalfampridine [Ampyra] is supplied in 10-mg extended-release tablets for oral dosing, with or without food. Tablets must be swallowed intact, without dividing, crushing, or chewing. For patients with normal kidney function or with mild renal impairment, the recommended dosage is 10 mg every 12 hours. Patients with moderate or severe renal impairment should not use this drug.

Ataxia and Tremor

Ataxia (loss of coordination) and tremor are relatively common and often disabling. Unfortunately, they are also largely unresponsive to treatment. Drugs that may offer some relief include *clonazepam* [Klonopin], *primidone* [Mysoline], and *propranolol* [Inderal]. A physical therapist can provide gait training, and an occupational therapist can provide equipment to help maintain independence.

Spasticity

Spasticity can range in severity from mild muscle tightness to painful muscle spasms, usually in the legs. Clinically significant spasticity occurs in more than 40% of patients. Interestingly, for some patients, spasticity can be beneficial: By making the legs more rigid, spasticity can facilitate standing and walking.

Spasticity can be managed with drug therapy and with nondrug measures (physical therapy, stretching, regular exercise). The drugs used most are *baclofen* [Lioresal] and *tizanidine* [Zanaflex]. However, dosage must be carefully controlled. Why? Because high doses of either agent can exacerbate MS-related muscle weakness. Tizanidine causes less weakness than baclofen, but poses a risk of liver injury, sedation, and dry mouth. Alternatives to baclofen and tizanidine include *diazepam* [Valium] and *botulinum toxin* [Botox]. Intrathecal infusion of baclofen is a very effective option, but is also very invasive.

Cognitive Dysfunction

About 50% of people with MS experience cognitive dysfunction at some time in the course of the disease. Fortunately, only 5% to 10% experience dysfunction severe enough to significantly interfere with daily living. Memory impairment is the most common problem. Other problems include impaired concentration, reasoning, and problem solving. Cognitive impairment is caused in part by demyelination of CNS neurons, and in part by depression, anxiety, stress, and fatigue. By protecting against demyelination, disease-modifying drugs can decrease the degree of cognitive loss. *Donepezil* [Aricept], a cholinesterase inhibitor developed for Alzheimer's disease, may offer modest benefits, as may *memantine* [Namenda], an NMDA receptor blocker developed for Alzheimer's disease (see Chapter 22).

Dizziness and Vertigo

Dizziness and vertigo result from lesions in CNS pathways that provide a sense of equilibrium. Both symptoms are relatively common, and can be reduced with several drugs. Among these are *meclizine* [Antivert, Dramamine] (a drug for motion sickness) and *ondansetron* [Zofran] (a powerful antiemetic).

KEY POINTS

- Multiple sclerosis is a chronic, inflammatory, autoimmune disorder that damages the myelin sheath of neurons in the CNS. Because of demyelination, axonal conduction is slowed or blocked, giving rise to a host of sensory, motor, and cognitive deficits. When inflammation subsides, some degree of recovery occurs, at least in the early stage of the disease.
- In addition to stripping off myelin, inflammation may injure the underlying axon, and may also injure nearby oligodendrocytes, the cells that make CNS myelin.
- What causes MS? There is general agreement that MS develops in genetically vulnerable people following exposure to an environmental or microbial factor that initiates autoimmune activity.
- There are four subtypes of MS: relapsing-remitting (the most common form), secondary progressive, primary progressive, and progressive-relapsing.
- Diagnosis of MS is based on clinical presentation supplemented by laboratory data (eg, MRI scans and CSF tests). A positive diagnosis requires objective evidence of two or more clinical attacks separated in time and space.
- In patients with MS, drugs are employed to (1) modify the disease process, (2) treat acute relapses, and (3) manage symptoms. We have no drugs to cure MS.
- Disease-modifying drugs can decrease the frequency and severity of relapses, reduce development of brain lesions, decrease future disability, and help maintain quality of life. In addition, they may prevent permanent damage to axons.
- There are two main groups of disease-modifying drugs: immunomodulators and immunosuppressants.
- The immunomodulators—interferon beta, glatiramer acetate, natalizumab, and fingolimod—are much safer than mitoxantrone (the only FDA-approved immunosuppressant for MS), and hence are generally preferred.
- All patients with relapsing-remitting MS should receive an immunomodulator—interferon beta, glatiramer acetate, natalizumab, or fingolimod—beginning as soon as possible after diagnosis and continuing indefinitely.
- Interferon beta, glatiramer, and fingolimod have nearly equal efficacy, but are considerably less effective than natalizumab.
- Interferon beta and glatiramer are administered by self-injection (IM or subQ) and fingolimod is administered PO. Natalizumab is administered by IV infusion in a specialized center.
- Interferon beta is generally well tolerated, although side effects—flu-like reactions, liver injury, myelosuppression, injection-site reactions—are relatively common.
- Glatiramer is less well tolerated than interferon beta, and requires more frequent injections.
- The most common side effects of glatiramer are injection-site reactions (pain, erythema, pruritus, induration), and the most disturbing side effect is brief but severe chest pain after the injection. Unlike interferon beta, glatiramer does not cause flu-like symptoms, myelosuppression, or liver toxicity.
- Fingolimod is the only oral disease-modifying agent for MS.
- Fingolimod (as fingolimod phosphate) binds with sphingosine 1-phosphate receptors on lymphocytes, and thereby keeps them sequestered in lymph nodes. As a result, fewer lymphocytes enter the brain, and hence axonal damage from inflammation is reduced.
- Although effective, fingolimod can cause a host of adverse effects (eg, bradycardia, infection, macular edema, liver injury, fetal harm), and hence should be reserved for patients who cannot tolerate injections, or have not responded to other first-line drugs for MS.
- Natalizumab can cause progressive multifocal leukoencephalopathy (PML), a severe CNS infection caused by reactivation of the JC virus. To reduce the risk of PML, natalizumab must not be combined with other immunosuppressant drugs, must not be given to patients with HIV/AIDS and other conditions that compromise cell-mediated immunity, and must be used in accord with the TOUCH Prescribing Program.
- Mitoxantrone is the only immunosuppressant currently approved for MS.
- Mitoxantrone suppresses immune function more strongly than the immunomodulators, but is also more toxic. Accordingly, the drug is generally reserved for patients who are unresponsive to or intolerant of an immunomodulator.
- In patients with MS, mitoxantrone suppresses production of immune system cells, and thereby decreases autoimmune destruction of myelin.
- The major side effects of mitoxantrone are myelosuppression, cardiotoxicity, and fetal injury.
- The risk of cardiotoxicity from mitoxantrone increases significantly if the lifetime cumulative dose exceeds 140 mg/m², and hence the total dose should not exceed this amount.
- A short course of high-dose IV glucocorticoids (eg, methylprednisolone) is the preferred treatment for an acute MS relapse. Intravenous gamma globulin is an option.

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Summary of Major Nursing Implications*

INTERFERON BETA

Interferon beta-1a [Avonex, Rebif]
Interferon beta-1b [Betaseron, Extavia]

Preadministration Assessment

Therapeutic Goal

All preparations of beta interferon are used to decrease the frequency and severity of relapses and slow disease progression in patients with relapsing forms of MS. In addition, interferon beta-1b [Betaseron, Extavia] is used to treat secondary progressive MS.

Baseline Data

Obtain baseline LFTs and complete blood count.

Identifying High-Risk Patients

Exercise caution in patients who abuse alcohol, in those with active liver disease or a history of liver disease, and in those taking drugs that can cause liver injury or suppress the bone marrow.

Implementation: Administration

Routes

Intramuscular. Avonex (interferon beta-1a).
Subcutaneous. Rebif (interferon beta-1a); Betaseron and Extavia (interferon beta-1b).

Administration

For all four formulations of interferon beta, instruct patients to store the drug under refrigeration, teach them how to self-inject, and advise them to rotate the injection site.
Avonex. Instruct patients to inject Avonex IM once a week.

Rebif. Instruct patients to inject Rebif subQ 3 times a week, preferably in the late afternoon or evening, at least 48 hours apart, and on the same days each week (eg, Monday, Wednesday, Friday).

Betaseron and Extavia. Instruct patients to reconstitute powdered Betaseron and Extavia just prior to use, and to inject them subQ every other day.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Indices of success include a reduction in the frequency and intensity of relapses, a reduction in new MRI-detectable lesions, and improvement in the EDSS score.

Minimizing Adverse Effects

Flu-like Reactions. Flu-like reactions—headache, fever, chills, malaise, muscle aches, stiffness—are common early in therapy, but later diminish. To minimize symptoms, begin therapy with low doses, and then slowly titrate to full doses. Inform patients that symptoms can be reduced by taking an analgesic/antipyretic medication (ie, acetaminophen; ibuprofen or another nonsteroidal anti-inflammatory drug).

Hepatotoxicity. Interferon beta can cause liver injury. To monitor for hepatotoxicity, obtain LFTs at baseline,

1 month later, then every 3 months for 1 year, and every 6 months thereafter. If LFTs indicate significant injury, interferon should be given in reduced dosage or discontinued. When liver function returns to normal, treatment can resume with careful monitoring.

Myelosuppression. Interferon beta can decrease production of all blood cell types. To monitor for myelosuppression, obtain complete blood counts at baseline, every 3 months for 1 year, and every 6 months thereafter.

Injection-Site Reactions. Subcutaneous injection (of Rebif, Betaseron, or Extavia) can cause pain, erythema, bumps, and itching. Inform patients that they can reduce discomfort by physical measures—rotating the injection site, applying ice (briefly) before and after the injection, and applying a warm moist compress—and that they can reduce persistent itching and erythema with oral diphenhydramine [Benadryl] or topical hydrocortisone. Instruct patients to avoid continuous exposure to topical hydrocortisone owing to a risk of skin damage.

Forewarn patients that IM injection (of Avonex) can cause discomfort and bruising.

Minimizing Adverse Interactions

Hepatotoxic and Myelosuppressant Drugs. Exercise caution when combining interferon beta with other drugs that can suppress the bone marrow or cause liver injury.

GLATIRAMER ACETATE

Preadministration Assessment

Therapeutic Goal

The goal is to decrease the frequency and severity of relapses and slow disease progression in patients with relapsing-remitting MS.

Implementation: Administration

Route

Subcutaneous.

Administration

Teach patients how to self-inject the drug (subQ) into the arm, abdomen, hip, or thigh. Advise patients to store glatiramer under refrigeration at 36°F to 46°F (2°C to 8°C).

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Indices of success include a reduction in the frequency and intensity of relapses, a reduction in new MRI-detectable lesions, and improvement in the EDSS score.

Minimizing Adverse Effects

Injection-Site Reactions. Forewarn patients that glatiramer may cause pain, erythema, pruritus, and induration at the injection site.

Immediate Postinjection Reaction. Forewarn patients that glatiramer may cause an uncomfortable and disturbing set of systemic symptoms—flushing, palpitations,

chest pain, anxiety, laryngeal constriction, urticaria—that may persist for 15 to 20 minutes after the injection. No specific intervention is needed.

NATALIZUMAB

Preadministration Assessment

Therapeutic Goal

Natalizumab is used to either (1) decrease the frequency and severity of relapses and slow disease progression in patients with relapsing forms of MS who have failed to respond to at least one other immunomodulating drug or (2) treat patients with moderate to severe Crohn's disease who have been unresponsive to or intolerant of other therapies, including inhibitors of TNF-alpha.

Baseline Data

Obtain an MRI scan of the brain at baseline and every 6 months thereafter. Obtain a baseline evaluation for PML.

Identifying High-Risk Patients

Natalizumab is contraindicated for patients with PML, for patients taking immunosuppressive drugs, and for patients with HIV/AIDS and other conditions that compromise cell-mediated immunity.

Implementation: Administration

Route

Intravenous.

Administration

Dilute concentrated natalizumab in 100 mL of 0.9% sodium chloride injection and infuse over a 1-hour span. If any signs of hypersensitivity develop, stop the infusion immediately.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Indices of success include a reduction in the frequency and intensity of relapses, a reduction in new MRI-detectable lesions, and improvement in the EDSS score.

Minimizing Adverse Effects

Progressive Multifocal Leukoencephalopathy. Natalizumab increases the risk of PML, a severe infection of the CNS with no effective treatment. To reduce the risk of PML, do not give natalizumab to patients taking immunosuppressants or to patients with HIV/AIDS and other conditions that compromise cell-mediated immunity. Screen for PML prior to each infusion. Inform patients about symptoms of PML (eg, progressive weakness on one side of the body; clumsiness of the limbs; disturbed vision; changes in thinking, memory, and orientation) and instruct them to report these immediately. All patients, prescribers, infusion nurses, infusion centers, and pharmacies associated with infusion centers must register with the *TPOCH Prescribing Program* and must comply with its provisions.

Hepatotoxicity. Natalizumab can injure the liver. Inform patients about signs of liver injury—jaundice, nausea,

Summary of Major Nursing Implications*—cont'd

vomiting, fatigue, darkening of the urine—and instruct them to report these immediately. Discontinue natalizumab if significant liver injury is diagnosed.

Hypersensitivity Reactions. Natalizumab can cause severe hypersensitivity reactions (eg, anaphylaxis), usually within 2 hours of starting the infusion. Monitor patients for a reaction during the infusion and for 1 hour after. If a severe reaction develops, discontinue natalizumab and never use it again.

Drug Interactions

Immunosuppressants (eg, mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate) increase the risk of PML and other opportunistic infections, and hence should be discontinued at least 3 months before starting natalizumab.

FINGOLIMOD

Preadministration Assessment

Therapeutic Goal

The goal is to decrease the frequency and severity of relapses and slow disease progression in patients with relapsing forms of MS.

Baseline Data

Obtain a pregnancy test, LFTs, complete blood count, ophthalmologic exam, and a test for varicella-zoster virus (VZV) antibodies. Obtain an ECG for patients with cardiovascular risk factors.

Identifying High-Risk Patients

Fingolimod is contraindicated during pregnancy and in patients with active infection. Use fingolimod with caution in patients with diabetes, averts, heart failure, ischemic heart diseases, or bradycardia, and in those taking ketoconazole, immunosuppressants, immunomodulators, anticancer drug beta blockers, verapamil, diltiazem, class IA antiarrhythmics, and class III antiarrhythmics.

Implementation: Administration

Route

Oral.

Administration

Instruct patients to take fingolimod once daily, with or without food.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Indices of success include a reduction in the frequency and intensity of relapses, a reduction in new MRI-detectable lesions, and improvement in the EDSS score.

Monitoring Summary

Obtain an ophthalmologic exam at baseline, 3 to 4 weeks after starting treatment, and whenever there is a change in vision.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Obtain LFTs at baseline and whenever signs of liver injury appear.

Minimizing Adverse Effects

Bradycardia. Fingolimod reduces heart rate, especially after the first dose. Symptoms include dizziness, fatigue, palpitations, and chest pain, all of which resolve within 24 hours. Inform patients that, after receiving the first dose, they must be observed in the provider's office for 6 hours. For patients who develop symptoms, heart rate can be increased with atropine or isoproterenol. Inform patients that the risk of bradycardia will return if treatment is interrupted for 2 weeks or longer, and hence observation for 6 hours will be needed when they first resume treatment.

Patients at risk for bradycardia include those with heart failure, ischemic heart disease, or pre-existing bradycardia, and those taking certain antidiarrhythmic drugs, especially beta blockers and two calcium channel blockers: verapamil or diltiazem. Obtain an ECG for these people if a recent ECG is unavailable.

Macular Edema. Fingolimod can cause macular edema. Risk is increased by diabetes and uveitis. To monitor for macular edema, patients should undergo an ophthalmologic exam at baseline, 3 to 4 months after starting treatment, and whenever their vision changes. Instruct patients to inform the prescriber if they experience vision problems (blurriness, shadows, sensitivity to light, altered color vision, blind spot in the center of the visual field).

Liver Injury. Fingolimod can injure the liver. Liver function tests (LFTs) should be performed at baseline and whenever signs of liver injury appear. Inform patients about signs of liver injury (nausea, vomiting, anorexia, stomach pain, fatigue, dark urine, jaundice) and instruct them to tell the prescriber if these develop. If LFTs confirm significant liver damage, fingolimod should be discontinued.

Infection. Fingolimod increases the risk of infection during treatment and for 2 months after stopping. Instruct patients to avoid live virus vaccines during this time. Do not start fingolimod in patients with an active infection. Inform patients about signs of infection (fever, fatigue, chills, body aches) and instruct them to contact the prescriber if these develop. If a serious infection is diagnosed, interruption of treatment should be considered.

Patients who have not had chickenpox (VZV infection) and have not received VZV vaccine should be tested for VZV antibodies before starting treatment. Give antibody-negative patients VZV vaccine, and start fingolimod 1 month later.

Fetal Harm. Fingolimod is teratogenic and embryolethal. Inform women of child-bearing age about the risk of fetal harm, and instruct them to use two effective forms of contraception, both during treatment and for 2 months after stopping.

Use During Breast-feeding. Fingolimod is excreted in the milk of rats, and probably in the milk of humans. Inform women about the potential risks to the infant, and advise them to avoid breast-feeding while using fingolimod, and for some time after stopping.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Monitoring Summary

Perform complete blood counts before each dose, 10 to 14 days after each dose, and whenever signs of infection develop.

Perform liver function tests before each dose.

Perform a pregnancy test before each dose.

Determine LVEF before each dose and whenever signs of heart failure develop.

Minimizing Adverse Effects

Myelosuppression. Mitoxantrone can decrease production of platelets and all blood cells. Neutrophil loss increases the risk of severe infection, and hence the drug should be withheld if the neutrophil count drops below 1500 cells/mm³. Advise patients to avoid contact with people who have infections, and instruct them to report signs of infection (fever, chills, cough, hoarseness) immediately. Do

*Patient education information is highlighted as blue text.

not give patients a live virus vaccine.

Cardiotoxicity. Mitoxantrone can cause irreversible injury to the heart, manifesting as a reduced LVEF or outright heart failure. Cardiotoxicity is directly related to the cumulative lifetime dose, which must not exceed 140 mg/m². Withhold mitoxantrone if the LVEF drops below 50%. Inform patients about symptoms of heart failure (eg, shortness of breath, fatigue, peripheral edema) and instruct them to report these immediately.

Fetal Harm. Mitoxantrone is classified in FDA Pregnancy Risk Category D, and hence must not be used during pregnancy. Rule out pregnancy before each infusion. Warn women of child-bearing age to avoid pregnancy. If pregnancy occurs, offer counseling about possible pregnancy termination.

Urine and Tissue Discoloration. Forewarn patients that mitoxantrone can impart a harmless, blue-green tint to the urine, skin, and sclera.

Summary of Major Nursing Implications*—cont'd

Reduced Lung Function. Fingolimod can cause a dose-dependent decrease in lung function. Advise patients to inform the prescriber if they experience new or worsening dyspnea.

Minimizing Adverse Interactions

Ketoconazole. Ketoconazole inhibits some CYP isoenzymes, and can thereby greatly increase fingolimod levels. Monitor patients closely for fingolimod toxicity.

Cardiac Drugs. Drugs that slow heart rate (eg, beta blockers, verapamil, diltiazem) can intensify fingolimod-induced bradycardia. Monitor these patients closely.

Combining fingolimod with a class IA antiarrhythmic drug (eg, quinidine, procainamide, disopyramide) or a class III antiarrhythmic drug (amiodarone, sotalol) may increase the risk of torsades de pointes, a potentially fatal dysrhythmia. Monitor these patients closely.

Drugs That Suppress Immune Function. Combining fingolimod with an immunosuppressant, certain anticancer drugs, or another immunomodulator will cause more immunosuppression than when fingolimod is used alone. Inform patients about the increased risk of infection.

Vaccines. Fingolimod can reduce the immune response to all vaccines, and can increase the risk of infection from live virus vaccines. Advise patients to avoid vaccines while using fingolimod or for 2 months after stopping.

MITOXANTRONE

Preadministration Assessment

Therapeutic Goal

The goal is to decrease the frequency and severity of relapses and slow disease progression in patients with secondary progressive MS, progressive-relapsing MS, and worsening relapsing-remitting MS.

Baseline Data

Obtain a pregnancy test, LFTs, complete blood count, and LVEF determination.

Identifying High-Risk Patients

Mitoxantrone is contraindicated during pregnancy and for patients with abnormal LFTs or an LVEF below 50%.

Implementation: Administration

Route

Intravenous.

Administration

Infuse over 5 to 30 minutes through a free-flowing IV line. If extravasation occurs, discontinue the infusion immediately and restart in a different vein. Don't mix mitoxantrone with other drugs.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Indices of success include a reduction in the frequency and intensity of relapses, a reduction in new MRI-detectable lesions, and improvement in the EDSS score.

Continued

*Patient education information is highlighted as blue text.

Seizure Generation

Types of Seizures

Partial Seizures

Generalized Seizures

Mixed Seizures: Lennox-Gastaut Syndrome

How Antiepileptic Drugs Work

Basic Therapeutic Considerations

Therapeutic Goal and Treatment Options

Diagnosis and Drug Selection

Drug Evaluation

Monitoring Plasma Drug Levels

Promoting Patient Adherence

Withdrawing Antiepileptic Drugs

Suicide Risk with Antiepileptic Drugs

Classification of Antiepileptic Drugs

Traditional Antiepileptic Drugs

Phenytoin

Carbamazepine

Valproic Acid

Ethosuximide

Phenobarbital

Primidone

Newer Antiepileptic Drugs

Oxcarbazepine

Lamotrigine

Gabapentin

Gabapentin Enacarbil

Pregabalin

Levetiracetam

Topiramate

Tiagabine

Zonisamide

Felbamate

Lacosamide

Rufinamide

Vigabatrin

Ezogabine

Management of Epilepsy During Pregnancy

Management of Generalized Convulsive Status Epilepticus



Box 24-1. Nondrug Therapies for Epilepsy: Neurosurgery, Vagus Nerve Stimulation, and the Ketogenic Diet

The term *epilepsy* refers to a group of chronic neurologic disorders characterized by recurrent seizures, brought on by excessive excitability of neurons in the brain. Symptoms can range from brief periods of unconsciousness to violent convulsions. Patients may also experience problems with learning, memory, and mood, which can be just as troubling as their seizures.

In the United States, about 2.3 million people have epilepsy, according to the Centers for Disease Control and Prevention (CDC). Every year, 140,000 new cases are diagnosed. The incidence is highest in the very young and the elderly. Between 60% and 70% of patients can be rendered seizure free with drugs. Unfortunately, this means that 30% to 40% cannot. The total direct and indirect costs of epilepsy are estimated at \$15.5 billion a year.

The terms *seizure* and *convulsion* are not synonymous. *Seizure* is a general term that applies to all types of epileptic events. In contrast, *convulsion* has a more limited meaning, applying only to abnormal motor phenomena, for example, the jerking movements that occur during a tonic-clonic (grand mal) attack. Accordingly, although all convulsions may be called seizures, it is not correct to call all seizures convulsions. Absence seizures, for example, manifest as brief periods of unconsciousness, which may or may not be accompanied by involuntary movements. Since not all epileptic seizures involve convulsions, we will refer to the agents used to treat epilepsy as *antiepileptic drugs* (AEDs), rather than anticonvulsants.

SEIZURE GENERATION

Seizures are initiated by synchronous, high-frequency discharge from a group of hyperexcitable neurons, called a *focus*. A focus may result from several causes, including congenital defects, hypoxia at birth, head trauma, brain infection, stroke, cancer, and genetic disorders. Seizures are seen when discharge from a focus spreads to other brain areas, thereby recruiting normal neurons to discharge abnormally along with the focus.

The overt manifestations of any particular seizure disorder depend on the location of the seizure focus and the neuronal connections to that focus. (The connections to the focus determine the brain areas to which seizure activity can spread.) If seizure activity invades a very limited part of the brain, a partial or local seizure occurs. In contrast, if seizure activity spreads to a large portion of the brain, a generalized seizure develops.

An experimental procedure referred to as *kindling* may explain how a focal discharge is eventually able to generate a seizure. Experimental kindling is performed by implanting a

small electrode into the brain of an animal. The electrode is used to deliver localized stimuli for a brief interval once a day. When stimuli are first administered, no seizures result. However, after repeated once-a-day delivery, these stimuli eventually elicit a seizure. If brief, daily stimulations are continued long enough, spontaneous seizures will begin to occur.

The process of kindling may tell us something about seizure development in humans. For example, kindling may account for the delay that can take place between injury to the head and eventual development of seizures. Furthermore, kindling may explain why the seizures associated with some forms of epilepsy become more frequent as time passes. Also, the progressive nature of kindling suggests that early treatment might prevent seizure disorders from becoming more severe over time.

TYPES OF SEIZURES

Seizure can be divided into two broad categories: *partial (focal) seizures* and *generalized seizures*. In partial seizures, seizure activity begins focally in the cerebral cortex and usually undergoes limited spread to adjacent cortical areas. In generalized seizures, focal seizure activity is conducted widely throughout both hemispheres. As a rule, partial seizures and generalized seizures are treated with different drugs (Table 24-1).

Partial Seizures

Partial seizures fall into three groups: simple partial seizures, complex partial seizures, and partial seizures that evolve into secondarily generalized seizures.

TABLE 24-1 ■ Drugs for Specific Types of Seizures

Seizure Type	Drugs Used for Treatment	
	Traditional AEDs	Newer AEDs
Partial		
Simple partial, complex partial, and secondarily generalized	Carbamazepine	Ezogabine
	Phenytoin	Oxcarbazepine
	Valproic acid	Gabapentin
	Phenobarbital	Lacosamide
	Primidone	Lamotrigine
		Levetiracetam
		Pregabalin
	Topiramate	
	Tiagabine	
	Vigabatrin	
	Zonisamide	
Primary Generalized		
Tonic-clonic	Carbamazepine	Lamotrigine
	Phenytoin	Levetiracetam
	Valproic acid	Topiramate
	Phenobarbital	
	Primidone	
Absence	Ethosuximide	Lamotrigine
	Valproic acid	
Myoclonic	Valproic acid	Lamotrigine
		Levetiracetam
		Topiramate

AEDs = antiepileptic drugs.

Simple Partial Seizures. These seizures manifest with discrete symptoms that are determined by the brain region involved. Hence, the patient may experience discrete motor symptoms (eg, twitching thumb), sensory symptoms (eg, local numbness; auditory, visual, or olfactory hallucinations), autonomic symptoms (eg, nausea, flushing, salivation, urinary incontinence), or psychoillusive symptoms (eg, feelings of unreality, fear, or depression). Simple partial seizures are distinguished from complex partial seizures in that there is *no loss of consciousness*. These seizures persist for 20 to 60 seconds.

Complex Partial Seizures. These seizures are characterized by *impaired consciousness* and lack of responsiveness. At seizure onset, the patient becomes motionless and stares with a fixed gaze. This state is followed by a period of *automatism*, in which the patient performs repetitive, purposeless movements, such as lip smacking or hand wringing. Seizures last 45 to 90 seconds.

Secondarily Generalized Seizures. These seizures begin as simple or complex partial seizures, and then evolve into generalized tonic-clonic seizures. Consciousness is lost. These seizures last 1 to 2 minutes.

Generalized Seizures

Generalized seizures may be convulsive or nonconvulsive. As a rule, they produce immediate loss of consciousness. The major generalized seizures are discussed briefly below.

Tonic-Clonic Seizures (Grand Mal). In tonic-clonic seizures, neuronal discharge spreads throughout both hemispheres of the cerebral cortex. These seizures manifest as major convulsions, characterized by a period of muscle rigidity (tonic phase) followed by synchronous muscle jerks (clonic phase). Tonic-clonic seizures often cause urination, but not defecation. Convulsions may be preceded by a loud cry, caused by forceful expiration of air across the vocal cords. Tonic-clonic seizures are accompanied by marked impairment of consciousness and are followed by a period of central nervous system (CNS) depression, referred to as the *postictal state*. The seizure itself lasts 90 seconds or less.

Absence Seizures (Petit Mal). Absence seizures are characterized by loss of consciousness for a brief time (10 to 30 seconds). Seizures usually involve mild, symmetric motor activity (eg, eye blinking) but may occur with no motor activity at all. The patient may experience hundreds of absence attacks a day. Absence seizures occur primarily in children and usually cease during the early teen years.

Atonic Seizures. These seizures are characterized by sudden loss of muscle tone. If seizure activity is limited to the muscles of the neck, "head drop" occurs. However, if the muscles of the limbs and trunk are involved, a "drop attack" can occur, causing the patient to suddenly collapse. Atonic seizures occur mainly in children.

Myoclonic Seizures. These seizures consist of sudden muscle contractions that last for just 1 second. Seizure activity may be limited to one limb (focal myoclonus) or it may involve the entire body (massive myoclonus).

Status Epilepticus. Status epilepticus (SE) is defined as a seizure that persists for 30 minutes or longer. There are several types of SE, including generalized convulsive SE, absence SE, and myoclonic SE. Generalized convulsive SE, which can be life threatening, is discussed later.

Febrile Seizures. Fever-associated seizures are common among children ages 6 months to 5 years. Febrile seizures typically manifest as generalized tonic-clonic convulsions of short duration. Children who experience these seizures are *not* at high risk of developing epilepsy later in life.

Mixed Seizures: Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy that usually develops during the preschool years. The syndrome is characterized by developmental delay and a mixture of partial and generalized seizures. Seizure types include partial, atonic, tonic, generalized tonic-clonic, and atypical absence. In children with LGS, seizures can be very difficult to treat.

HOW ANTIEPILEPTIC DRUGS WORK

We have long known that AEDs can (1) suppress discharge of neurons within a seizure focus and (2) suppress propagation of seizure activity from the focus to other areas of the brain. However, until recently we didn't know how these effects were achieved. It now appears that nearly all AEDs act through five basic mechanisms: suppression of sodium influx, suppression of calcium influx, promotion of potassium efflux, blockade of receptors for glutamate, and potentiation of gamma-aminobutyric acid (GABA).

Suppression of Sodium Influx. Before discussing AED actions, we need to review sodium channel physiology. Neuronal action potentials are propagated by influx of sodium through sodium channels, which are gated pores in the cell membrane that control sodium entry. For sodium influx to occur, the channel must be in an *activated state*. Immediately following sodium entry, the channel goes into an *inactivated state*, during which further sodium entry is prevented. Under normal circumstances, the inactive channel very quickly returns to the activated state, thereby permitting more sodium entry and propagation of another action potential.

Several AEDs, including phenytoin, carbamazepine, valproic acid, and lamotrigine, reversibly bind to sodium channels while they are in the inactivated state, and thereby prolong channel inactivation. By delaying return to the active state, these drugs decrease the ability of neurons to fire at high frequency. As a result, seizures that depend on high-frequency discharge are suppressed.

Suppression of Calcium Influx. In axon terminals, influx of calcium through voltage-gated calcium channels promotes transmitter release. Hence, drugs that block these calcium channels can suppress transmission. Several AEDs, including valproic acid and ethosuximide, act by this mechanism.

Promotion of Potassium Efflux. During an action potential, influx of sodium causes neurons to depolarize, and then efflux of potassium causes neurons to repolarize. One AED—ezogabine—acts on voltage-gated potassium channels to facilitate potassium efflux. This action is believed to underlie the drug's ability to slow repetitive neuronal firing and thereby provide seizure control.

Antagonism of Glutamate. Glutamic acid (glutamate) is the primary excitatory transmitter in the CNS. The compound works through two receptors, known as (1) NMDA receptors (*N*-methyl-D-aspartate receptors) and (2) AMPA receptors (alpha-amino-3-hydroxy-5-methyl-4-isoxazole pro-

ponic acid receptors). Two drugs—felbamate and topiramate—block the actions of glutamate at NMDA and AMPA receptors, and thereby suppress neuronal excitation.

Potentiation of GABA. Several AEDs potentiate the actions of GABA, an inhibitory neurotransmitter that is widely distributed throughout the brain. By augmenting the inhibitory influence of GABA, these drugs decrease neuronal excitability and thereby suppress seizure activity. Drugs increase the influence of GABA by several mechanisms. Benzodiazepines and barbiturates enhance the effects of GABA by mechanisms that involve direct binding to GABA receptors. Gabapentin promotes GABA release. Tiagabine inhibits GABA reuptake, and vigabatrin inhibits the enzyme that degrades GABA, and thereby increases GABA availability.

BASIC THERAPEUTIC CONSIDERATIONS

Therapeutic Goal and Treatment Options

The goal in treating epilepsy is to reduce seizures to an extent that enables the patient to live a normal or near-normal life. Ideally, treatment should eliminate seizures entirely. However, this may not be possible without causing intolerable side effects. Therefore, we must balance the desire for complete seizure control against the acceptability of side effects.

Epilepsy may be treated with drugs or with nondrug therapies. As noted, drugs can benefit 60% to 70% of patients. This means that, of the 2.3 million Americans with epilepsy, between 690,000 and 920,000 *cannot* be treated successfully with drugs. For these people, nondrug therapy may well help. Three options exist: neurosurgery, vagus nerve stimulation, and the ketogenic diet. Of the three, neurosurgery has the best success rate, but vagus nerve stimulation is used most widely. All three nondrug therapies are discussed in Box 24-1.

Diagnosis and Drug Selection

Control of seizures requires proper drug selection. As indicated in Table 24-1, many AEDs are selective for specific seizure disorders. Phenytoin, for example, is useful for treating tonic-clonic and partial seizures but not absence seizures. Conversely, ethosuximide is active against absence seizures but not against tonic-clonic or partial seizures. Only one drug—valproic acid—appears effective against practically all forms of epilepsy. Since most AEDs are selective for certain seizure disorders, effective treatment requires a proper match between the drug and the seizure. To make this match, the seizure type must be accurately diagnosed.

Making a diagnosis requires physical, neurologic, and laboratory evaluations along with a thorough history. The history should determine the age at which seizures began, the frequency and duration of seizure events, precipitating factors, and times when seizures occur. Physical and neurologic evaluations may reveal signs of head injury or other disorders that could underlie seizure activity, although in many patients the physical and neurologic evaluations may be normal. An electroencephalogram (EEG) is essential for diagnosis. Other diagnostic tests that may be employed include computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI).

Very often, patients must try several AEDs before a regimen that is both effective and well tolerated can be estab-



NONDRUG THERAPIES FOR EPILEPSY: NEUROSURGERY, VAGUS NERVE STIMULATION, AND THE KETOGENIC DIET

Neurosurgery: The Cure That's Rarely Used

For patients with *temporal lobe epilepsy*, surgery is highly effective, but used infrequently. At this time, surgical intervention is the only *cure* for epilepsy. (Drugs may control symptoms, but they don't cure.) The safety and efficacy of surgery have been documented in literally hundreds of studies. Among patients with forms of epilepsy that can be treated surgically, the procedure can render between 60% and 90% seizure free—and, even when seizures do continue, their frequency is often decreased. This degree of success is all the more remarkable when we consider that, in order to qualify for surgery, candidates must first be proved refractory to drugs. Put another way, surgery is only performed on patients who have epilepsy that is especially hard to treat. Yet, despite its proven efficacy, surgery remains grossly underutilized: Each year, only 500 or so surgeries are performed in the United States, although more than 100,000 patients are eligible. This is especially unfortunate because, among people who are refractory to drugs, surgery can greatly improve seizure control, thereby improving quality of life, along with attendance at work and at school.

Temporal lobe surgery is not without risk. Between 5% and 10% of patients experience adverse effects, including infection, visual field defects, memory loss, and paralysis. The death rate is very low—about 0.2%. Prior to surgery, patients undergo a battery of tests designed to locate the seizure focus as well as nearby areas associated with language and other critical functions. This information allows the surgeon to remove as little tissue as possible, thereby minimizing disruption of normal brain function.

Vagus Nerve Stimulation: Fighting Impulses with Impulses

The vagus nerve stimulator (VNS) is the first medical device for reducing seizures. The only commercial VNS available—the VNS Therapy System (formerly known as the NeuroCybernetic Prosthesis System)—received FDA approval in 1997. The system is intended for use in conjunction with drugs by patients with severe, uncontrolled seizures. Responses to vagal stimulation develop slowly: Initial responses usually occur in 3 months, and full responses take even longer to develop. Vagal nerve stimulation is now the most widely used nondrug therapy for drug-resistant seizures.

The heart of the VNS is a small, programmable pulse generator that is implanted under the collarbone, much like a cardiac pacemaker. Subcutaneous leads connect the generator to the left branch of the vagus nerve in the neck. Stimulation is typically applied for 30 seconds every 5 minutes around the clock. When needed, stimulation parameters (voltage, frequency, duration) can be adjusted externally by the physician. By holding a small magnet over the generator, patients can activate the device manually if they feel a seizure coming on. In addition, patients can use the magnet to turn the generator off. VNS batteries last 3 to 5 years. Replacement is done in an outpatient procedure that takes 30 to 60 minutes.

In clinical trials, some patients responded dramatically and most showed at least some improvement. However, with a few patients, seizures *increased*. Specific results were as follows:

- In 26% of patients, seizure frequency decreased by 25% to 50%.
- In 11% of patients, seizure frequency decreased by more than 75%.
- In one patient, seizures stopped entirely.
- In 6% of patients, seizure frequency increased.

Vagal stimulation does not eliminate the need for drugs—but it can permit a simpler regimen. Up to 50% of patients can decrease the number of drugs they are taking (eg, two instead of three; one instead of two). Please note, however, that stimulation does *not* permit a reduction in dosage of the drugs that remain.

Vagal stimulation is well tolerated by most patients, although side effects occur often. During stimulation, patients experience hoarseness (100%), coughing (50%), voice alteration (73%), and shortness of breath (25%). In addition, there is a 2% to 3% risk of infection at the implant site. Stimulation does not cause cognitive effects and, perhaps surprisingly, does not cause autonomic effects (eg, bradycardia, GI disturbances, hypotension).

How does vagal stimulation decrease seizure frequency? No one knows. What we do know is that vagal fibers project to the brainstem, and from there to areas of the brain involved in seizure generation. When we stimulate the vagus, the resultant impulses in some way interrupt or prevent abnormal neuronal firing.

In 2005, the VNS Therapy System was approved for treating depression. This application is discussed in Chapter 32.

The Ketogenic Diet: It's Tough but It Works

The ketogenic diet for epilepsy can decrease seizure frequency, but it's hard to implement and potentially dangerous. The diet was introduced in the 1920s, but fell out of use when AEDs became available. Today, the diet is under renewed study as a way to control seizures when drug therapy fails—and even as first-line therapy for some patients. Because the diet is both difficult and hazardous, close medical supervision is essential.

The ketogenic diet has two cornerstones: high intake of fat and very low intake of carbohydrates. Fats—usually butter or heavy cream—comprise 80% of daily calories. The remaining 20% come from carbohydrates and proteins. With strict adherence to the diet, ketosis develops in a few days. However, with just a minor deviation from the diet (eg, ingestion of two cookies), ketosis will be lost in hours.

How does a high-fat, low-carbohydrate diet reduce seizures? The answer is unclear. For years, we believed that benefits derived from causing *ketoacidosis*. (Because carbohydrate availability is low, the body burns fat to meet energy needs. Burning fat produces large amounts of ketone bodies—beta-hydroxybutyric acid, acetoacetic acid, and acetone—whose presence creates a state of ketoacidosis.) However, although the diet does indeed cause



NONDRUG THERAPIES FOR EPILEPSY: NEUROSURGERY, VAGUS NERVE STIMULATION, AND THE KETOGENIC DIET—cont'd

ketoacidosis, there are no data showing that ketoacidosis is the reason for seizure control. In fact, another high-fat diet (a modified form of the Atkins diet), which does *not* cause ketoacidosis, can nonetheless reduce seizure occurrence. The bottom line? High intake of fat and low intake of carbohydrates are probably both playing a role in seizure control.

The principal candidates for dietary therapy are children under the age of 10 who have not responded to AEDs. About two-thirds of these children respond to the diet. Among the responders, seizure reduction occurs rapidly, typically within a few days. In a trial reported in 2008, seizure frequency was reduced by more than 50%.

Adverse effects of the diet are considerable. The most consistent—and obvious—is elevation of blood cholesterol. In one

study, cholesterol levels rose from a mean of 170 mg/dL to 245 mg/dL. In another study, five children developed severe hypercholesterolemia, with an average level of 367 mg/dL. Since cholesterol contributes to coronary artery disease (CAD), and since CAD is known to begin early in life, elevation of cholesterol is a significant drawback. Other adverse effects include poor linear growth, poor weight gain, kidney stones, dehydration, acidosis, constipation, and vomiting. However, although the side effects of the diet are a concern, keep in mind that AEDs can also cause harm—perhaps even more than the diet. Hence, if the diet allows a reduction in AED use, there may be little or no net increase in harm.

lished. Initial treatment should be done with just one AED. If this drug fails, it should be discontinued and a different AED should be tried. If this second drug fails, two options are open: (1) treatment with a third AED alone, or (2) treatment with a combination of AEDs.

Drug Evaluation

Once an AED has been selected, a trial period is needed to determine its effectiveness. During this time there is no guarantee that seizures will be controlled. Until seizure control is certain, the patient should be warned not to participate in driving and other activities that could be hazardous should a seizure occur.

During the process of drug evaluation, adjustments in dosage are often needed. No drug should be considered ineffective until it has been tested in sufficiently high dosage and for a reasonable time. Knowledge of plasma drug levels can be a valuable tool for establishing dosage and evaluating the effectiveness of a specific drug.

Maintenance of a seizure frequency chart is important. The chart should be kept by the patient or a family member and should contain a complete record of all seizure events. This record will enable the prescriber to determine if treatment has been effective. The nurse should teach the patient how to create and use a seizure frequency chart.

Monitoring Plasma Drug Levels

Monitoring plasma levels of AEDs is common. Safe and effective levels have been firmly established for most AEDs (Table 24-2). Monitoring these levels can help guide dosage adjustments.

Monitoring plasma drug levels is especially helpful when treating major convulsive disorders (eg, tonic-clonic seizures). Since these seizures can be dangerous, and since delay of therapy may allow the condition to worsen, rapid control of seizures is desirable. However, because these seizures occur infrequently, a long time may be needed to establish control if clinical outcome is relied on as the only means of determining

an effective dosage. By adjusting initial doses on the basis of plasma drug levels (rather than on the basis of seizure control), we can readily achieve drug levels that are likely to be effective, thereby increasing our chances of establishing control quickly.

Measurements of plasma drug levels are less important for determining effective dosages for absence seizures. Why? Because absence seizures occur very frequently (up to several hundred a day), and hence observation of the patient is the best means for establishing an effective dosage: if seizures stop, dosage is sufficient; if seizures continue, more drug is needed.

In addition to serving as a guide for dosage adjustment, knowledge of plasma drug levels can serve as an aid to (1) monitoring patient adherence, (2) determining the cause of lost seizure control, and (3) identifying causes of toxicity, especially in patients taking more than one drug.

Promoting Patient Adherence

Epilepsy is a chronic condition that requires regular and continuous therapy. As a result, seizure control is highly dependent on patient adherence. In fact, it is estimated that nonadherence accounts for about 50% of all treatment failures. Accordingly, promoting adherence should be a priority for all members of the healthcare team. Measures that can help include

- Educating patients and families about the chronic nature of epilepsy and the importance of adhering to the prescribed regimen.
- Monitoring plasma drug levels to encourage and evaluate adherence.
- Deepening patient and family involvement by having them maintain a seizure frequency chart.

Withdrawing Antiepileptic Drugs

Some forms of epilepsy undergo spontaneous remission, and hence discontinuing treatment may eventually be appropriate. Unfortunately, there are no firm guidelines to indicate the most appropriate time to withdraw AEDs. However, once the

TABLE 24-2 ■ Clinical Pharmacology of the Oral Antiepileptic Drugs (AEDs)

Drug	Product Name	Daily Dosing	Daily Maintenance Dosage		Target Serum Level ^a (mcg/mL)	Induces Hepatic Drug Metabolism
			Adults (mg)	Children (mg/kg)		
Traditional AEDs						
Carbamazepine	Tegretol	3 times	600–1800	10–35	4–12	Yes
	Epitol	3 times				
	Tegretol-XR, Tegretol CR [★]	Twice				
	Carbatrol	Twice				
	Equetro	Twice				
Ethosuximide	Zarontin	1 or 2 times	750	15–40	40–100	No
	Generic only	1 or 2 times	60–120	3–6	15–45	Yes
Phenytoin	Dilantin-125	2 or 3 times	200–300	4–8	10–20	Yes
	Dilantin Infatab	2 or 3 times				
	Phenytek (ER capsules)	Once				
	Dilantin (ER capsules)	Once				
Primidone	Mysoline	3 or 4 times	500–750	10–25	5–15 ^b	Yes
	Valproic acid	3 or 4 times	750–3000	15–45	40–100	No
Valproic acid	Depakene	3 or 4 times				
	Depakote, Epival [★]	3 or 4 times				
	Depakote ER	Twice				
	Stavzor	2 or 3 times				
Newer AEDs						
Gabapentin	Neurontin	3 times	1200–3600	25–50	12–20	No
Lacosamide	Vimpat	Twice	200–400	ND	ND	No
Lamotrigine	Lamictal, Lamictal ODT	Twice	400 ^{c,d}	5 ^{c,d}	3–14	No
	Lamictal XR	Once				
Levetiracetam	Keppra	Twice	2000–3000	40–100	10–40	No
Oxcarbazepine	Trileptal	Twice	900–2400	30–46	3–40	No ^e
Pregabalin	Lyrica	2 or 3 times	150–600	ND	ND	No
Rufinamide	Banzel	Twice	3200	45	ND	Yes ^f
Tiagabine	Gabitril	2 to 4 times	16–32	0.4 ^d	ND	No
Topiramate	Topamax	Twice	100–400	3–9	5–25	No
Vigabatrin	Sabril	Twice	3000–6000	50–150	ND	Yes
Zonisamide	Zonegran	1 or 2 times	200–400	4–12	10–40	No

CR = extended-release, ER = extended-release, ODT = orally disintegrating tablet, XR = extended-release.

^aND = not determined.

^bTarget serum level is 5 to 15 mcg/mL for primidone itself, and 15 to 40 mcg/mL for phenobarbital derived from primidone.

^cDosage must be decreased in patients taking valproic acid.

^dDosage must be increased in patients taking drugs that induce hepatic drug-metabolizing enzymes.

^eOxcarbazepine does not induce enzymes that metabolize AEDs, but does induce enzymes that metabolize other drugs.

^fRufinamide produces mild induction of CYP3A4.

decision to discontinue treatment has been made, agreement does exist on how drug withdrawal should be accomplished. The most important rule is that *AEDs be withdrawn slowly* (over a period of 6 weeks to several months). Failure to gradually reduce dosage is a frequent cause of SE. If the patient is taking two drugs to control seizures, they should be withdrawn sequentially, not simultaneously.

Suicide Risk with Antiepileptic Drugs

In 2008, the Food and Drug Administration (FDA) warned that all AEDs can increase suicidal thoughts and behavior. However, data gathered since 2008 suggest that the risk may

be lower than previously believed, and may apply only to certain AEDs.

The FDA based its warning on data from 199 placebo-controlled studies involving 11 different AEDs taken by 43,892 patients being treated for epilepsy, psychiatric disorders, and various pain disorders. After analyzing these data, the FDA concluded that, compared with patients taking a placebo, patients taking AEDs had twice the risk of suicidal thoughts and behaviors (0.43% vs. 0.22%). The reason underlying the increased risk was unknown. Of note, risk was higher among patients taking AEDs for epilepsy than among patients taking these drugs for other conditions, such as migraine, neuropathic pain, or psychiatric illness. Although the

analysis was limited to 11 drugs, the FDA applied their warning to *all* AEDs. However, in the FDA's own analysis, the association between suicide and AED use had statistical significance with just two drugs: topiramate and lamotrigine. Furthermore, with two other drugs—valproic acid and carbamazepine—their analysis showed some *protection* against suicidality.

Since the FDA issued its warning, other large studies have been conducted to clarify the relationship between AEDs and suicidality. Unfortunately, these studies have yielded conflicting results. Nonetheless, they do suggest three things. First, only some AEDs—especially topiramate and lamotrigine—are likely to increase suicidality, not all AEDs as warned by the FDA. Second, the risk of suicidal behavior may be related more to the illness than the medication: By analyzing data on 5,130,795 patients, researchers in the United Kingdom found that AEDs produced a small increase in suicidal behavior in patients with *depression*, but did *not* increase suicidal behavior in patients with *epilepsy* or *bipolar disorder*. And third, even if AEDs do promote suicidality, AED-related suicide attempts and completed suicides are very rare.

Given the uncertainty regarding AEDs and suicidality, what should the clinician do? Because epilepsy itself carries a risk for suicide, and because patients with epilepsy often have depression and/or anxiety (which increase the risk of suicide), prudence dictates screening all patients for suicide risk, whether or not AEDs increase that risk. In addition, once treatment begins, all patients should be monitored for increased anxiety, agitation, mania, and hostility—signs that may indicate the emergence or worsening of depression, and an increased risk of suicidal thoughts or behavior. Patients, families, and caregivers should be alerted to these signs and advised to report them immediately. Finally, two AEDs—topiramate and lamotrigine—should be used with special caution, given their significant association with suicidality.

CLASSIFICATION OF ANTIEPILEPTIC DRUGS

The AEDs can be grouped into two major categories: *traditional AEDs* and *newer AEDs*. The traditional group has six major members, the last of which—valproic acid—was approved in 1978. The group of newer AEDs has thirteen members, all of which were approved in 1993 or later. As summarized in Table 24-3, both groups have their advantages and disadvantages. For example, clinical experience with the older AEDs is more extensive than with the newer ones, and the older drugs cost less. Both facts make the older drugs attractive. However, the older AEDs also have drawbacks, including troublesome side effects and complex drug interactions. Of importance, drugs in both groups appear equally effective—although few direct comparisons have been made. The bottom line? Neither group is clearly superior to the other. Hence, when selecting an AED, drugs in both groups should be considered.

TRADITIONAL ANTIEPILEPTIC DRUGS

The traditional AEDs have been in use for many years. Anti-seizure properties of phenobarbital, the oldest member of the group, were demonstrated in 1912. Even the youngest member—valproic acid—has been in use for over three decades.

TABLE 24-3 • Comparison of Traditional and Newer Antiepileptic Drugs

Area of Comparison	AED Group	
	Traditional AEDs*	Newer AEDs†
Efficacy	Well established	Equally good (probably), but less well established
Clinical experience	Extensive	Less extensive
Therapeutic niche	Well established	Evolving
Tolerability	Less well tolerated	Better tolerated (usually)
Pharmacokinetics	Often complex	Less complex
Drug interactions	Extensive, owing to induction of drug-metabolizing enzymes	Limited, owing to little or no induction of drug-metabolizing enzymes
Safety in pregnancy	Less safe	Safer
Cost	Less expensive	More expensive

*Carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid.

†Gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide.

Because of this extensive clinical experience, the efficacy and therapeutic niche of the traditional AEDs are well established. As a result, these drugs are prescribed more widely than the newer AEDs. In the discussion below, we focus on six of the traditional AEDs: phenytoin, carbamazepine, valproic acid, ethosuximide, phenobarbital, and primidone. The group has other members, but they are less important.

Although familiarity makes the traditional AEDs appealing, these drugs do have drawbacks. In general, they are less well tolerated than the newer AEDs, and they pose a greater risk to the developing fetus. Furthermore, owing to effects on drug-metabolizing enzymes (either induction or inhibition), they have complex interactions with other drugs, including other AEDs.

Phenytoin

Phenytoin [Dilantin, Phenytek] is our most widely used AED, despite having tricky kinetics and troublesome side effects. The drug is active against partial seizures as well as primary generalized tonic-clonic seizures. Phenytoin is of historic importance in that it was the first drug to suppress seizures without depressing the entire CNS. Hence, phenytoin heralded the development of selective medications that could treat epilepsy while leaving most CNS functions undiminished.

Mechanism of Action

At the concentrations achieved clinically, phenytoin causes selective inhibition of sodium channels. Specifically, the drug slows recovery of sodium channels from the inactive state back to the active state. As a result, entry of sodium into neu-

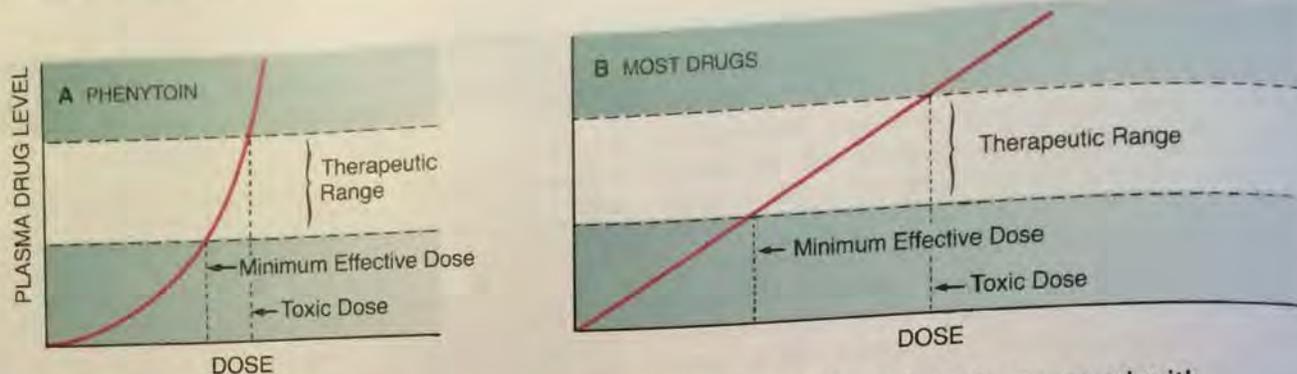


Figure 24-1 ■ Relationship between dose and plasma level for phenytoin compared with most other drugs.

A. Within the therapeutic range, small increments in phenytoin dosage produce sharp increases in plasma drug levels. This relationship makes it difficult to maintain plasma phenytoin levels within the therapeutic range. **B.** Within the therapeutic range, small increments in dosage of most drugs produce small increases in drug levels. With this relationship, moderate fluctuations in dosage are unlikely to result in either toxicity or therapeutic failure.

rons is inhibited, and hence action potentials are suppressed. Blockade of sodium entry is limited to neurons that are hyperactive. As a result, the drug suppresses activity of seizure-generating neurons while leaving healthy neurons unaffected.

Pharmacokinetics

Phenytoin has unusual pharmacokinetics that must be accounted for in therapy. Absorption varies substantially among patients. In addition, because of saturable kinetics, small changes in dosage can produce disproportionately large changes in serum drug levels. As a result, a dosage that is both effective and safe is difficult to establish.

Absorption. Absorption varies between the different oral formulations of phenytoin. With the oral suspension and chewable tablets absorption is relatively fast, whereas with the extended-release capsules absorption is delayed and prolonged.

In the past, there was concern that absorption also varied between preparations of phenytoin made by different manufacturers. However, it is now clear that all FDA-approved equivalent products have equivalent bioavailability. As a result, switching from one brand of phenytoin to another produces no more variability than switching between different lots of phenytoin produced by the same manufacturer.

Metabolism. The capacity of the liver to metabolize phenytoin is very limited. As a result, the relationship between dosage and plasma levels of phenytoin is unusual. Doses of phenytoin needed to produce therapeutic effects are only slightly smaller than the doses needed to saturate the hepatic enzymes that metabolize phenytoin. Consequently, if phenytoin is administered in doses only slightly greater than those needed for therapeutic effects, the liver's capacity to metabolize the drug will be overwhelmed, causing plasma levels of phenytoin to rise dramatically. This unusual relationship between dosage and plasma levels is illustrated in Figure 24-1A. As you can see, once plasma levels have reached the therapeutic range, small changes in dosage produce large changes in plasma levels. As a result, small increases in dosage can cause toxicity, and small decreases can cause therapeutic failure. This relationship makes it difficult to establish and maintain a dosage that is both safe and effective.

Figure 24-1B indicates the relationship between dosage and plasma levels that exists for most drugs. As indicated, this relationship is *linear*; in contrast to the nonlinear relationship that exists for phenytoin. Accordingly, for most drugs, if the patient is taking doses that produce plasma levels that are within the therapeutic range, small deviations from that dosage produce only small deviations in plasma drug levels. Because of this relationship, with most drugs it is relatively easy to maintain plasma levels that are safe and effective.

Because of saturation kinetics, the half-life of phenytoin varies with dosage. At low doses, the half-life is relatively short—about 8 hours. However, at higher doses, the half-life becomes prolonged—in some cases up to 60 hours. Why? Because, at higher doses, there is more drug present than the liver can process. As a result, metabolism is delayed, causing the half-life to increase.

Therapeutic Uses

Epilepsy. Phenytoin can be used to treat all major forms of epilepsy except absence seizures. The drug is especially effective against tonic-clonic seizures, and is a drug of choice for treating these seizures in adults and older children. (Carbamazepine is preferred to phenytoin for treating tonic-clonic seizures in young children.) Although phenytoin can be used to treat simple and complex partial seizures, the drug is less effective against these seizures than against tonic-clonic seizures. Phenytoin can be administered IV to treat generalized convulsive SE, but other drugs are preferred.

Cardiac Dysrhythmias. Phenytoin is active against certain types of dysrhythmias. Antidysrhythmic applications are discussed in Chapter 49.

Adverse Effects

Effects on the CNS. Although phenytoin acts on the CNS in a relatively selective fashion to suppress seizures, the drug is not completely devoid of CNS side effects—especially when dosage is excessive. At therapeutic levels (10 to 20 mcg/mL), sedation and other CNS effects are mild. At plasma levels above 20 mcg/mL, toxicity can occur. Nystagmus (continuous back-and-forth movements of the eyes) is relatively

common. Other manifestations of excessive dosage include sedation, ataxia (staggering gait), diplopia (double vision), and cognitive impairment.

Gingival Hyperplasia. Gingival hyperplasia (excessive growth of gum tissue) is characterized by swelling, tenderness, and bleeding of the gums. In extreme cases, patients require gingivectomy (surgical removal of excess gum tissue). Gingival hyperplasia is seen in about 20% of patients. Can risk be reduced? Yes. Recent evidence indicates that supplemental folic acid (0.5 mg/day) may prevent gum overgrowth. In addition, risk can be minimized by good oral hygiene, including dental flossing and gum massage. Patients should be taught these techniques and encouraged to practice them.

Dermatologic Effects. Between 2% and 5% of patients develop a morbilliform (measles-like) rash. Rarely, morbilliform rash progresses to much more severe reactions: *Stevens-Johnson syndrome* (SJS) or *toxic epidermal necrolysis* (TEN). According to a 2008 alert from the FDA, the risk of developing SJS/TEN may be increased by a genetic mutation known as *human leukocyte antigen (HLA)-B*1502*, which occurs almost exclusively in people of Asian descent. However, data in support of this association are preliminary. As discussed below, vulnerability to SJS/TEN in patients taking another AED—carbamazepine—is clearly linked to HLA-B*1502. Because of this clear association, and because of the possible association between phenytoin-induced SJS/TEN and HLA-B*1502, patients with the mutation should definitely avoid carbamazepine, and should probably avoid phenytoin too. At this time, the FDA recommends testing for HLA-B*1502 in Asian patients taking carbamazepine, but not yet for Asian patients taking phenytoin.

Effects in Pregnancy. Phenytoin is a teratogen in animals and humans. In animals, the drug can cause cleft palate, hydrocephalus, renal defects, and micromelia (small or shortened limbs). In humans, phenytoin can cause cleft palate, heart malformations, and *fetal hydantoin syndrome*, characterized by growth deficiency, motor or mental deficiency, microcephaly, craniofacial distortion, positional deformities of the limbs, hypoplasia of the nails and fingers, and impaired neurodevelopment. Because of these effects, phenytoin is classified in FDA Pregnancy Category D, and hence should be used during pregnancy only if the benefits of seizure control are deemed to outweigh the risk to the fetus.

Phenytoin can decrease synthesis of vitamin K-dependent clotting factors, and can thereby cause *bleeding tendencies in newborns*. The risk of neonatal bleeding can be decreased by giving the mother prophylactic vitamin K for 1 month prior to and during delivery, and to the infant immediately after delivery.

Cardiovascular Effects. When phenytoin is administered by IV injection (to treat SE), cardiac dysrhythmias and hypotension may result. These dangerous responses can be minimized by injecting phenytoin slowly and in dilute solution.

Purple Glove Syndrome. Very rarely, IV phenytoin has been associated with purple glove syndrome, a painful condition characterized by swelling and discoloration of the hands and arms.

Other Adverse Effects. Hirsutism (overgrowth of hair in unusual places) can be a disturbing response, especially in young women. Interference with vitamin D metabolism may cause *rickets* and *osteomalacia* (softening of the bones). Interference with vitamin K metabolism can lower prothrombin levels, thereby causing *bleeding tendencies in newborns*. Very rarely, *liver damage* occurs, probably because of drug allergy.

Drug Interactions

Phenytoin interacts with a large number of drugs. The more important interactions are discussed below.

Interactions Resulting from Induction of Hepatic Drug-Metabolizing Enzymes. Phenytoin stimulates synthesis of hepatic drug-metabolizing enzymes. As a result, phenytoin can decrease the effects of other drugs, including *oral contraceptives*, *warfarin* (an anticoagulant), and *glucocorticoids* (anti-inflammatory/immunosuppressive drugs). Because avoiding pregnancy is desirable while taking antiseizure medications, and because phenytoin can decrease the effectiveness of oral contraceptives, women should increase the contraceptive dosage, or switch to an alternative form of contraception.

Drugs That Increase Plasma Levels of Phenytoin. Since the therapeutic range of phenytoin is narrow, slight increases in phenytoin levels can cause toxicity. Consequently, caution must be exercised when phenytoin is used with drugs that can increase its level. Drugs known to elevate phenytoin levels include *diazepam* (an antianxiety agent and AED), *isoniazid* (a drug for tuberculosis), *cimetidine* (a drug for gastric ulcers), and *alcohol* (when taken acutely). These agents increase phenytoin levels by reducing the rate at which phenytoin is metabolized. *Valproic acid* (an AED) elevates levels of free phenytoin by displacing phenytoin from binding sites on plasma proteins.

Drugs That Decrease Plasma Levels of Phenytoin. *Carbamazepine*, *phenobarbital*, and *alcohol* (when used chronically) can accelerate the metabolism of phenytoin, thereby decreasing its level. Breakthrough seizures can result.

CNS Depressants. The depressant effects of *alcohol*, *barbiturates*, and *other CNS depressants* will add with those of phenytoin. Advise patients to avoid alcohol and all other drugs with CNS-depressant actions.

Preparations, Dosage, and Administration

Preparations. Phenytoin [Dilantin, Phenytek] is available in solution for injection and in three oral formulations: (1) chewable tablets (50-mg), marketed as *Dilantin Infatab*; (2) an oral suspension (125 mg/5 mL), marketed as *Dilantin-125*; and extended-release capsules (30, 100, 200, and 300 mg), marketed as *Dilantin* and *Phenytek*. Phenytoin products made by different manufacturers have equivalent bioavailability. Hence, although switching between products from different manufacturers was a concern in the past, it is not a concern today.

Dosage. Dosing is highly individualized. Initial doses are usually given twice daily. Once a maintenance dosage has been established, once-a-day dosing is often possible (using extended-release capsules). For *adults*, a typical initial dosage is 100 to 125 mg 3 times a day; maintenance dosages usually range between 300 and 400 mg/day. For *children*, a typical initial dosage is 2.5 mg/kg twice a day; maintenance dosages usually range between 4 and 8 mg/kg/day.

Plasma drug levels are often monitored as an aid to establishing dosage. *The dosing objective is to produce levels between 10 and 20 mcg/mL.* Levels below 10 mcg/mL are too low to control seizures; levels above 20 mcg/mL produce toxicity. Because phenytoin has a relatively narrow therapeutic range (between 10 and 20 mcg/mL), and because of the nonlinear relationship between phenytoin dosage and phen-

ytoin plasma levels, *once a safe and effective dosage has been established, the patient should adhere to it rigidly.*

When treatment is discontinued, dosage should be reduced gradually. Abrupt withdrawal may precipitate seizures.

Administration. Oral preparations may cause gastric discomfort. Patients should be informed that gastric upset can be reduced by administering phenytoin with or immediately after a meal. Patients using the oral suspension should shake it well before dispensing, since failure to do so can result in uneven dosing.

Intravenous administration is used to treat generalized convulsive SE. *It is imperative that infusions be performed slowly* (no faster than 50 mg/min). Why? Because rapid administration can cause cardiovascular collapse. Phenytoin should not be added to an existing IV infusion, since mixing phenytoin with other solutions is likely to produce a precipitate. Solutions of phenytoin are highly alkaline and can cause local venous irritation. Irritation can be reduced by flushing the IV needle or catheter with sterile saline immediately after completing the infusion.

Carbamazepine

Carbamazepine [Tegretol, Tegretol-XR, Tegretol CR \clubsuit , Carbatrol, Epitol, Equetro] is a cornerstone of epilepsy therapy. The drug is active against partial seizures and tonic-clonic seizures but not absence seizures.

Mechanism of Action

Carbamazepine suppresses high-frequency neuronal discharge in and around seizure foci. The mechanism appears to be the same as that of phenytoin: delayed recovery of sodium channels from their inactivated state.

Pharmacokinetics

Absorption of carbamazepine is delayed and variable. Levels peak 4 to 12 hours after dosing. Overall bioavailability is about 80%. The drug distributes well to tissues.

Elimination is by hepatic metabolism. Carbamazepine is unusual in that its half-life decreases as therapy progresses. During the initial phase of treatment, the half-life is about 40 hours. With continued treatment, the half-life decreases to about 15 hours. Why? Because carbamazepine, like phenytoin and phenobarbital, induces hepatic drug-metabolizing enzymes; by increasing its own metabolism, carbamazepine causes its own half-life to decline.

Therapeutic Uses

Epilepsy. Carbamazepine is effective against tonic-clonic, simple partial, and complex partial seizures. Because the drug causes fewer adverse effects than phenytoin and phenobarbital, it is often preferred to these agents. Many prescribers consider carbamazepine the drug of first choice for partial seizures. Carbamazepine is not effective against absence, myoclonic, or atonic seizures.

Bipolar Disorder. Carbamazepine can provide symptomatic control in patients with bipolar disorder (manic-depressive illness), and is often effective in patients who are refractory to lithium. The role of carbamazepine in bipolar disorder is discussed in Chapter 33.

Trigeminal and Glossopharyngeal Neuralgias. A neuralgia is a severe, stabbing pain that occurs along the course of a nerve. Carbamazepine can reduce neuralgia associated with the trigeminal and glossopharyngeal nerves. The mechanism is unknown. It should be noted that, although carbamazepine can reduce pain in these specific neuralgias, it is not generally effective as an analgesic, and is not indicated for other kinds of pain.

Adverse Effects

CNS Effects. In contrast to phenytoin and phenobarbital, carbamazepine has minimal effects on cognitive function. This is a primary reason for selecting carbamazepine over these other drugs.

Carbamazepine can cause a variety of *neurologic effects*, including visual disturbances (nystagmus, blurred vision, diplopia), ataxia, vertigo, unsteadiness, and headache. These reactions are common during the first weeks of treatment, affecting 35% to 50% of patients. Fortunately, tolerance usually develops with continued use. These effects can be minimized by initiating therapy at low doses and giving the largest portion of the daily dose at bedtime.

Hematologic Effects. Carbamazepine-induced bone marrow suppression can cause *leukopenia, anemia, and thrombocytopenia*. However, serious reactions are rare. Thrombocytopenia and anemia, which have an incidence of 5%, respond to drug discontinuation. Leukopenia, which has an incidence of 10%, is usually transient and subsides even with continued drug use. Accordingly, carbamazepine should not be withdrawn unless the white blood cell count drops below 3000/mm³.

Fatal *aplastic anemia* has occurred during carbamazepine therapy. This reaction is extremely rare, having an incidence of 1 in 200,000. Very few cases have been reported since 1964, and in many of these, a direct cause-and-effect relationship could not be established.

To reduce the risk of serious hematologic effects, complete blood counts should be performed before treatment and periodically thereafter. Patients with pre-existing hematologic abnormalities should not use this drug. Patients should be informed about manifestations of hematologic abnormalities (fever, sore throat, pallor, weakness, infection, easy bruising, petechiae) and instructed to notify the prescriber if these occur.

Birth Defects. Carbamazepine is teratogenic. In humans, the drug is associated with a 2.6-fold increase in the risk of spina bifida, a neural tube defect. In mice, the drug can cause cleft palate, dilated cerebral ventricles, and growth retardation. Because it can harm the fetus, carbamazepine is classified in FDA Pregnancy Risk Category D, and hence should be used only if the benefits of seizure control are deemed to outweigh risks to the fetus.

Hypo-Osmolarity. Carbamazepine can inhibit renal excretion of water, apparently by promoting secretion of antidiuretic hormone. Water retention can reduce the osmolarity of blood and other body fluids, thereby posing a threat to patients with heart failure. Periodic monitoring of serum sodium content is recommended.

Dermatologic Effects. Carbamazepine has been associated with several dermatologic effects, including morbilliform rash (10% incidence), photosensitivity reactions, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Mild reactions can often be treated with prednisone (an anti-inflammatory agent) or an antihistamine. Severe reactions—SJS and TEN—necessitate drug withdrawal.

A major risk factor for SJS/TEN is HLA-B*1502, a genetic variation seen primarily in people of Asian descent. Among people with the variant gene, about 5% develop SJS/TEN with carbamazepine. Accordingly, to reduce the risk of severe reactions, the FDA recommends that, before receiving carbamazepine, patients of Asian descent be tested for HLA-B*1502. Of note, this was the first time that the FDA recom-

mended genetic screening for a major drug. As discussed above, the presence of HLA-B*1502 may also increase the risk of SJS/TEN in patients taking phenytoin. Accordingly, phenytoin should not be used as an alternative to carbamazepine in patients with the mutation.

Drug-Drug and Drug-Food Interactions

Induction of Drug-Metabolizing Enzymes. Carbamazepine induces hepatic drug-metabolizing enzymes, and hence can increase the rate at which it and other drugs are inactivated. Accelerated inactivation of *oral contraceptives* and *warfarin* is of particular concern.

Phenytoin and Phenobarbital. Both phenytoin and phenobarbital induce hepatic drug metabolism. Hence, if either drug is taken with carbamazepine, induction of metabolism is likely to be greater than with carbamazepine alone. Accordingly, phenytoin and phenobarbital can further accelerate the metabolism of carbamazepine, thereby decreasing its effects.

Grapefruit Juice. As discussed in Chapter 6, grapefruit juice can inhibit the metabolism of many drugs, thereby causing their plasma levels to rise. Grapefruit juice can increase peak and trough levels of carbamazepine by 40%. Advise patients to avoid grapefruit juice.

Preparations, Dosage, and Administration

Carbamazepine [Tegretol, Tegretol-XR, Tegretol CR \clubsuit , Carbatrol, Eptol, Equitro] is available in immediate-release tablets (200 mg), sold as *Tegretol* and *Eptol*; chewable tablets (100 mg), sold as *Tegretol*; extended-release tablets (100, 200, and 400 mg), sold as *Tegretol-XR* and *Tegretol CR \clubsuit* ; extended-release capsules (200 and 300 mg), sold as *Carbatrol* and *Equetro*; and an oral suspension (20 mg/mL), sold as *Tegretol*. The drug should be administered with meals to reduce gastric upset. Administering the largest portion of the daily dose at bedtime can help reduce adverse CNS effects. Carbamazepine suspension should not be administered with other liquid-formulation medicines.

To minimize side effects, dosage is low initially (100 to 200 mg twice a day) and then increased gradually (every 1 to 3 weeks) until seizure control is achieved. Maintenance dosages for *adults* range from 600 to 1800 mg/day, administered in divided doses. Maintenance dosages for *children* range from 10 to 35 mg/kg/day, administered in divided doses.

Valproic Acid

Valproic acid [Depakene, Depakote, Depacon, Stavzor, Epival \clubsuit] is an important AED used widely to treat all major seizure types. Although generally very safe, valproic acid has caused rare cases of severe hepatotoxicity and pancreatitis, both of which can be fatal. Also, the drug is highly teratogenic, and should not be used during pregnancy. In addition to its use in epilepsy, valproic acid is used for bipolar disorder and migraine headache.

Nomenclature

Valproic acid is available in three closely related chemical forms (Table 24-4): (1) valproic acid itself, (2) the sodium salt of valproic acid, known as *valproate*, and (3) *divalproex sodium*, a combination of valproic acid plus its sodium salt. All three forms have identical antiseizure actions. In this chapter, the term *valproic acid* is used in reference to all three.

Mechanism of Action

Valproic acid appears to act by three mechanisms. First, it shares the same mechanism as phenytoin and carbamazepine: suppression of high-frequency neuronal firing through blockade of sodium channels. Second, it suppresses calcium influx through T-type calcium channels. Third, it may augment the inhibitory influence of GABA.

Pharmacokinetics

Valproic acid is readily absorbed from the GI tract and is widely distributed throughout the body. The drug undergoes extensive hepatic metabolism followed by renal excretion.

Therapeutic responses are often seen at plasma levels of 40 to 100 mcg/mL. However, the correlation between plasma levels and therapeutic effects is not very tight.

Therapeutic Uses

Seizure Disorders. Valproic acid is considered a first-line drug for all partial and generalized seizures.

Bipolar Disorder. Like carbamazepine, valproic acid can provide symptomatic control in patients with bipolar disorder (manic-depressive illness). This application is discussed in Chapter 33.

TABLE 24-4 ■ Oral Preparations of Valproic Acid and Its Derivatives

Chemical Form	Trade Name	Product Description	Comments
Valproic acid	Depakene	Capsules (250 mg)	Immediate release; GI upset is common.
	Stavzor	Capsule, delayed-release, enteric-coated (125, 250, 500 mg)	Capsule is smaller than Depakene and Depakene ER tablets, and hence easier to swallow. Enteric coating may reduce GI upset, but there are no clinical data to show that Stavzor is better tolerated than Depakene.
Valproate sodium	Depakene	Syrup (250 mg/5 mL)	Immediate release; GI upset is common.
Divalproex sodium	Depakote, Epival \clubsuit	Tablets, delayed-release, enteric-coated (125, 250, 500 mg)	Released over 8–12 hr, and hence <i>not</i> for once-daily administration. <i>Not interchangeable with Depakote ER</i> (extended-release tablets) because rate of drug release is different. Less GI upset than Depakene.
		Tablets, extended-release, enteric-coated (250 and 500 mg)	Released over 18–24 hr, and hence <i>can</i> be administered once daily. <i>Not interchangeable with regular Depakote</i> (delayed-release tablets) because rate of drug release is different. Not approved for epilepsy (but used anyway). Less GI upset than Depakene.
	Depakote	"Sprinkle" capsules containing enteric-coated granules (125 mg)	Immediate release. Less GI upset than Depakene. May swallow capsule whole or open and sprinkle granules on a small amount (1 tsp) of soft food.

Migraine. Valproic acid is approved for prophylaxis of migraine (see Chapter 30).

Adverse Effects

Valproic acid is generally well tolerated and causes minimal sedation and cognitive impairment. Gastrointestinal effects are most common. Hepatotoxicity and pancreatitis are rare but serious. Owing to teratogenic effects, valproic acid should be avoided during pregnancy.

Gastrointestinal Effects. Nausea, vomiting, and indigestion are common but transient. These effects are most intense with formulations that are not enteric coated. Gastrointestinal reactions can be minimized by administering valproic acid with food and by using an enteric-coated product (see Table 24-4).

Hepatotoxicity. Rarely, valproic acid has been associated with fatal liver failure. Most deaths have occurred within the first few months of therapy. The overall incidence of fatal hepatotoxicity is about 1 in 40,000. However, in high-risk patients—children under the age of 2 years receiving multi-drug therapy—the incidence is much higher: 1 in 500. To minimize the risk of fatal liver injury, the following guidelines have been established:

- Don't use valproic acid in conjunction with other drugs in children under 2 years old.
- Don't use valproic acid in patients with pre-existing liver dysfunction.
- Evaluate liver function at baseline and periodically thereafter. (Unfortunately, monitoring liver function may fail to provide advance warning of severe hepatotoxicity: Fatal liver failure can develop so rapidly that it is not preceded by an abnormal test result.)
- Inform patients about signs and symptoms of liver injury (reduced appetite, malaise, nausea, abdominal pain, jaundice) and instruct them to notify the prescriber if these develop.
- Use valproic acid in the lowest effective dosage.

Pancreatitis. Life-threatening pancreatitis may develop in children and adults. Some cases have been hemorrhagic, progressing rapidly from initial symptoms to death. Pancreatitis can develop soon after starting therapy or following years of drug use. Patients should be informed about signs of pancreatitis (abdominal pain, nausea, vomiting, anorexia) and instructed to obtain immediate evaluation if these develop. If pancreatitis is diagnosed, valproic acid should be withdrawn, and alternative medication should be substituted as indicated.

Pregnancy-Related Harm. Valproic acid is highly teratogenic, especially when taken during the first trimester. The risk of a major congenital malformation (MCM) is 4 times higher than with other AEDs. Neural tube defects (eg, spina bifida) are the greatest concern. The risk is 1 in 20 among women taking valproic acid, versus 1 in 1000 among women in the general population. In addition to neural tube defects, valproic acid can cause five other MCMs: atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis.

Exposure to valproic acid *in utero* can impair cognitive function, as shown by interim results of the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, issued in 2010. Children exposed to valproic acid had IQ scores that were significantly lower than those of children exposed to other AEDs (carbamazepine, phenytoin, or lamotrigine).

These deficits persist for at least 4.5 years, and perhaps longer (the NEAD study is still ongoing).

Valproic acid is classified in FDA Pregnancy Risk Category D, and should be avoided by women of child-bearing potential—unless it is the only AED that will work. Women who must use the drug should use an effective form of contraception, and should take folic acid supplements (5 mg/day), which can help protect against neural tube damage in case pregnancy occurs.

Hyperammonemia. Combining valproic acid with topiramate poses a risk of hyperammonemia (excessive ammonia in the blood), which may occur with or without encephalopathy. Symptoms include vomiting, lethargy, altered level of consciousness, and altered cognitive function. If these symptoms develop, hyperammonemic encephalopathy should be suspected, and blood ammonia should be measured. As a rule, symptoms abate following removal of either drug.

Other Adverse Effects. Valproic acid may cause rash, weight gain, hair loss, tremor, and blood dyscrasias (leukopenia, thrombocytopenia, red blood cell aplasia). Significant CNS effects are uncommon.

Drug Interactions

Phenobarbital. Valproic acid decreases the rate at which phenobarbital is metabolized. Blood levels of phenobarbital may rise by 40%, resulting in significant CNS depression. When the combination is used, levels of phenobarbital should be monitored and, if they rise too high, phenobarbital dosage should be reduced.

Phenytoin. Valproic acid can displace phenytoin from binding sites on plasma proteins. The resultant increase in free phenytoin may lead to toxicity. Phenytoin levels and clinical status should be monitored.

Topiramate. See discussion of *Hyperammonemia* above.

Carbapenem Antibiotics. Two carbapenem antibiotics—meropenem and imipenem/cilastatin—can reduce plasma levels of valproic acid. Breakthrough seizures have occurred. Of note, increasing the dosage of valproic acid may be insufficient to overcome this effect. Accordingly, meropenem and imipenem/cilastatin should be avoided in patients taking valproic acid.

Preparations, Dosage, and Administration

Preparations. Valproic acid is available in several oral formulations (see Table 24-4) and in a 100-mg/mL solution [Depacon] for IV use.

Oral Dosage and Administration. Daily doses are small initially and then gradually increased. For *adults and older children*, the initial dosage is 5 to 15 mg/kg/day, usually administered in two divided doses. The usual maintenance dosage is 0.75 to 3 gm/day. For *children ages 1 to 12 years*, the initial dosage is 10 to 30 mg/kg/day, usually administered in divided doses. The usual maintenance dosage is 15 to 45 mg/kg/day. For both adults and children, the dosage should be increased if phenobarbital or another inducer of hepatic drug metabolism is taken concurrently.

Patients should be instructed to swallow the tablets and capsules intact, without chewing or crushing. Gastric discomfort can be decreased by administering valproic acid with meals and by using an enteric-coated formulation.

Ethosuximide

Therapeutic Use. Ethosuximide [Zarontin] is the drug of choice for absence seizures, the only indication it has. Absence seizures are abolished in 60% of patients, and, in newly diagnosed patients, practical control is achieved in 80% to 90%. In a trial reported in 2010, which compared ethosuximide with lamotrigine and valproic acid, ethosuximide was more effective than lamotrigine, and better tolerated than valproic acid; seizure reduction with ethosuximide and valproic acid was the same.

Mechanism of Action. Ethosuximide suppresses neurons in the thalamus that are responsible for generating absence seizures. The specific mechanism is inhibition of low-threshold calcium currents, known as T currents. Ethosuximide does not block sodium channels and does not enhance GABA-mediated neuronal inhibition.

Pharmacokinetics. Ethosuximide is well absorbed following oral administration. Therapeutic plasma levels range between 40 and 100 mcg/mL.

The drug is eliminated by a combination of hepatic metabolism and renal excretion. Its half-life is 60 hours in adults and 30 hours in children. Ethosuximide does not induce drug-metabolizing enzymes.

Adverse Effects and Drug Interactions. Ethosuximide is generally devoid of significant adverse effects and interactions. During initial treatment, it may cause *drowsiness*, *dizziness*, and *lethargy*. These diminish with continued use. *Nausea* and *vomiting* may occur and can be reduced by administering the drug with food. Rare but serious reactions include *systemic lupus erythematosus*, *leukopenia*, *aplastic anemia*, and *Stevens-Johnson syndrome*.

Preparations, Dosage, and Administration. Ethosuximide [Zarontin] is available in capsules (250 mg), a syrup (250 mg/5 mL), and oral solution (250 mg/5 mL). For children ages 3 to 6 years, the initial dosage is 250 mg/day. For older children and adults, the initial dosage is 500 mg/day. Dosage should be gradually increased until seizure control is obtained. The usual maintenance dosage is 750 mg/day for adults, and between 15 and 40 mg/kg/day for children. Because ethosuximide has a long half-life, dosing can be done just once a day. However, dosing twice a day is better tolerated.

Since absence seizures occur many times each day, monitoring the clinical response rather than plasma drug levels is the preferred method for dosage determination. Dosage should be increased until seizures have been controlled or until adverse effects become too great.

When withdrawing ethosuximide, dosage should be reduced gradually.

Phenobarbital

Phenobarbital is one of our oldest AEDs. The drug is effective and inexpensive, and can be administered just once a day. Unfortunately, certain side effects—lethargy, depression, learning impairment—can be significant. Hence, although phenobarbital was used widely in the past, it has largely been replaced by newer drugs that are equally effective but better tolerated.

Phenobarbital belongs to the barbiturate family. However, in contrast to most barbiturates, which produce generalized depression of the CNS, phenobarbital is able to suppress seizures at doses that produce only moderate disruption of CNS function. Because it can reduce seizures without causing sedation, phenobarbital is classified as an *anticonvulsant barbiturate* (to distinguish it from most other barbiturates, which are employed as daytime sedatives or “sleeping pills”).

The basic pharmacology of the barbiturates is discussed in Chapter 34. Discussion here is limited to the use of phenobarbital for seizures.

Mechanism of Antiseizure Action

Phenobarbital suppresses seizures by potentiating the effects of GABA. Specifically, the drug binds to GABA receptors, causing the receptors to respond more intensely to GABA itself.

Pharmacokinetics

Phenobarbital is administered orally, and absorption is complete. Elimination occurs through hepatic metabolism and renal excretion. Phenobarbital has a long half-life—about 4 days. As a result, once-daily dosing is adequate for most patients. In addition to permitting once-daily dosing, the long half-life has another consequence: 2 to 3 weeks are required for plasma levels to reach plateau. (Recall that, in the absence of a loading dose, an interval equivalent to four half-lives is required to reach plateau.)

Therapeutic Uses

Epilepsy. Phenobarbital is effective against partial seizures and generalized tonic-clonic seizures but not absence seizures. In the past, phenobarbital was a drug of choice for tonic-clonic seizures and partial seizures in older children and adults. However, most clinicians now prefer to treat these epilepsies with carbamazepine, phenytoin, or valproic acid—drugs that cause less neurologic effects than phenobarbital. Intravenous phenobarbital can be used for generalized convulsive SE, but lorazepam and phenytoin are preferred.

Sedation and Induction of Sleep. Like other barbiturates, phenobarbital can be used for daytime sedation and to promote sleep at night. These applications are discussed in Chapter 34.

Adverse Effects

Neuropsychologic Effects. Drowsiness is the most common CNS effect. During the initial phase of therapy, sedation develops in practically all patients. With continued treatment, tolerance to sedation develops. Some children experience paradoxical responses: Instead of becoming sedated, they may become irritable and hyperactive. Depression may occur in adults. Elderly patients may experience agitation and confusion.

Physical Dependence. Like all other barbiturates, phenobarbital can cause physical dependence. However, at the doses employed to treat epilepsy, significant dependence is unlikely.

Exacerbation of Intermittent Porphyrria. Phenobarbital and other barbiturates can increase the risk of acute intermittent porphyria. Accordingly, barbiturates are absolutely contraindicated for patients with a history of this disorder. The relationship of barbiturates to intermittent porphyria is discussed further in Chapter 34.

Use in Pregnancy. Use of phenobarbital during pregnancy poses a significant risk of major fetal malformations. Women who take phenobarbital during pregnancy or become pregnant while taking the drug should be informed of the potential risk to the fetus.

Like phenytoin, phenobarbital can decrease synthesis of vitamin K-dependent clotting factors, and can thereby cause *bleeding tendencies in newborns*. The risk of neonatal bleeding can be decreased by administering vitamin K to the mother for 1 month prior to delivery and during delivery, and to the infant immediately after delivery.

Other Adverse Effects. Like phenytoin, phenobarbital can interfere with the metabolism of vitamins D and K. Disruption of vitamin D metabolism can cause *rickets* and *osteomalacia*.

Toxicity

When taken in moderately excessive doses, phenobarbital causes nystagmus and ataxia. Severe overdose produces generalized CNS depression; death results from depression of respiration. Barbiturate toxicity and its treatment are discussed at length in Chapter 34.

Drug Interactions

Induction of Drug-Metabolizing Enzymes. Phenobarbital induces hepatic drug-metabolizing enzymes, and can thereby accelerate the metabolism of other drugs, causing a loss of therapeutic effects. This is of particular concern with oral contraceptives and warfarin.

CNS Depressants. Being a CNS depressant itself, phenobarbital can intensify CNS depression caused by other drugs (eg, alcohol, benzodiazepines, opioids). Severe respiratory depression and coma could result. Patients should be warned against combining phenobarbital with other drugs that have CNS-depressant actions.

Valproic Acid. Valproic acid is an AED that has been used in combination with phenobarbital. By competing with phenobarbital for drug-metabolizing enzymes, valproic acid can increase plasma levels of phenobarbital by approximately 40%. Hence, when this combination is used, the dosage of phenobarbital must be reduced.

Drug Withdrawal

When phenobarbital is withdrawn, dosage should be reduced gradually, since abrupt withdrawal can precipitate SE. Patients should be warned of this danger and instructed not to discontinue phenobarbital too quickly.

Preparations, Dosage, and Administration

Preparations. Phenobarbital is available in three oral formulations—tablets, capsules, and elixir—and in solution (as *Luminal*) for IM and IV administration.

Dosage. *Adult* maintenance dosages range from 60 to 120 mg/day administered as a single dose or two divided doses. *Pediatric* maintenance dosages range from 3 to 6 mg/kg/day. When dosage is being established, plasma drug levels may be used as a guide; target levels are 15 to 45 mcg/mL.

Loading doses may be needed. Because phenobarbital has a long half-life, several weeks are required for drug levels to reach plateau. If plateau must be reached sooner, a loading schedule can be employed. For example, doses that are twice normal can be given for 4 days. Unfortunately, these large doses are likely to produce substantial CNS depression.

Administration. Phenobarbital may be administered PO, IV, or IM. Oral administration is employed for routine therapy. Intravenous administration is needed for SE. Intramuscular administration is used only when oral dosing is not feasible.

Intravenous injection must be done slowly. If done too fast, excessive CNS depression may result. Phenobarbital is highly alkaline and may cause local tissue injury if extravasation occurs.

Primidone

Primidone [Mysoline] is active against all major seizure disorders except absence seizures. The drug is nearly identical in structure to phenobarbital. As a result, the pharmacology of both agents is very similar.

Pharmacokinetics. Primidone is readily absorbed following oral dosing. In the liver, much of the drug undergoes conversion to two active metabolites: phenobarbital and phenylethylmalonamide. Seizure control is produced by primidone itself and by its metabolites. Therapeutic plasma levels range from 5 to 15 mcg/mL.

Therapeutic Uses. Primidone is effective against tonic-clonic, simple partial, and complex partial seizures. The drug is not active against absence seizures.

As a rule, primidone is employed in combination with another AED, usually phenytoin or carbamazepine. Primidone is never taken together with phenobarbital. Why? Because phenobarbital is an active metabolite of primidone, and hence concurrent use would be irrational.

Adverse Effects. Sedation, ataxia, and dizziness are common during initial treatment but diminish with continued drug use. Like phenobarbital, primidone can cause confusion in the elderly and paradoxical hyperexcitability in children. A sense of acute intoxication can occur shortly after dosing. As with phenobarbital, primidone is absolutely contraindicated for patients with acute intermittent porphyria. Serious adverse reactions (acute psychosis, leukopenia, thrombocytopenia, systemic lupus erythematosus) can occur but are rare.

Drug Interactions. Drug interactions for primidone are similar to those for phenobarbital. Primidone can induce hepatic drug-metabolizing enzymes and can thereby reduce the effects of oral contraceptives, warfarin, and other drugs. In addition, primidone can intensify responses to other CNS depressants.

Preparations, Dosage, and Administration. Primidone [Mysoline] is available in 50- and 250-mg tablets. For adults, dosage is low initially (100 to 125 mg at bedtime) and then gradually increased over the next 10 days to a maintenance level of 250 mg 2 or 3 times a day. The maximum dosage is 500 mg 4 times a day.

NEWER ANTIEPILEPTIC DRUGS

The group of newer AEDs has thirteen members. The oldest of these—gabapentin—was introduced in 1993, and the most recent—ezogabine—was introduced in 2011. Although most newer AEDs have not been compared directly with the traditional AEDs (or with each other, for that matter), all of these drugs appear equally effective. However, because clinical experience with the newer drugs is still limited, they are prescribed less often than the traditional AEDs. Oxcarbazepine and lamotrigine are the primary exceptions to this rule.

Do the newer AEDs have properties that make them appealing? Certainly. As a group, they are better tolerated than the traditional AEDs, and may pose a smaller risk to the developing fetus. Furthermore, only one—oxcarbazepine—induces drug-metabolizing enzymes to a significant degree, and hence interactions with other drugs, including other AEDs, are relatively minor.

The subject of approved indications for the newer AEDs requires comment. When these drugs were introduced, FDA-approved indications were limited to *adjunctive* therapy of certain seizure disorders. None of these drugs was approved for *monotherapy*. Why? Because clinical trials were limited to patients who were refractory to traditional AEDs. When the trials were conducted, rather than switching patients from a traditional AED to the experimental AED, the experimental AED was *added* to the existing regimen. Hence, when the trials were completed, all we knew for sure was that the new AED was effective when used together with an older AED. We had no data on use of the newer AED alone. As a result, the FDA had no option but to approve the new drug for *adjunctive* therapy. Since being released, several of the newer AEDs have received FDA approval for monotherapy.

To help prescribers be more comfortable with the newer AEDs, two organizations—the American Academy of Neurology (AAN) and American Epilepsy Society (AES)—convened a panel to evaluate the efficacy and tolerability of these drugs. For some of the newer AEDs, the AAN/AES panel recommended uses not yet approved by the FDA. These recommendations, along with FDA-approved indications, are discussed below.

Oxcarbazepine

Actions and Uses. Oxcarbazepine [Trileptal], a derivative of carbamazepine, is indicated for monotherapy and adjunctive therapy of partial seizures in adults and children. The drug is as effective as carbamazepine and better tolerated. However, it's also more expensive. Antiseizure effects result from blockade of voltage-sensitive sodium channels in neuronal membranes, an action that stabilizes hyperexcitable neurons and thereby suppresses seizure spread. The drug does not affect neuronal GABA receptors.

Pharmacokinetics. Oxcarbazepine is well absorbed both in the presence and absence of food. In the liver, the drug undergoes rapid conversion to a 10-monohydroxy metabolite (MHD), its active form. MHD has a half-life of 9 hours and undergoes excretion in the urine.

Adverse Effects. The most common adverse effects are dizziness (22% to 49%), drowsiness (19% to 36%), double vision (14% to 40%), nystagmus (7% to 26%), headache (13% to 32%), nausea (15% to 29%), vomiting (7% to 36%), and ataxia (5% to 31%). Patients should avoid driving and other hazardous activities, unless the degree of drowsiness is low.

Clinically significant *hyponatremia* (sodium concentration below 125 mmol/L) develops in 2.5% of patients. Signs include nausea, drowsiness, headache, and confusion. If oxcarbazepine is combined with other drugs that can decrease sodium levels (especially diuretics), monitoring of sodium levels may be needed.

Like carbamazepine, oxcarbazepine can cause *serious skin reactions*, including Stevens-Johnson syndrome and toxic epidermal necrolysis. There is 30% cross sensitivity among patients with hypersensitivity to carbamazepine. Accordingly, patients with a history of severe reactions to either drug should probably not use the other.

Oxcarbazepine has not caused the severe hematologic abnormalities seen with carbamazepine. Accordingly, routine monitoring of blood counts is not required.

Oxcarbazepine has been associated with serious *multiorgan hypersensitivity reactions*. Although manifestations vary, patients typically present with fever and rash, associated with one or more of the following: lymphadenopathy, hematologic abnormalities, pruritus, hepatitis, nephritis, hepatorenal syndrome, oliguria, arthralgia, or asthenia. If this reaction is suspected, oxcarbazepine should be discontinued.

Use in Pregnancy and Breast-Feeding. Like carbamazepine (FDA Pregnancy Risk Category D), oxcarbazepine (FDA Pregnancy Risk Category C) may pose a risk of birth defects. Accordingly, women of child-bearing age should use effective contraception. Clearly, the drug should be avoided by women who are already pregnant. In addition, since both oxcarbazepine and its metabolite are excreted in breast milk, the drug should be avoided by women who are breast-feeding.

Drug Interactions. Oxcarbazepine induces some drug-metabolizing enzymes and inhibits others. It does not induce

enzymes that metabolize other AEDs. However, it does induce enzymes that metabolize *oral contraceptives*, and can thereby render them less effective. Accordingly, women should employ an alternative birth control method.

Oxcarbazepine inhibits the enzymes that metabolize phenytoin, and can thereby raise phenytoin levels. Toxicity can result. Phenytoin levels should be monitored and dosage adjusted accordingly.

Drugs that induce drug-metabolizing enzymes (eg, phenytoin, phenobarbital, carbamazepine) can reduce levels of MHD, the active form of oxcarbazepine. Accordingly, dosage of oxcarbazepine may need to be increased.

Alcohol can intensify CNS depression caused by oxcarbazepine, and hence should be avoided.

As noted, oxcarbazepine should be used with caution in patients taking *diuretics* and other drugs that can lower sodium levels.

Preparations, Dosage, and Administration. Oxcarbazepine [Tripletal] is available in film-coated tablets (150, 300, and 600 mg) and an oral suspension (60 mg/mL).

For *monotherapy in adults*, the initial dosage is 300 mg twice daily. The maximum dosage is 1200 mg twice daily.

For *adjunctive therapy in adults*, the initial dosage is 300 mg twice daily. The maximum dosage is 600 mg twice daily.

For *monotherapy in children* (ages 4 to 16), the initial dosage is 8 to 10 mg/kg/day in two divided doses. Maintenance dosages are related to body weight (see manufacturer's recommendations).

For *adjunctive therapy in children* (ages 2 to 16), the initial dosage is 8 to 10 mg/kg/day in two divided doses. Maintenance dosages are related to body weight: For children weighing 20 to 29 kg, the dosage is 900 mg/day; for children weighing 29.1 to 30 kg, the dosage is 1200 mg/day; and for children weighing above 39 kg, the dosage is 1800 mg/day.

Lamotrigine

Therapeutic Uses. Lamotrigine [Lamictal], introduced in 1994, has a broad spectrum of antiseizure activity. The drug is FDA approved for (1) adjunctive therapy of partial seizures in adults and children over 2 years old, (2) adjunctive therapy of generalized seizures associated with Lennox-Gastaut syndrome in adults and children over 2 years old, (3) adjunctive therapy of primary generalized tonic-clonic seizures in adults and children over 2 years old, and (4) monotherapy of partial seizures in patients at least 13 years old who are converting from another AED. In addition, the AAN/AES guidelines recommend using lamotrigine for absence seizures. LAES guidelines also FDA approved for long-term maintenance therapy of bipolar disorder (see Chapter 33). Investigational uses include myoclonic, absence, and temporal lobe seizures.

Mechanism of Action. Benefits derive mainly from blocking sodium channels and partly from blocking calcium channels. Both actions decrease release of glutamate, an excitatory neurotransmitter.

Pharmacokinetics. Administration is oral, and absorption is nearly complete, both in the presence and absence of food. Blood levels peak 1.5 to 5 hours after dosing and decline with a half-life of 24 hours. The drug undergoes hepatic metabolism followed by renal excretion.

Drug Interactions. The half-life is dramatically affected by drugs that induce or inhibit hepatic drug-metabolizing enzymes. Enzyme inducers (eg, carbamazepine, phenytoin, phenobarbital) decrease the half-life of lamotrigine to 10 hours, whereas valproate (an enzyme inhibitor) increases the half-life to about 60 hours. Lamotrigine itself is not an inducer or inhibitor of drug metabolism.

Adverse Effects. Common side effects include *dizziness, diplopia (double vision), blurred vision, nausea, vomiting, and headache*. Of much greater concern, patients may develop severe skin reactions or aseptic meningitis, as discussed immediately below.

Lamotrigine can cause *life-threatening rashes*, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Deaths have occurred. The incidence of severe rash is about 0.8% in patients under 16 years old and 0.3% in adults. Concurrent use of valproic acid increases risk. If rash develops, lamotrigine should be withdrawn immediately.

Very rarely, patients experience *aseptic meningitis* (inflammation of the meninges in the absence of bacterial infection). Patients who develop symp-

ptoms of meningitis—headache, fever, stiff neck, nausea, vomiting, rash, sensitivity to light—should undergo immediate evaluation to determine the cause. Treatable causes should be managed as indicated. If no clear cause other than lamotrigine is identified, discontinuation of lamotrigine should be considered.

Risk for *suicide* may be greater than with most other AEDs. Screen patients for suicidality before starting treatment, and monitor for suicidality during the treatment course.

When used during pregnancy, lamotrigine may pose a small risk of *cleft lip and cleft palate*. Whether the drug poses other risks in pregnancy or in breast-feeding has not been determined.

Preparations, Dosage, and Administration. Lamotrigine is available in immediate-release tablets (25, 100, 150, and 200 mg) sold as *Lamictal*, chewable dispersible tablets (2, 5, 25, 50, 100, and 200 mg) sold as *Lamictal*, orally disintegrating tablets (25, 50, 100, and 200 mg) sold as *Lamictal ODT*, and extended-release tablets (25, 50, 100, and 200 mg) sold as *Lamictal XR*. To reduce the risk of serious rash, dosage is low initially and then gradually increased. The initial dose depends on which other AEDs are being taken. For patients taking an *inducer* of drug metabolism (eg, carbamazepine, phenytoin, phenobarbital), the dosage is 50 mg/day initially, and then gradually increased to between 150 and 500 mg twice a day for maintenance. For patients taking *valproate* (an inhibitor of drug metabolism), dosing is begun at 25 mg every other day, and then gradually increased to between 50 and 75 mg twice daily for maintenance (using an immediate-release formulation).

Gabapentin

Therapeutic Uses. Gabapentin [Neurontin, Gralise], introduced in 1993, has a broad spectrum of antiseizure activity. However, its only FDA-approved use in epilepsy is adjunctive therapy of partial seizures (with or without secondary generalization). The AAN/AES guidelines also recommend the drug for monotherapy of partial seizures. In 2002, gabapentin was approved for treating postherpetic neuralgia. Interestingly, more than 80% of prescriptions are written for off-label uses, including relief of neuropathic pain (other than postherpetic neuralgia), prophylaxis of migraine, treatment of fibromyalgia, and relief of postmenopausal hot flashes. However, benefits in these disorders are modest, at best. Gabapentin does not appear effective in bipolar disorder.

Mechanism of Action. Gabapentin's precise mechanism of action is unknown. The drug is an analog of GABA, but does not directly affect GABA receptors. Rather, it may enhance GABA release, thereby increasing GABA-mediated inhibition of neuronal firing.

Pharmacokinetics. Gabapentin is rapidly absorbed following oral dosing and reaches peak plasma levels in 2 to 3 hours. Absorption is not affected by food. However, as the dosage gets larger, the percentage absorbed gets smaller. Why? Because at high doses, the intestinal transport system for uptake of the drug becomes saturated. Gabapentin is not metabolized and is excreted intact in the urine. Its half-life is 5 to 7 hours.

Drug Interactions. Unlike most AEDs, gabapentin is devoid of significant interactions. It doesn't induce or inhibit drug-metabolizing enzymes, and doesn't affect the metabolism of other drugs. As a result, gabapentin is well suited for combined use with other AEDs.

Adverse Reactions. Gabapentin is very well tolerated. The most common side effects are somnolence, dizziness, ataxia, fatigue, nystagmus, and peripheral edema. These are usually mild to moderate and often diminish with continued drug use. Patients should avoid driving and other hazardous activities until they are confident they are not impaired. Safety in pregnancy and breast-feeding has not been established.

Preparations, Dosage, and Administration. Gabapentin, sold as Neurontin, is available in capsules (100, 300, and 400 mg), immediate-release tablets (600 and 800 mg), and an oral solution (50 mg/mL). For adults with *epilepsy*, treatment begins with a 300-mg dose at bedtime, followed the next day by 600 mg (in two divided doses), and the next day by 900 mg (in three divided doses). Thereafter, the dosage can be raised rapidly to maintenance levels, typically 1200 to 3600 mg/day in three divided doses. Dosage should be reduced in patients with renal impairment.

Gabapentin extended-release tablets (300 and 600 mg), sold as Gralise, are approved only for *postherpetic neuralgia*. Dosing is done once daily with the evening meal. Doses are low initially and then gradually increased to 1800 mg/day for maintenance. Owing to differences in pharmacokinetics, Gralise tablets are not interchangeable with other gabapentin products.

Gabapentin Enacarbil

In 2011, the FDA approved *gabapentin enacarbil* [Horizant], a prodrug form of gabapentin, for treatment of moderate to severe *restless legs syndrome*, but not for epilepsy or neuropathic pain. Following ingestion, gabap-

entin enacarbil undergoes rapid hepatic conversion to gabapentin, its active form. The most common adverse effects are lethargy (20% to 27%) and dizziness (13% to 22%). Accordingly, patients should be warned against driving and other hazardous activities. Gabapentin enacarbil is supplied in 600-mg extended-release tablets. The usual dosage is 600 mg once daily, taken with the evening meal. Owing to differences in pharmacokinetics, gabapentin enacarbil is not interchangeable with other gabapentin products.

Pregabalin

Pregabalin [Lyrica], an analog of GABA, is much like gabapentin. Like gabapentin, pregabalin is used for seizures and neuropathic pain. In addition, pregabalin is approved for fibromyalgia. Pregabalin has very few interactions with other drugs, but adverse effects are common, especially dizziness and sleepiness. In contrast to most other antiseizure agents, pregabalin is regulated under the Controlled Substances Act. The drug was introduced in 2005.

Therapeutic Uses. Pregabalin has four approved indications: neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, adjunctive therapy of partial seizures, and fibromyalgia. Of the four indications, fibromyalgia deserves special comment. The disorder is a chronic condition characterized by generalized muscle pain, fatigue, and disturbed sleep. In 2007, pregabalin became the first drug approved for treatment. Unfortunately, benefits are modest. In clinical trials, pregabalin produced a 50% reduction in pain in 28% of patients, compared with 13% of patients taking placebo. Also, for many patients with fibromyalgia, benefits fade within weeks or months. Fibromyalgia is discussed further in Chapter 107.

Mechanism of Action. Although the precise mechanism of action has not been established, we do know that pregabalin can bind with calcium channels on nerve terminals, and can thereby inhibit calcium influx, which in turn can inhibit release of several neurotransmitters, including glutamate, norepinephrine, and substance P. Reduced transmitter release may underlie seizure control and relief of neuropathic pain. Although pregabalin is an analog of GABA, the drug does not bind with GABA receptors or with benzodiazepine receptors, and hence does not work by mimicking or enhancing the inhibitory actions of GABA.

Pharmacokinetics. Pregabalin is well absorbed after oral dosing. Plasma levels peak in 1.5 hours. Food reduces the rate of absorption but not the extent. Oral bioavailability is 90% or greater. Pregabalin does not bind with plasma proteins, but does cross the blood-brain and placental barriers. Elimination is renal, 98% as unchanged drug. Metabolism is negligible. The half-life is 6.3 hours.

Adverse Effects. Pregabalin can cause a variety of adverse effects. The most common are *dizziness* (29%) and *somnolence* (22%), which often persist as long as the drug is being taken. *Blurred vision* (6%) develops early, but resolves with continued drug use. About 8% of patients experience significant *weight gain* (7% or more of body weight in just a few months). Other adverse effects include *difficulty thinking* (6%), *headache* (5%), *peripheral edema* (6%), and *dry mouth* (4%).

Postmarketing reports indicate a risk of *hypersensitivity reactions*, including life-threatening *angioedema*, characterized by swelling of the face, tongue, lip, gums, throat, and larynx. Patients should discontinue pregabalin immediately at the first sign of angioedema, or any other hypersensitivity reaction (blisters, hives, rash, dyspnea, wheezing).

In clinical trials, three patients developed *rhabdomyolysis* (muscle breakdown). However, it is not clear that pregabalin was the cause. Nonetheless, patients should be instructed to report signs of muscle injury (pain, tenderness, weakness). If rhabdomyolysis is diagnosed, or even suspected, pregabalin should be withdrawn.

Abuse Potential and Physical Dependence. In clinical trials, 4% to 12% of patients reported euphoria as a side effect. When given to recreational users of sedative-hypnotic drugs, pregabalin produced subjective effects perceived as similar to those of diazepam [Valium]. On the basis of these data, the Drug Enforcement Agency has classified pregabalin under Schedule V of the Controlled Substances Act.

Abrupt discontinuation can cause insomnia, nausea, headache, diarrhea, and other symptoms that suggest physical dependence. To avoid withdrawal symptoms, pregabalin should be discontinued slowly, over 1 week or more.

Reproductive Toxicity. Pregabalin has adverse effects on reproduction and development when taken by females or males.

When given to pregnant female rats and rabbits, pregabalin caused fetal growth retardation, fetal death, structural abnormalities (eg, skeletal and visceral malformation), and impaired function of the nervous system and reproductive system. Data on human reproduction are lacking. At this time, pregabalin is classified in FDA Pregnancy Risk Category C. Animal studies show a risk of fetal harm, but no controlled studies in women have been done.

When given to male rats prior to and during mating with untreated females, pregabalin decreased sperm counts and motility, decreased fertility, reduced fetal weight, and caused fetal abnormalities. Men using the drug should be informed about the possibility of decreased fertility and male-mediated teratogenicity.

Drug Interactions. Alcohol, opioids, benzodiazepines, and other CNS depressants may intensify the depressant effects of pregabalin. Accordingly, such combinations should be avoided.

Extensive studies have failed to show pharmacokinetic interactions with any other drugs. Pregabalin does not inhibit cytochrome P450 isozymes. Whether it can induce these isozymes is unknown. Pregabalin does not interact with oral contraceptives, and does not alter the kinetics of any antiseizure drugs studied (carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid, and tiagabine).

Preparations, Dosage, and Administration. Pregabalin [Lyrica] is available in solution (20 mg/mL) and capsules (25, 50, 75, 100, 150, 200, 225, and 300 mg) for oral dosing with or without food. Dosage depends on the indication. For patients with renal impairment, dosage should be reduced. When pregabalin is discontinued, dosage should be gradually tapered, over 1 week or longer.

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy. Dosing is begun at 150 mg/day (50 mg 3 times a day) and may be increased in a week, as needed and tolerated, to a maintenance level of 300 mg/day (100 mg 3 times a day). Dosages above 300 mg/day are unlikely to increase benefits but will increase the risk of adverse effects.

Postherpetic Neuralgia. Dosing should begin at 150 mg/day (75 mg twice daily or 50 mg 3 times a day) and may be increased, as needed and tolerated, to the usual maintenance level of 300 mg/day (150 mg twice daily or 100 mg 3 times a day). For patients with significant pain after 2 to 4 weeks at 300 mg/day, dosage may be increased to a maximum of 600 mg/day (300 mg twice daily or 200 mg 3 times a day).

Epilepsy. Dosing is the same as for postherpetic neuralgia, with a maximum dosage of 600 mg/day.

Fibromyalgia. Dosing begins at 75 mg twice daily, and may be increased to 225 mg twice daily, if tolerated. Doses above this level increase the risk of side effects, but offer no increase in benefits.

Levetiracetam

Levetiracetam [Keppra], introduced in 1999, is a unique agent that is chemically and pharmacologically different from all other AEDs. How levetiracetam acts is unknown. All we do know is that it does not bind to receptors for GABA or any other known neurotransmitter. In the United States, the drug is approved for adjunctive therapy of (1) myoclonic seizures in adults and adolescents age 12 years and older, (2) partial-onset seizures in adults and children age 4 years and older, and (3) primary generalized tonic-clonic seizures in adults and children age 6 years and older. Unlabeled uses include migraine, bipolar disorder, and new-onset pediatric epilepsy. In Europe, the drug is approved for monotherapy of partial seizures, for which it is highly effective.

Following oral dosing, levetiracetam undergoes rapid and complete absorption both in the presence and absence of food. Metabolism is minimal and not mediated by hepatic P450 enzymes. Levetiracetam is excreted in the urine, largely (66%) unchanged.

Adverse effects are generally mild to moderate. The most common are drowsiness (14.8%) and asthenia (14.7%). Neuropsychiatric symptoms (agitation, anxiety, depression, psychosis, hallucinations, depersonalization) occur in less than 1% of patients. In contrast to other AEDs, levetiracetam does not impair speech, concentration, or other cognitive functions. Safety for use during pregnancy or breast-feeding has not been determined.

Unlike most other AEDs, levetiracetam does not interact with other drugs. It does not alter plasma concentrations of oral contraceptives, warfarin, digoxin, or other AEDs. Given that levetiracetam is not metabolized by P450 enzymes, its lack of interactions is no big surprise.

Levetiracetam, under the trade name *Keppra*, is available in immediate-release tablets (250, 500, 750, and 1000 mg), an oral solution (100 mg/mL), and a solution for IV injection (100 mg/mL). In addition, the drug is available in extended-release tablets (500 mg), sold as *Keppra XR*. With all oral formulations, the initial adult dosage is 500 mg twice daily, and the maximum dosage is 3000 mg/day. Because levetiracetam is eliminated by the kidneys, dosage should be reduced in patients with significant renal impairment.

Topiramate

Actions and Uses. Topiramate [Topamax], introduced in 1996, is another broad-spectrum antiseizure agent. The drug is FDA approved for (1) adjunctive treatment of adults and children 2 years and older with

tial seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome; (2) *monotherapy* of adults and children 10 years and older with partial seizures or primary generalized tonic-clonic seizures; and (3) prophylaxis of migraine in adults (see Chapter 30). Seizure reduction occurs by four mechanisms: (1) potentiation of GABA-mediated inhibition, (2) blockade of voltage-dependent sodium channels, (3) blockade of calcium channels, and (4) blockade of receptors for glutamate, an excitatory neurotransmitter. Unlabeled uses include bipolar disorder, cluster headaches, neuropathic pain, infantile spasms, alcohol and cocaine dependence, binge-eating disorder, bulimia nervosa, and weight loss.

Pharmacokinetics. With oral administration, absorption is rapid and not affected by food. Plasma levels peak 2 hours after dosing. Most of the drug is eliminated unchanged in the urine.

Adverse Effects. Although topiramate is generally well tolerated, it can cause multiple adverse effects. Common effects include somnolence (30%), dizziness (28%), ataxia (21%), nervousness (20%), diplopia (15%), nausea (13%), anorexia (12%), and weight loss (12%). Cognitive effects (confusion, memory difficulties, altered thinking, reduced concentration, difficulty finding words) can occur, but the incidence is low at recommended dosages. Kidney stones and paresthesias occur rarely.

Topiramate can cause *metabolic acidosis*. The drug inhibits carbonic anhydrase, and thereby increases renal excretion of bicarbonate, which causes plasma pH to fall. Hyperventilation is the most characteristic symptom. Mild to moderate metabolic acidosis develops in 30% of adult patients, but severe acidosis is rare. Risk factors include renal disease, severe respiratory disorders, diarrhea, and a ketogenic diet (see Box 24-1). Prolonged metabolic acidosis can lead to kidney stones, fractures, and growth retardation. Serum bicarbonate should be measured at baseline and periodically thereafter. Advise patients to inform the prescriber if they experience hyperventilation and other symptoms (fatigue, anorexia). If metabolic acidosis is diagnosed, topiramate should be given in reduced dosage or discontinued.

Topiramate can cause *hypohidrosis* (reduced sweating), thereby posing a risk of hyperthermia. Significant hyperthermia is usually associated with vigorous activity and an elevated environmental temperature.

There have been case reports of *angle-closure glaucoma*. Left untreated, this rapidly leads to blindness. Patients should be informed about symptoms of glaucoma (ocular pain, unusual redness, sudden worsening or blurring of vision) and instructed to seek immediate attention if these develop. Fortunately, topiramate-induced glaucoma is rare.

When taken during the first trimester of pregnancy, topiramate increases the risk of two *birth defects*: cleft lip and cleft palate. Although the *relative* risk seems high (a 20-fold increase), the *absolute* risk is still low (between 0.07% and 1.4%). Topiramate is classified in FDA Pregnancy Category D, and hence should be used only if the benefits of maternal seizure control are deemed to outweigh the risk to the fetus. Women using topiramate should use an effective form of birth control, or should switch to a safer antiseizure drug if pregnancy is intended.

Risk for *suicide* may be greater than with most other AEDs. Screen patients for suicidality before starting treatment, and monitor for suicidality during the treatment course.

Drug Interactions. Phenytoin and carbamazepine can decrease levels of topiramate by about 45%. Topiramate may increase levels of phenytoin.

Preparations, Dosage, and Administration. Topiramate [Topamax] is available in tablets (25, 50, 100, and 200 mg) and "sprinkle" capsules (15 and 25 mg). *Adult* dosing is begun at 50 mg/day and then gradually increased to 200 mg twice daily for maintenance. *Pediatric* dosing is begun at 25 mg (or less) per day and gradually increased to 3 to 9 mg/kg/day administered in two divided doses. Advise patients not to break the tablets because bitter taste will result. The capsules can be swallowed whole or opened and sprinkled onto a small amount (1 tsp) of soft food.

Tiagabine

Actions and Uses. Tiagabine [Gabitril], introduced in 1997, is FDA approved only for adjunctive therapy of partial seizures in patients at least 12 years old. The drug blocks reuptake of GABA by neurons and glia. As a result, the inhibitory influence of GABA is intensified, and seizures are suppressed. Off-label uses include migraine prophylaxis, bipolar disorder, and insomnia. However, owing to a risk of seizures (see below), such off-label use is discouraged.

Pharmacokinetics. Tiagabine has uncomplicated kinetics. Administration is oral. Absorption is rapid and nearly complete. Food reduces the rate of absorption but not the extent. Plasma levels peak about 45 minutes after dosing. In the blood, tiagabine is highly (96%) bound to plasma proteins. Elimination is by hepatic metabolism followed by excretion

in the bile and, to a lesser extent, the urine. The serum half-life is 7 to 9 hours.

Adverse Effects. Tiagabine is generally well tolerated. Common adverse effects are dizziness (27%), somnolence (18%), asthenia (20%), nausea (11%), nervousness (10%), and tremor (9%). Like most other AEDs, tiagabine can cause dose-related cognitive effects (eg, confusion, abnormal thinking, trouble concentrating).

Tiagabine has *caused* seizures in some patients—but only in those using the drug off-label (ie, those using the drug for a condition other than epilepsy). A few patients have developed status epilepticus, which can be life threatening. In most cases, seizures occurred soon after starting tiagabine or after increasing the dosage. Because of seizure risk, off-label use of tiagabine should be avoided. Why are people without epilepsy at risk? Possibly because they are not taking AEDs. Remember, tiagabine is approved only for adjunctive use with other AEDs. It may be that these drugs protect against tiagabine-induced seizures. Since people without epilepsy take tiagabine by itself, they are not protected from seizure development.

Drug Interactions. Tiagabine does not alter the metabolism or serum concentrations of other AEDs. However, levels of tiagabine can be decreased by phenytoin, phenobarbital, and carbamazepine—all of which induce drug-metabolizing enzymes.

Preparations, Dosage, and Administration. Tiagabine [Gabitril] is available in tablets (2, 4, 12, and 16 mg) for oral dosing with food. The initial dosage for adults and children is 4 mg once a day. Dosage can be increased by 4 to 8 mg/day at weekly intervals. The maximum daily dose, administered in two to four divided doses, is 56 mg for adults and 32 mg for children under age 18 years. Dosage should be increased in patients taking drugs that can accelerate tiagabine metabolism.

Zonisamide

Actions and Uses. Zonisamide [Zonegran], introduced in 2000, is approved only for adjunctive therapy of partial seizures in adults. The drug belongs to the same chemical family as the sulfonamide antibiotics, but lacks antimicrobial activity. In animal models, zonisamide suppresses focal seizure activity and spread. The underlying mechanism appears to be blockade of neuronal sodium channels and calcium channels.

Pharmacokinetics. Zonisamide undergoes rapid absorption from the GI tract. Bioavailability is nearly 100%, both in the presence and absence of food. In the blood, zonisamide is extensively bound to erythrocytes. As a result, its concentration in erythrocytes is 8 times higher than in plasma. Zonisamide is metabolized in the liver by the 3A4 isozyme of cytochrome P450 (CYP3A4). Excretion occurs in the urine, in the form of zonisamide itself (30%) and metabolites. The plasma half-life is 63 hours.

Adverse Effects. The most common adverse effects are drowsiness (17%), dizziness (13%), anorexia (13%), headache (10%), and nausea (9%). As discussed below, metabolic acidosis is also common. Like most other AEDs, zonisamide can impair speech, concentration, and other cognitive processes. Because the drug can reduce alertness and impair cognition, patients should avoid driving and other hazardous activities until they know how the drug affects them.

Zonisamide can have severe *psychiatric effects*. During clinical trials, 2.2% of patients either discontinued treatment or were hospitalized because of severe depression; 1.1% attempted suicide. Development of psychosis caused another 2.2% to stop treatment.

Like all other sulfonamides, zonisamide can trigger *hypersensitivity reactions*, including some that are potentially fatal (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis). Accordingly, zonisamide is contraindicated for patients with a history of sulfonamide hypersensitivity. Patients who develop a rash should be followed closely, because rash can evolve into a more serious event. If severe hypersensitivity reactions, zonisamide should be withdrawn immediately. Fortunately, serious reactions and fatalities are rare.

Zonisamide has adverse effects on the kidneys. In clinical trials, about 4% of patients developed *nephrolithiasis* (kidney stones). The risk can be reduced by drinking 6 to 8 glasses of water a day (to maintain hydration and urine flow). Patients should be informed about signs of kidney stones (sudden back pain, abdominal pain, painful urination, bloody or dark urine) and instructed to report them immediately. In addition to nephrolithiasis, zonisamide can *impair glomerular filtration*. Because of its effects on the kidney, zonisamide should be used with caution in patients with kidney disease.

Like topiramate, zonisamide inhibits carbonic anhydrase, and can thereby cause *metabolic acidosis*. The condition develops in up to 90% of children and 43% of adults, usually early in treatment. Risk is increased by renal disease, respiratory disease, diarrhea, and following a ketogenic diet. Metabolic acidosis can retard growth in children, and, over time, can lead to kidney

stones and fractures in all patients. Advise patients to report hyperventilation and other signs of metabolic acidosis (eg, fatigue, anorexia). Determine plasma bicarbonate at baseline and periodically thereafter. If metabolic acidosis is diagnosed, zonisamide should be discontinued, or given in reduced dosage.

Rarely, zonisamide causes *hypohidrosis* (decreased sweating) and *hyperthermia* (elevation of body temperature). Pediatric patients may be at special risk. In warm weather, hypohidrosis may lead to heat stroke and subsequent hospitalization. Patients should be monitored closely for reduced sweating and increased body temperature.

Use in Pregnancy and Breast-Feeding. Zonisamide is teratogenic and embryolethal in laboratory animals. Cardiovascular abnormalities are common. Women of child-bearing age should use effective contraception. Zonisamide is classified in FDA Pregnancy Risk Category C, and hence should be avoided during pregnancy unless the benefits to the mother are deemed to outweigh the potential risks to the fetus. We do not know if zonisamide enters breast milk. Until more is known, prudence dictates that women who are breast-feeding should not take the drug.

Drug and Food Interactions. Levels of zonisamide can be affected by agents that induce or inhibit CYP3A4. Inducers of CYP3A4—including St. John's wort (an herbal supplement used for depression) and several AEDs (eg, phenytoin, phenobarbital, carbamazepine)—can accelerate the metabolism of zonisamide, and can thereby reduce the drug's half-life (to as little as 27 hours). Conversely, inhibitors of CYP3A4—including grapefruit juice, azole antifungal agents (eg, ketoconazole), and several protease inhibitors (eg, ritonavir)—can slow the metabolism of zonisamide, and thereby prolong and intensify its effects.

Preparations, Dosage, and Administration. Zonisamide [Zonegran] is available in capsules (25, 50, and 100 mg). The initial dosage is 100 mg once daily. The maximum dosage is 600 mg/day in one or two divided doses.

Felbamate

Felbamate [Felbatol], introduced in 1993, is an effective AED with a broad spectrum of antiseizure activity. Unfortunately, the drug has potentially fatal adverse effects: aplastic anemia and liver failure. Accordingly, use is restricted to patients with severe epilepsy refractory to all other therapy.

Mechanism of Action. Felbamate increases seizure threshold and suppresses seizure spread. The underlying mechanism is unknown. Unlike some AEDs, such as phenobarbital and benzodiazepines, felbamate does not interact with GABA receptors and does not enhance the inhibitory actions of GABA.

Pharmacokinetics. Felbamate is well absorbed following oral dosing, both in the presence and absence of food. Plasma levels peak in 1 to 4 hours. The drug readily penetrates to the CNS. Although therapeutic plasma levels have not been established, levels of 20 to 120 mcg/mL have been measured during clinical trials. Felbamate is eliminated in the urine, primarily unchanged. Its half-life is 14 to 23 hours.

Therapeutic Uses. Felbamate is approved for (1) adjunctive or monotherapy in adults with partial seizures (with or without generalization), and (2) adjunctive therapy in children with Lennox-Gastaut syndrome. However, because of toxicity, use of the drug is very limited.

Adverse Effects. Felbamate can cause *aplastic anemia* and *liver damage*. Aplastic anemia has occurred in at least 21 patients, 3 of whom died. Acute liver failure occurred in 8 patients, 4 of whom died. Because of the risk of liver failure, felbamate should not be used by patients with pre-existing liver dysfunction. In addition, patients taking the drug should be monitored for indications of liver injury.

The most common adverse effects are GI disturbances (anorexia, nausea, vomiting) and CNS effects (insomnia, somnolence, dizziness, headache, diplopia). These occur more frequently when felbamate is combined with other drugs.

Drug Interactions. Felbamate can alter plasma levels of other AEDs and vice versa. Felbamate increases levels of phenytoin and valproic acid. Levels of felbamate are increased by valproic acid and reduced by phenytoin and carbamazepine. Increased levels of phenytoin and valproic acid (and possibly felbamate) could lead to toxicity; reduced levels of felbamate could lead to therapeutic failure. Therefore, to keep levels of these drugs within the therapeutic range, their levels should be monitored and dosages adjusted accordingly.

Preparations, Dosage, and Administration. Felbamate [Felbatol] is available in tablets (400 and 600 mg) and an oral suspension (120 mg/mL). For *older children* (over 14 years old) and *adults*, the initial dosage is 1200 mg/day in three divided doses, and the maximum dosage is 3600 mg/day in three di-

vided doses. For *younger children* (2 to 14 years old), the initial dosage is 15 mg/kg/day in three divided doses, and the maximum dosage is 45 mg/kg/day or 3600 mg/day, whichever is less, administered in three divided doses.

Lacosamide

Actions and Uses. Lacosamide [Vimpat], approved in 2008, is indicated for add-on therapy of partial-onset seizures in patients age 17 years and older. Benefits appear to derive from slow inactivation of sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and subsequent inhibition of repetitive firing. In patients with refractory partial-onset seizures, adding lacosamide to the regimen reduced seizure frequency by 50% or more in roughly 40% of those treated. Compared with other drugs for partial-onset seizures, lacosamide has two advantages. First, it has few drug interactions. Second, it can be administered IV as well as by mouth.

Pharmacokinetics. Lacosamide undergoes complete absorption following oral administration, and hence oral doses produce the same effect as an equivalent IV dose. Drug levels peak 1 to 4 hours after oral dosing, and then decline with a half-life of 13 hours. Elimination is by a combination of hepatic metabolism and renal excretion.

Adverse Effects. Lacosamide is generally well tolerated. The most common adverse effects are dizziness (46%), headache (21%), diplopia (19%), and nasopharyngitis (14%). Other effects include vomiting, fatigue, incoordination, blurred vision, tremor, somnolence, and cognitive changes (eg, impaired memory, confusion, attention disruption). Lacosamide can prolong the PR interval, and hence should be used with caution in patients with cardiac conduction problems, and in those taking other drugs that prolong the PR interval. About 1% of patients experience euphoria. As a result, lacosamide is classified as a Schedule V drug under the Controlled Substances Act. Like other AEDs, lacosamide carries a small risk of suicidal thoughts or behavior.

Drug Interactions. Lacosamide is largely devoid of drug interactions. In clinical trials, it had little effect on plasma levels of other AEDs. As noted, lacosamide should be used with caution in patients taking other drugs that can prolong the PR interval (eg, beta blockers, calcium channel blockers).

Preparations, Dosage, and Administration. Lacosamide [Vimpat] is supplied in solution (10 mg/mL) and tablets (50, 100, 150, and 200 mg) for oral therapy, and in solution (10 mg/mL) for IV therapy. With both routes, dosing is done twice daily, and the same dosage is employed. Intravenous doses are infused over 30 to 60 minutes. Dosing begins at 100 mg/day (50 mg twice daily), and can be increased weekly by 100 mg/day to achieve 200 to 400 mg/day for maintenance. In patients with severe renal impairment, or with mild to moderate hepatic impairment, the dosage should not exceed 300 mg/day. In patients with severe hepatic impairment, lacosamide should be avoided. Like other AEDs, lacosamide should be withdrawn gradually.

Rufinamide

Actions and Uses. Rufinamide [Banzel] was approved in 2008 as add-on therapy for seizures associated with Lennox-Gastaut syndrome, a severe form of childhood epilepsy. Like some other AEDs (eg, phenytoin, carbamazepine), rufinamide appears to suppress seizure activity by prolonging the inactive state of neuronal sodium channels. In clinical trials, the drug reduced both seizure frequency and severity.

Pharmacokinetics. Rufinamide is well absorbed following oral dosing, especially in the presence of food. Plasma levels peak in 4 to 6 hours. Elimination is by enzymatic conversion to inactive products, followed by excretion in the urine. Of note, inactivation does not involve P450 enzymes. The plasma half-life is 6 to 10 hours.

Adverse Effects. Adverse effects differ somewhat between children and adults. In children, the most common adverse effects are somnolence (17% vs. 9% with placebo), vomiting (17% vs. 7%), and headache (16% vs. 8%). In adults, the most common effects are dizziness (19% vs. 12% with placebo), fatigue (16% vs. 10%), nausea (12% vs. 9%), and somnolence (11% vs. 7%). Rufinamide can reduce the QT interval on the electrocardiogram, and hence should not be used by patients with familial short QT syndrome. Like all other AEDs, rufinamide may increase suicidal thoughts and behavior.

Drug Interactions. Four AEDs—carbamazepine, phenobarbital, phenytoin, and primidone—can significantly reduce levels of rufinamide. Since rufinamide is not metabolized by P450 enzymes, induction of P450 cannot be the mechanism. One AED—valproic acid—can increase rufinamide levels by

up to 70%. Rufinamide causes mild induction of CYP3A4, and can thereby reduce levels of ethinyl estradiol and norethindrone, common components of oral contraceptives. An alternative form of contraception may be needed. Because rufinamide shortens the QT interval, other drugs that shorten the interval (eg, digoxin) should be used with caution.

Preparations, Dosage, and Administration. Rufinamide [Banzel] is available in tablets (200 and 400 mg) and a suspension (40 mg/mL). The tablets can be administered whole, cut in half, or crushed. Dosing should be done twice daily, using equally divided doses. All doses should be taken with food to enhance absorption.

For children at least 4 years old, dosing begins at 10 mg/kg/day (in two divided doses). Dosage is then increased by 10 mg/kg/day every 2 days up to a target of 45 mg/kg/day or 3200 mg/day, whichever is less.

For adults, dosing begins at 400 to 800 mg/day (in two divided doses). Dosage is then increased by 400 to 800 mg/day every 2 days up to a target of 3200 mg/day.

Vigabatrin

Actions and Uses. Vigabatrin [Sabril], approved in 2009, has two indications: (1) add-on therapy of complex partial seizures in adults who are refractory to other drugs and (2) monotherapy of infantile spasms in children ages 6 months to 2 years. Vigabatrin is the first drug approved in the United States for infantile spasms, a severe seizure disorder that occurs in children during the first year of life. Benefits in adults and children derive from inhibiting GABA transaminase, the enzyme that inactivates GABA in the CNS. By preventing GABA inactivation, vigabatrin increases GABA availability, and thereby enhances GABA-mediated inhibition of neuronal activity. Unfortunately, although vigabatrin is effective, it is also dangerous: The drug can cause permanent loss of vision.

Pharmacokinetics. Vigabatrin is administered by mouth, with or without food. Plasma levels peak in 0.5 to 2 hours. Bioavailability is nearly 100%. The drug undergoes little or no metabolism, and is eliminated primarily by renal excretion, with a half-life of 7.5 hours. Monitoring plasma drug levels does not help optimize treatment.

Adverse Effect: Vision Loss. Vigabatrin can cause irreversible damage to the retina, usually manifesting as progressive narrowing of the visual field. Severe damage can produce tunnel vision. Some degree of visual field reduction occurs in 30% or more of patients. Damage to the central part of the retina can reduce visual acuity. Some patients experience retinal damage within days to weeks of treatment onset, while others may use the drug for months to years before damage occurs.

To reduce the extent of damage, vision should be tested at baseline and every 3 months thereafter. If vision loss is detected, vigabatrin should be discontinued. Stopping will not reverse damage that has already occurred, but may limit development of further damage. Unfortunately, even with periodic testing, some patients will develop severe vision loss.

Owing to the risk of vision loss, vigabatrin is available only through a restricted use program, known as SHARE (Support, Help, and Resources for Epilepsy). The goal is to monitor for vision damage and discontinue the drug as soon as possible when damage is detected. SHARE requires registration by prescribers, pharmacists, adult patients, and parents/guardians of young patients. In addition, the program requires that adult and pediatric patients undergo regular vision testing.

Other Adverse Effects. In clinical trials, the most common adverse effects in adults (who received vigabatrin plus other AEDs) were headache (18%), somnolence (17%), fatigue (16%), dizziness (15%), convulsions (11%), increased weight (10%), visual field defects (9%), and depression (8%). Like other AEDs, vigabatrin can promote suicidal thoughts and behavior. Among children, the most common adverse effects were somnolence (45% vs. 30% with placebo), bronchitis (10% vs. 5%), and otitis media (10% vs. 0%).

Drug Interactions. The risk of retinal damage is increased by combining vigabatrin with other drugs that can directly damage the retina (eg, hydroxychloroquine) or with drugs that can promote glaucoma (eg, glucocorticoids, tricyclic antidepressants). Vigabatrin can reduce levels of phenytoin (by inducing CYP2C9, the 2C9 isozyme of cytochrome P450), and can increase levels of clonazepam (by a mechanism that is unknown).

Preparations, Dosage, and Administration. Vigabatrin [Sabril] is available in two oral formulations: (1) 500-mg tablets for treating adults and (2) a powder (500 mg/packet) to be dissolved in 10 mL of water for treating children. Dosing is done twice daily, with or without food.

For adults, the usual regimen is 500 mg twice daily for 1 week, followed by 1000 mg twice daily for 1 more week, followed by 1500 mg twice daily

thereafter. If needed, dosage may be increased to a maximum of 3000 mg twice daily.

For infants and young children, the regimen is 50 mg/kg/day (in two divided doses) for 3 days, followed by increases of 25 to 50 mg/kg/day every 3 days up to a maximum of 150 mg/kg/day.

For all patients, treatment should employ the lowest effective dosage for the shortest time needed. If vigabatrin fails to produce a significant clinical benefit, it should be discontinued after 2 to 4 weeks (in young children) or after 3 months (in adults).

When vigabatrin is discontinued, dosage should be tapered off gradually.

Ezogabine

Ezogabine [Potiga] is a first-in-class potassium channel opener. The drug was approved in 2011 for adjunctive treatment of partial-onset seizures. Ezogabine activates voltage-gated potassium channels in the neuronal membrane, and thereby facilitates potassium efflux. As a result, repetitive neuronal firing and related seizure activity are reduced. Unfortunately, ezogabine also activates potassium channels in the bladder epithelium, and thereby promotes urinary hesitancy or urinary retention, a unique side effect among the AEDs. Because of its effects on the bladder, ezogabine should be used with caution (if at all) in patients with pre-existing voiding difficulty. The drug can impart a red-orange color to urine. This effect is harmless and unrelated to urinary retention. The most common adverse reactions are somnolence, dizziness, fatigue, confusion, vertigo, tremor, incoordination, double vision, memory impairment, and reduced strength. In addition, ezogabine can cause hallucinations and other symptoms of psychosis. There have been no reports of rash, vision impairment, liver damage, or adverse hematologic effects. Ezogabine has the potential for abuse, and is under review for possible regulation as a controlled substance. Like all other AEDs, ezogabine may increase the risk of suicidal thinking or behavior. In contrast to many AEDs, ezogabine has few interactions with other drugs. A dosage of 900 mg/day provides a good balance between efficacy and tolerability, although many patients can tolerate up to 1200 mg/day.

MANAGEMENT OF EPILEPSY DURING PREGNANCY

Managing epilepsy during pregnancy is a challenge. Why? Because AEDs can harm the fetus, but so can uncontrolled seizures. There is solid evidence that all of the conventional AEDs increase the risk of minor malformations, major malformations, and growth retardation. At this time, the teratogenic potential of the newer AEDs is less clear—although they do appear to be safer than the traditional AEDs. The most common malformations associated with AEDs are oral-facial clefts and midline heart defects. Valproic acid poses an especially high risk of spina bifida and other neural tube defects, and can also impair cognitive development. The risk of malformation is proportional to AED dosage and to the number of AEDs used. As with other teratogens, the risk of birth defects is greatest from exposure during the first trimester. How do AEDs cause birth defects? One likely mechanism is conversion to reactive epoxide metabolites. In addition to causing birth defects, certain AEDs can cause neonatal hemorrhage.

Uncontrolled seizures carry their own risks—although they don't cause fetal malformation. Generalized tonic-clonic seizures can induce labor and, very rarely, miscarriage. Major seizures during the last month of pregnancy can injure the baby. Seizures of all types can delay development and promote epilepsy in the child. Of course, seizures also pose a risk of falls and injury to the mother.

Given that seizures and AEDs both carry risks, what should we do? Should the drugs be withdrawn, thereby increasing the risk of injury from seizures? Or should the drugs be continued, thereby posing a risk of drug-induced injury?

Most authorities agree that the risk to the fetus from uncontrolled seizures is greater than the risk from AEDs. Hence, as a general rule, women with major seizure disorders should continue to take AEDs throughout pregnancy. To minimize fetal risk, the lowest effective dosage should be determined and maintained. In addition, since the risk of malformation is proportional to the number of drugs taken, just one drug should be used whenever possible. Lastly, valproic acid should be avoided, unless it is the only AED that will work.

As discussed in Chapter 9, drug disposition changes during pregnancy. In particular, renal excretion of drugs increases, as do hepatic metabolism and protein binding. As a result, the level of free (active) drug falls, posing a risk of breakthrough seizures. Accordingly, dosage should be increased. To determine dosing requirements, drug levels should be measured at least once a month.

To reduce the risk of neural tube defects, women should take supplemental folic acid prior to conception and throughout pregnancy. A dose of 2 mg/day has been recommended. (This is 5 times the dosage recommended for women not taking AEDs.) Although supplemental folic acid can prevent neural tube defects in the absence of AEDs, it may not prevent AED-induced defects.

Four drugs—*phenobarbital*, *phenytoin*, *carbamazepine*, and *primidone*—reduce levels of vitamin K-dependent clotting factors (by inducing hepatic enzymes). As a result, these drugs increase the risk of bleeding. To reduce this risk, women should be given 10 mg of vitamin K daily during the last few weeks of pregnancy, and the baby should be given a 1-mg IM injection of vitamin K at birth.

In addition to their influence on clotting, inducers of hepatic metabolism can decrease blood levels of oral contraceptives, thereby rendering them ineffective. All women of child-bearing age should be informed of this drug interaction, and dosages of oral contraceptives should be increased as required.

To advance our understanding of the effects of AEDs on the fetus, pregnant patients should be encouraged to enroll with the *Antiepileptic Drug Pregnancy Registry*. The primary goal of the registry is to determine the frequency of major fetal malformations that occur with individual AEDs. Women can call the Registry at 1-888-233-2334 to enroll.

MANAGEMENT OF GENERALIZED CONVULSIVE STATUS EPILEPTICUS

Convulsive SE is defined as a continuous series of tonic-clonic seizures that lasts for at least 20 to 30 minutes. Consciousness is lost during the entire attack. Tachycardia, elevation of blood pressure, and hyperthermia are typical. Metabolic sequelae include hypoglycemia and acidosis. If SE persists for more than 20 minutes, it can cause permanent neurologic injury (cognitive impairment, memory loss, worsening of the underlying seizure disorder) and even death. About 125,000 Americans suffer SE each year. About 20% die.

Generalized convulsive SE is a medical emergency that requires immediate treatment. Ideally, treatment should commence within 5 minutes of seizure onset. Speed is important because, as time passes, SE becomes more and more resistant to therapy.

The goal of treatment is to maintain ventilation, correct hypoglycemia, and terminate the seizure. An IV line is established to draw blood for analysis of glucose levels, electrolyte levels, and drug levels. The line is also used to administer glucose and AEDs.

An IV benzodiazepine—either *lorazepam* [Ativan] or *diazepam* [Valium]—is used initially. Both drugs can terminate seizures quickly. Diazepam has a short duration of action, and hence must be administered repeatedly. In contrast, effects of lorazepam last up to 72 hours. Because of its prolonged effects, lorazepam is generally preferred. The dosage for lorazepam is 0.1 mg/kg administered at a rate of 2 mg/min. The initial dose for diazepam is 0.2 mg/kg administered at a rate of 5 mg/min.

Once seizures have been stopped with a benzodiazepine, either *phenytoin* [Dilantin] or *fosphenytoin* [Cerebyx]* may be given for long-term suppression. Because the effects of diazepam are short lived, follow-up treatment with a long-acting drug is essential when diazepam is used for initial control. However, when lorazepam is used for initial control, follow-up therapy may be unnecessary.

*Fosphenytoin is a prodrug form of phenytoin indicated only for convulsive SE. The drug is given IV and undergoes immediate conversion to phenytoin. Compared with solutions of phenytoin, solutions of fosphenytoin are less irritating to veins and can be infused faster without risk of cardiovascular collapse.

KEY POINTS

- Seizures are initiated by discharge from a group of hyperexcitable neurons, called a focus.
- In partial seizures, excitation undergoes limited spread from the focus to adjacent cortical areas.
- In generalized seizures, excitation spreads widely throughout both hemispheres of the brain.
- AEDs act through four basic mechanisms: blockade of sodium channels, blockade of calcium channels, blockade of receptors for glutamate (an excitatory neurotransmitter), and potentiation of GABA (an inhibitory neurotransmitter).
- The goal in treating epilepsy is to reduce seizures to an extent that enables the patient to live a normal or near-

- normal life. Complete elimination of seizures may not be possible without causing intolerable side effects.
- AEDs can be divided into two main groups: traditional AEDs and newer AEDs, which were introduced in 1993 or later.
- Many AEDs are selective for particular seizures, and hence successful treatment depends on choosing the correct drug.
- Monitoring plasma drug levels can be valuable for adjusting dosage, monitoring adherence, determining the cause of lost seizure control, and identifying the cause of toxicity, especially in patients taking more than one drug.

- Nonadherence accounts for nearly half of all treatment failures. Hence, promoting adherence is a priority.
- Withdrawal of AEDs must be done gradually, because abrupt withdrawal can trigger SE.
- Some AEDs may pose a risk of suicidal thoughts and behavior.
- Most AEDs cause CNS depression, which can be deepened by concurrent use of other CNS depressants (eg, alcohol, antihistamines, opioids, other AEDs).
- Phenytoin is active against partial seizures and tonic-clonic seizures but not absence seizures.
- The capacity of the liver to metabolize phenytoin is limited. As a result, doses only slightly greater than those needed for therapeutic effects can push phenytoin levels into the toxic range.
- The therapeutic range for phenytoin is 10 to 20 mcg/mL.
- When phenytoin levels rise above 20 mcg/mL, CNS toxicity develops. Signs include nystagmus, sedation, ataxia, diplopia, and cognitive impairment.
- Phenytoin causes gingival hyperplasia in 20% of patients.
- Rarely, phenytoin causes severe skin reactions: Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Risk *may* be increased by the HLA-B*1502 gene variation, seen almost exclusively in patients of Asian descent.
- Like phenytoin, carbamazepine is active against partial seizures and tonic-clonic seizures.
- Because carbamazepine is better tolerated than phenytoin, it is often preferred.
- Carbamazepine can cause leukopenia, anemia, and thrombocytopenia—and, very rarely, fatal aplastic anemia. To reduce the risk of serious hematologic toxicity, complete blood counts should be obtained at baseline and periodically thereafter.
- Like phenytoin, carbamazepine can cause SJS/TEN. Risk is *clearly* increased by the HLA-B*1502 gene variation. Accordingly, the FDA recommends that Asian patients should be screened for this variant before using the drug.
- Valproic acid is a very-broad-spectrum AED, having activity against partial seizures and most generalized sei-

zures, including tonic-clonic, absence, atonic, and myoclonic seizures.

- Valproic acid can cause potentially fatal liver injury, especially in children under 2 years old who are taking other AEDs.
- Valproic acid can cause potentially fatal pancreatitis.
- Valproic acid is highly teratogenic, and can reduce the IQ of children exposed to it *in utero*. Accordingly, valproic acid should not be used during pregnancy, unless it is the only AED that works.
- In contrast to other barbiturates, phenobarbital is able to suppress seizures without causing generalized CNS depression.
- Phenytoin, carbamazepine, and phenobarbital induce the synthesis of hepatic drug-metabolizing enzymes, and can thereby accelerate inactivation of other drugs. Inactivation of oral contraceptives and warfarin is of particular concern.
- AEDs can interact with one another in complex ways, causing their blood levels to change. Dosages must be adjusted to compensate for these interactions.
- All traditional AEDs (and some newer AEDs) can harm the developing fetus, especially during the first trimester. However, the fetus and mother are at greater risk from uncontrolled seizures than from AEDs. Accordingly, women with major seizure disorders should continue taking AEDs throughout pregnancy.
- Fetal risk can be minimized by avoiding valproic acid, and by using just one AED (if possible) in the lowest effective dosage.
- Initial control of generalized convulsive SE is accomplished with an IV benzodiazepine—either diazepam or lorazepam. When diazepam is used, follow-up treatment with phenytoin or fosphenytoin is essential for prolonged seizure suppression.

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Summary of Major Nursing Implications*

NURSING IMPLICATIONS THAT APPLY TO ALL ANTIPILEPTIC DRUGS

Preadministration Assessment

Therapeutic Goal

The goal of treatment is to minimize or eliminate seizure events, thereby allowing the patient to live a normal or near-normal life.

Baseline Data

Before initiating treatment, it is essential to know the type of seizure involved (eg, absence, generalized tonic-clonic) and how often seizure events occur.

Implementation: Administration

Dosage Determination

Dosages are often highly individualized and difficult to establish. Clinical evaluation of therapeutic and adverse effects is essential to establish a dosage that is both safe and effective. For several AEDs (especially those used to treat tonic-clonic seizures), knowledge of plasma AED levels can facilitate dosage adjustment.

Promoting Adherence

Seizure control requires rigid adherence to the prescribed regimen; nonadherence is a major cause of therapeutic

Continued.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

failure. To promote adherence, educate patients about the importance of taking AEDs exactly as prescribed. Monitoring plasma AED levels can motivate adherence and facilitate assessment of nonadherence.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects
Teach the patient (or a family member) to maintain a seizure frequency chart, indicating the date, time, and nature of all seizure events. The prescriber can use this record to evaluate treatment, make dosage adjustments, and alter drug selections.

Minimizing Danger from Uncontrolled Seizures

Advise patients to avoid potentially hazardous activities (eg, driving, operating dangerous machinery) until seizure control is achieved. Also, because seizures may recur after they are largely under control, advise patients to carry some form of identification (eg, Medic Alert bracelet) to aid in diagnosis and treatment if a seizure occurs.

Minimizing Adverse Effects

CNS Depression. Most AEDs depress the CNS. Signs of CNS depression (sedation, drowsiness, lethargy) are most prominent during the initial phase of treatment and decline with continued drug use. Forewarn patients about CNS depression, and advise them to avoid driving and other hazardous activities if CNS depression is significant.

Withdrawal Seizures. Abrupt discontinuation of AEDs can lead to status epilepticus (SE). Consequently, medication should be withdrawn slowly (over 6 weeks to several months) inform patients about the dangers of abrupt drug withdrawal, and instruct them never to discontinue drug use without consulting the prescriber. Advise patients who are planning a trip to carry extra medication to ensure an uninterrupted supply in the event they become stranded where medication is unavailable.

Usage in Pregnancy. In most cases, the risk from uncontrolled seizures exceeds the risk from medication, hence women with major seizure disorders should continue to take AEDs during pregnancy. However, the lowest effective dosage should be employed and, if possible, only one drug should be used. One AED—valproic acid—should be avoided. The drug is highly teratogenic and can decrease the IQ of children exposed to it *in utero*. To reduce the risk of neural tube defects, advise women to take folic acid supplements prior to and throughout pregnancy.

Suicidal Thoughts and Behavior. The AEDs pose small risk of suicidal thoughts and behavior. Screen for suicidality before starting treatment. Educate patients, families, and caregivers about signs that may precede suicidal behavior (eg, increased anxiety, agitation, mania, or hostility) and advise them to report these immediately.

Minimizing Adverse Interactions

CNS Depressants. Drugs with CNS-depressant actions (eg, alcohol, antihistamines, barbiturates, opioids) will intensify the depressant effects of AEDs, thereby posing a

serious risk. Warn patients against using alcohol and other CNS depressants.

PHENYTOIN

Nursing implications for phenytoin include those presented below as well as those presented above under *Nursing Implications That Apply to All Antiepileptic Drugs*.

Preadministration Assessment

Therapeutic Goal
Oral phenytoin is used to treat partial seizures (simple and complex) and tonic-clonic seizures. Intravenous phenytoin is used to treat convulsive SE.

Identifying High-Risk Patients

Intravenous phenytoin is *contraindicated* for patients with sinus bradycardia, sinoatrial block, second- or third-degree atrioventricular block, or Stokes-Adams syndrome.

Implementation: Administration

Routes

Oral, IV, and (rarely) IM.

Administration

Oral. Instruct patients to take phenytoin exactly as prescribed. Inform them that, once a safe and effective dosage has been established, small deviations in dosage can lead to toxicity or to loss of seizure control.

Advise patients to take phenytoin with meals to reduce gastric discomfort.

Instruct patients to shake the phenytoin oral suspension before dispensing in order to provide consistent dosing.

Intravenous. To minimize the risk of severe reactions (eg, cardiovascular collapse), infuse phenytoin slowly (no faster than 50 mg/min).

Do not mix phenytoin solutions with other drugs. To minimize venous inflammation at the injection site, flush the needle or catheter with saline immediately after completing the phenytoin infusion.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

CNS Effects. Inform patients that excessive doses can produce sedation, ataxia, diplopia, and interference with cognitive function. Instruct them to notify the prescriber if these occur.

Gingival Hyperplasia. Inform patients that phenytoin often promotes overgrowth of gum tissue. To minimize harm and discomfort, teach them proper techniques of brushing, flossing, and gum massage—and suggest taking 0.5 mg of folic acid every day.

Use in Pregnancy. Phenytoin can cause fetal hydantoin syndrome and bleeding tendencies in the neonate. Decrease bleeding risk by giving the mother vitamin K for 1 month prior to delivery and during delivery and to the infant immediately after delivery. Decrease the risk of fetal

hydantoin syndrome by using the lowest effective phenytoin dosage.

Dermatologic Reactions. Inform patients that phenytoin can cause a morbilliform (measles-like) rash that may progress to much more serious conditions: Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Instruct patients to notify the prescriber immediately if a rash develops. Use of phenytoin should stop. As with carbamazepine (see below) the risk of SJS/TEN may be increased by a genetic variation known as HLA-B*1502, seen primarily in patients of Asian descent.

Withdrawal Seizures. Abrupt discontinuation of phenytoin can trigger convulsive SE. Warn patients against abrupt cessation of treatment.

Minimizing Adverse Interactions

Phenytoin is subject to a large number of significant interactions with other drugs; a few are noted below. Warn patients against use of any drugs not specifically approved by the prescriber.

CNS Depressants. Warn patients against use of alcohol and all other drugs with CNS-depressant properties, including opioids, barbiturates, and antihistamines.

Warfarin and Oral Contraceptives. Phenytoin can decrease the effects of these agents (as well as other drugs) by inducing hepatic drug-metabolizing enzymes. Dosages of warfarin and oral contraceptives may need to be increased.

CARBAMAZEPINE

Nursing implications for carbamazepine include those presented below as well as those presented above under *Nursing Implications That Apply to All Antiepileptic Drugs*.

Preadministration Assessment

Therapeutic Goal

Carbamazepine is used to treat partial seizures (simple and complex) and tonic-clonic seizures.

Baseline Data

Obtain complete blood counts prior to treatment.

Identifying High-Risk Patients

Carbamazepine is *contraindicated* for patients with a history of bone marrow depression or adverse hematologic reactions to other drugs. Screen Asian patients for the HLA-B*1502 gene variation, which increases the risk of SJS/TEN.

Implementation: Administration

Route

Oral.

Administration

Advise patients to administer carbamazepine with meals to decrease gastric upset.
To minimize adverse CNS effects, use low initial doses and give the largest portion of the daily dose at bedtime.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Ongoing Evaluation and Interventions

Minimizing Adverse Effects
CNS Effects. Carbamazepine can cause headache, visual disturbances (nyctalgia, blurred vision, diplopia), ataxia, vertigo, and unsteadiness. To minimize these effects, initiate therapy with low doses and have the patient take the largest part of the daily dose at bedtime.

Hematologic Effects. Carbamazepine can cause leukopenia, anemia, thrombocytopenia, and, very rarely, fatal aplastic anemia. To reduce the risk of serious hematologic effects: (1) obtain complete blood counts at baseline and periodically thereafter, (2) avoid carbamazepine in patients with pre-existing hematologic abnormalities, and (3) inform patients about manifestations of hematologic abnormalities: fever, sore throat, pallor, weakness, infection, easy bruising, petechiae, and instruct them to notify the prescriber if these occur.

Birth Defects. Carbamazepine can cause neural tube defects. Use in pregnancy only if the benefits of seizure suppression outweigh the risks to the fetus.

Severe Skin Reactions. Carbamazepine can cause SJS/TEN, especially among patients with HLA-B*1502, a genetic variation seen almost exclusively in patients of Asian descent. To reduce risk, the FDA recommends that patients of Asian descent be tested for HLA-B*1502. If SJS/TEN develops, carbamazepine should be discontinued. Since HLA-B*1502 may also increase the risk of SJS/TEN in response to phenytoin, phenytoin should not be used as an alternative to carbamazepine in patients with the mutation.

Minimizing Adverse Interactions

Interactions Due to Induction of Drug Metabolism. Carbamazepine can decrease responses to other drugs by inducing hepatic drug-metabolizing enzymes. Effects on oral contraceptives and warfarin are of particular concern. Patients using these drugs will require increased dosages to maintain therapeutic responses.

Phenytoin and Phenobarbital. These drugs can decrease responses to carbamazepine by inducing drug-metabolizing enzymes (beyond the degree of induction caused by carbamazepine itself). Dosage of carbamazepine may need to be increased.

Grapefruit Juice. Grapefruit juice can increase levels of carbamazepine. Instruct patients not to drink grapefruit juice.

VALPROIC ACID

Nursing implications for valproic acid include those presented below as well as those presented above under *Nursing Implications That Apply to All Antiepileptic Drugs*.

Preadministration Assessment

Therapeutic Goal

Valproic acid is used to treat all major seizure disorders: tonic-clonic, absence, myoclonic, atonic, and partial (simple, complex, and secondarily generalized).

Continued

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Baseline Data

Obtain baseline tests of liver function.

Identifying High-Risk Patients

Valproic acid is *contraindicated* for patients with significant hepatic dysfunction and for children under the age of 3 years who are taking other AEDs. Avoid valproic acid during pregnancy.

Implementation: Administration

Oral, IV.

Administration

Advise patients to take valproic acid with meals, and instruct them to ingest tablets and capsules intact, without crushing or chewing.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Gastrointestinal Effects. Nausea, vomiting, and indigestion are common. These can be reduced by using an enteric-coated formulation (see Table 24-4) and by taking valproic acid with meals.

Hepatotoxicity. Rarely, valproic acid has caused fatal liver injury. To minimize risk, (1) don't use valproic acid in conjunction with other drugs in children under the age of 3 years; (2) don't use valproic acid in patients with pre-existing liver dysfunction; (3) evaluate liver function at baseline and periodically thereafter; (4) inform patients about signs and symptoms of liver injury (reduced appetite, malaise, nausea, abdominal pain, jaundice), and instruct them to notify the prescriber if these develop; and (5) use valproic acid in the lowest effective dosage.

Pancreatitis. Valproic acid can cause life-threatening pancreatitis. Inform patients about signs of pancreatitis (abdominal pain, nausea, vomiting, anoxia) and instruct them to get an immediate evaluation if these develop. If pancreatitis is diagnosed, valproic acid should be withdrawn.

Pregnancy-Related Harm. Valproic acid may cause neural tube defects and other congenital malformations, especially when taken during the first trimester. In addition, the drug can reduce the IQ of children exposed to it *in utero*. Valproic acid is classified in FDA Pregnancy Risk Category D, and should be avoided by women of child-bearing potential—unless it is the only AED that will work. Advise women who must use valproic acid to use an effective form of birth control and to take 5 mg of folic acid daily (to reduce the risk of neural tube defects if pregnancy should occur).

Hyperammonemia. Combining valproic acid with topiramate poses a risk of hyperammonemia. If symptoms develop (vomiting, lethargy, altered level of consciousness and/or cognitive function), blood ammonia should be measured. If the level is excessive, either valproic acid or topiramate should be withdrawn.

*Patient education information is highlighted as blue text.

Minimizing Adverse Interactions

Antiepileptic Drugs. Valproic acid can elevate plasma levels of phenytoin and phenobarbital. Levels of phenobarbital and phenytoin should be monitored and their dosages adjusted accordingly.

Topiramate. See *Hyperammonemia* above.

Carbapenem Antibiotics. Meropenem and imipenem cilastatin can reduce plasma levels of valproic acid. Breakthrough seizures have occurred. These antibiotics should be avoided in patients taking valproic acid.

PHENOBARBITAL

Nursing implications that apply to the antiseizure applications of phenobarbital include those presented below and those presented above under *Nursing Implications That Apply to All Antiepileptic Drugs*. Nursing implications that apply to the barbiturates as a group are summarized in Chapter 34.

Preadministration Assessment

Therapeutic Goal

Oral phenobarbital is used for partial seizures (simple and complex) and tonic-clonic seizures. Intravenous therapy is used for convulsive SE.

Identifying High-Risk Patients

Phenobarbital is *contraindicated* for patients with a history of acute intermittent porphyria.

Use with *caution* during pregnancy.

Implementation: Administration

Routes

Oral and IV.

Administration

Oral. A loading schedule may be employed to initiate treatment. Monitor for excessive CNS depression when these large doses are used.

Intravenous. Rapid IV infusion can cause severe adverse effects. Perform infusions slowly.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Neuropsychologic Effects. Warn patients that sedation may occur during the initial phase of treatment. Advise them to avoid hazardous activities if sedation is significant. Inform parents that children may become irritable and hyperactive, and instruct them to notify the prescriber if these behaviors occur.

Exacerbation of Intermittent Porphyria. Phenobarbital can exacerbate acute intermittent porphyria, and hence is absolutely contraindicated for patients with a history of this disorder.

Use in Pregnancy. Warn women of child-bearing age that barbiturates may cause birth defects.

Withdrawal Seizures. Abrupt withdrawal of phenobarbital can trigger seizures. Warn patients against abrupt cessation of treatment.

Minimizing Adverse Interactions

Interactions Caused by Induction of Drug Metabolism. Phenobarbital induces hepatic drug-metabolizing enzymes, and can thereby decrease responses to other drugs.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Effects on oral contraceptives and warfarin are a particular concern; their dosages should be increased.

CNS Depressants. Warn patients against use of alcohol and all other drugs with CNS-depressant properties (eg, opioids, benzodiazepines).

Valproic Acid. Valproic acid increases blood levels of phenobarbital. To avoid toxicity, reduce phenobarbital dosage.

Drugs for Muscle Spasm and Spasticity

Drug Therapy of Muscle Spasm: Centrally Acting Muscle Relaxants

Drugs for Spasticity

Baclofen

Diazepam

Dantrolene

In this chapter we consider two groups of drugs that cause skeletal muscle relaxation. One group is used for localized muscle spasm. The other is used for spasticity. With only one exception (dantrolene), these drugs produce their effects through actions in the central nervous system (CNS). As a rule, the drugs used to treat spasticity do not relieve acute muscle spasm and vice versa. Hence, the two groups are not interchangeable.

DRUG THERAPY OF MUSCLE SPASM: CENTRALLY ACTING MUSCLE RELAXANTS

Muscle spasm is defined as involuntary contraction of a muscle or muscle group. Muscle spasm is often painful and reduces the ability to function. Spasm can result from a variety of causes, including epilepsy, hypocalcemia, acute and chronic pain syndromes, and trauma (localized muscle in-

jury). Discussion here is limited to spasm resulting from muscle injury.

Treatment of spasm involves physical measures as well as drug therapy. Physical measures include immobilization of the affected muscle, application of cold compresses, whirlpool baths, and physical therapy. For drug therapy, two groups of medicines are used: (1) analgesic anti-inflammatory agents (eg, aspirin), and (2) centrally acting muscle relaxants. The analgesic anti-inflammatory agents are discussed in Chapter 71. The centrally acting muscle relaxants are discussed below.

The family of centrally acting muscle relaxants consists of 9 drugs (Table 25-1). All have similar pharmacologic properties. Hence, we will consider these agents as a group.

Mechanism of Action

For most centrally acting muscle relaxants, the mechanism of spasm relief is unclear. In laboratory animals, high doses can depress spinal motor reflexes. However, these doses are much higher than those used in humans. Hence, many investigators believe that relaxation of spasm results primarily from the *sedative properties* of these drugs, and not from specific actions exerted on CNS pathways that control muscle tone.

Two drugs—diazepam and tizanidine—are thought to relieve spasm by enhancing presynaptic inhibition of motor neurons in the CNS. Diazepam promotes presynaptic inhibition by enhancing the effects of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. Tizanidine promotes inhibition by acting as an agonist at presynaptic α_2 receptors.

TABLE 25-1 • Drugs for Muscle Spasm: Centrally Acting Muscle Relaxants

Generic Name	Trade Names	Usual Adult Oral Maintenance Dosage
Baclofen	Lioresal	15–20 mg 3 or 4 times/day
Carisoprodol	Soma	350 mg 3 or 4 times/day
Chlorzoxazone	Paraflex, Parafon Forte DSC, Remular-S, Relax-DS	250 mg 3 or 4 times/day
Cyclobenzaprine	Flexeril, Fexmid	10 mg 3 times/day
Cyclobenzaprine ER*	Amrix	15 or 30 mg once daily
Diazepam	Valium	2–10 mg 3 or 4 times/day
Metaxalone	Skelaxin	800 mg 3 or 4 times/day
Methocarbamol	Robaxin	1000 mg 4 times/day
Orphenadrine	Banflex, Flexon, Norflex	100 mg morning and evening
Tizanidine	Zanaflex	4 mg 3 or 4 times/day

*ER = extended release.

Therapeutic Use

The centrally acting muscle relaxants are used to relieve localized spasm resulting from muscle injury. These agents can decrease local pain and tenderness and can increase range of motion. Treatment is almost always associated with sedation. Benefits of treatment equal those of aspirin and the other analgesic anti-inflammatory drugs. Since there are no studies to indicate the superiority of one centrally acting muscle relaxant over another, drug selection is based largely on prescriber preference and patient response. With the exception of diazepam, the central muscle relaxants are not useful for treating spasticity or other muscle disorders resulting from CNS pathology.

Adverse Effects

CNS Depression. All of the centrally acting muscle relaxants can produce generalized depression of the CNS. *Drowsiness*, *dizziness*, and *lightheadedness* are common. Patients should be warned not to participate in hazardous activities (eg, driving) if CNS depression is significant. In addition, they should be advised to avoid alcohol and all other CNS depressants.

Hepatic Toxicity. *Tizanidine* [Zanaflex] and *metaxalone* [Skelaxin] can cause liver damage. Liver function should be assessed before starting treatment and periodically thereafter. If liver injury develops, these drugs should be discontinued. If the patient has pre-existing liver disease, these drugs should be avoided.

Chlorzoxazone [Paraflex, Parafon Forte DSC, others] can cause hepatitis and potentially fatal hepatic necrosis. Because of this potential for harm, and because the benefits of chlorzoxazone are questionable, the drug should not be used.

Physical Dependence. Chronic, high-dose therapy can cause physical dependence, manifesting as a potentially life-threatening abstinence syndrome if these drugs are abruptly withdrawn. Accordingly, withdrawal should be done slowly.

Other Adverse Effects. *Cyclobenzaprine* and *orphenadrine* have significant anticholinergic (atropine-like) properties, and hence may cause dry mouth, blurred vision, photophobia, urinary retention, and constipation. *Methocarbamol* may turn urine brown, black, or dark green; patients should be forewarned of this harmless effect. *Tizanidine* can cause dry mouth, hypotension, hallucinations, and psychotic symptoms. *Carisoprodol* can be hazardous to patients predisposed to intermittent porphyria, and hence is contraindicated for this group.

Dosage and Administration

All centrally acting skeletal muscle relaxants can be administered orally. In addition, two agents—methocarbamol and diazepam—can be administered by injection (IM and IV). Average oral maintenance dosages for adults are listed in Table 25-1.

DRUGS FOR SPASTICITY

The term *spasticity* refers to a group of movement disorders of CNS origin. These disorders are characterized by heightened muscle tone, spasm, and loss of dexterity. The most common causes are multiple sclerosis and cerebral palsy. Other causes include traumatic spinal cord lesions and stroke. Spasticity is managed with a combination of drugs and physical therapy.

Three drugs—baclofen, diazepam, and dantrolene—can relieve spasticity. Two of these—baclofen and diazepam—act in the CNS. In contrast, dantrolene acts directly on skeletal

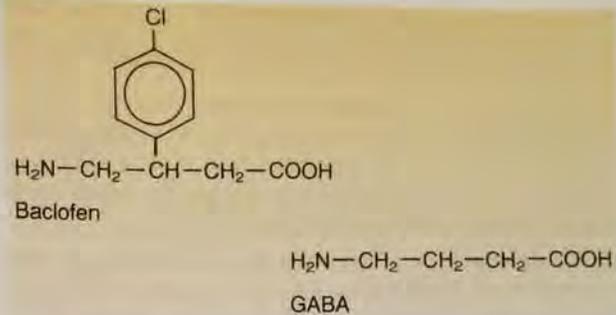


Figure 25-1 ■ Structural similarity between baclofen and gamma-aminobutyric acid (GABA).

muscle. With the exception of diazepam, the drugs employed to treat muscle spasm (ie, the centrally acting muscle relaxants) are not effective against spasticity.

Baclofen

Mechanism of Action

Baclofen [Lioresal] acts within the spinal cord to suppress hyperactive reflexes involved in regulation of muscle movement. The precise mechanism of reflex attenuation is unknown. Since baclofen is a structural analog of the inhibitory neurotransmitter GABA (Fig. 25-1), it may act by mimicking the actions of GABA on spinal neurons. Baclofen has no direct effects on skeletal muscle.

Therapeutic Use

Baclofen can reduce spasticity associated with multiple sclerosis, spinal cord injury, and cerebral palsy—but not with stroke. The drug decreases flexor and extensor spasms and suppresses resistance to passive movement. These actions reduce the discomfort of spasticity and allow increased performance. Because baclofen has no direct muscle-relaxant action, and hence does not decrease muscle strength, baclofen is preferred to dantrolene when spasticity is associated with significant muscle weakness. Baclofen does not relieve the spasticity of Parkinson's disease or Huntington's chorea.

Adverse Effects

The most common side effects involve the CNS and GI tract. Serious adverse effects are rare.

CNS Effects. Baclofen is a CNS depressant and hence frequently causes *drowsiness*, *dizziness*, *weakness*, and *fatigue*. These responses are most intense during the early phase of therapy and diminish with continued drug use. CNS depression can be minimized with doses that are small initially and then gradually increased. Patients should be cautioned to avoid alcohol and other CNS depressants, because baclofen will potentiate the depressant actions of these drugs.

Overdose can produce *coma* and *respiratory depression*. Since there is no antidote to baclofen poisoning, treatment is supportive.

Withdrawal. Although baclofen does not appear to cause physical dependence, abrupt discontinuation has been associated with adverse reactions. Abrupt stoppage of *oral* baclofen can cause visual hallucinations, paranoid ideation, and sei-

zures. Accordingly, withdrawal should be done slowly (over 1 to 2 weeks). Abrupt stoppage of *intrathecal* baclofen can be more dangerous. Potential reactions include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity that, in rare cases, has advanced to rhabdomyolysis (muscle breakdown), multiple organ system failure, and death. To avoid disaster, the infusion system must be programmed properly and carefully monitored.

Other Adverse Effects. Baclofen frequently causes *nausea, constipation, and urinary retention*. Patients should be warned about these possible reactions.

Preparations, Dosage, and Administration

Oral. Baclofen [Lioresal] is available in tablets (10 and 20 mg) for oral use. Dosages are low initially (eg, 5 mg 3 times a day) and then gradually increased. Maintenance dosages range from 15 to 20 mg administered 3 to 4 times a day.

Intrathecal. Baclofen can be administered by intrathecal infusion using an implantable pump. The average maintenance dosage is 300 to 800 mcg/day. Intrathecal administration is reserved for patients who are unresponsive to or intolerant of oral baclofen.

Diazepam

Diazepam [Valium] is a member of the benzodiazepine family. Although diazepam is the only benzodiazepine labeled for treating spasticity, other benzodiazepines would probably be effective. The basic pharmacology of the benzodiazepines is discussed in Chapter 34.

Actions. Like baclofen, diazepam acts in the CNS to suppress spasticity. Beneficial effects appear to result from mimicking the actions of GABA at receptors in the spinal cord and brain. Diazepam does not affect skeletal muscle directly. Since diazepam has no direct effects on muscle strength, the drug is preferred to dantrolene when muscle strength is marginal.

Adverse Effects. *Sedation* is common when treating spasticity. To minimize sedation, initial doses should be low. Other adverse effects are discussed in Chapter 34.

Preparations, Dosage, and Administration. For oral use, diazepam [Valium] is available in tablets (2, 5, and 10 mg) and solution (1 and 5 mg/mL). The drug is also available in solution (5 mg/mL) for IM and IV administration, and as a gel (2.5, 10, and 20 mg) for rectal administration. The usual oral dosage for adults is 2 to 10 mg 3 or 4 times a day.

Dantrolene

Mechanism of Action

Unlike baclofen and diazepam, which act within the CNS, dantrolene [Dantrium] acts directly on skeletal muscle. The drug relieves spasm by suppressing release of calcium from the sarcoplasmic reticulum (SR), and hence the muscle is less able to contract. Fortunately, therapeutic doses have only minimal effects on contraction of smooth muscle and cardiac muscle.

Therapeutic Uses

Spasticity. Dantrolene can relieve spasticity associated with multiple sclerosis, cerebral palsy, and spinal cord injury. Unfortunately, since dantrolene suppresses spasticity by causing a generalized reduction in the ability of skeletal muscle to contract, treatment may be associated with a significant reduction in strength. As a result, overall function may be reduced rather than improved. Accordingly, care must be taken to ensure that the benefits of therapy (reduced spasticity) outweigh the harm (reduced strength).

Malignant Hyperthermia. Malignant hyperthermia is a rare, life-threatening syndrome that can be triggered by any general anesthetic (except nitrous oxide) and by succinylcholine, a neuromuscular blocking agent. Onset of symptoms is most abrupt with succinylcholine (when used alone or in combination with an anesthetic). Prominent symptoms are muscle rigidity and profound elevation of temperature. The heat of malignant hyperthermia is generated by muscle contraction occurring secondary to massive release of calcium from the SR. Dantrolene relieves symptoms by acting on the SR to block calcium release. Malignant hyperthermia is discussed further in Chapter 16.

Adverse Effects

Hepatic Toxicity. Dose-related liver damage is the most serious adverse effect. The incidence is 1 in 1000. Deaths have occurred. Hepatotoxicity is most common in women over age 35 years. By contrast, liver injury is rare in children under 10 years. To reduce the risk of liver damage, liver function tests (LFTs) should be performed at baseline and periodically thereafter. If LFTs indicate liver injury, dantrolene should be withdrawn. Because of the potential for liver damage, dantrolene should be administered in the lowest effective dosage and for the shortest time necessary.

Other Adverse Effects. *Muscle weakness, drowsiness, and diarrhea* are the most common side effects. Muscle weakness is a direct extension of dantrolene's pharmacologic action. Other disturbing reactions include *anorexia, nausea, vomiting, and acne-like rash*.

Preparations, Dosage, and Administration

Preparations. Dantrolene sodium [Dantrium] is available in capsules (25, 50, and 100 mg) for oral use and as a powder to be reconstituted for IV injection.

Use in Spasticity. For treatment of spasticity, dosing is oral. The initial adult dosage is 25 mg once daily. The usual maintenance dosage is 100 mg 2 to 4 times a day. If beneficial effects do not develop within 45 days, dantrolene should be stopped.

Use in Malignant Hyperthermia. Preoperative Prophylaxis. Patients with a history of malignant hyperthermia can be given dantrolene for prophylaxis prior to elective surgery. The dosage is 4 to 8 mg/kg/day in four divided doses for 1 to 2 days preceding surgery.

Treatment of an Ongoing Crisis. For treatment of malignant hyperthermia, dantrolene is administered by IV push. The initial dose is 2 mg/kg. Administration is repeated until symptoms are controlled or until a total dose of 10 mg/kg has been given. Other management measures are discussed in Chapter 16.

KEY POINTS

- Localized muscle spasm is treated with centrally acting muscle relaxants and aspirin-like drugs.
- Spasticity is treated with three drugs: baclofen, diazepam, and dantrolene.
- All centrally acting muscle relaxants produce generalized CNS depression.
- Chlorzoxazone, a central muscle relaxant, is marginally effective and can cause fatal hepatic necrosis. Accordingly, the drug should be avoided.
- Baclofen and diazepam relieve spasticity by mimicking the inhibitory actions of GABA in the CNS.
- Like the centrally acting muscle relaxants, baclofen and diazepam cause generalized CNS depression.
- In contrast to all other drugs discussed in this chapter, dantrolene acts directly on muscle to promote relaxation.
- Abrupt discontinuation of intrathecal baclofen can lead to rhabdomyolysis, multiple organ system failure, and death.
- With prolonged use, dantrolene can cause potentially fatal liver damage. Monitor liver function and minimize dosage and duration of treatment.
- In addition to relief of spasticity, dantrolene is used to treat malignant hyperthermia, a potentially fatal condition caused by succinylcholine and general anesthetics.

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Summary of Major Nursing Implications*

DRUGS USED TO TREAT MUSCLE SPASM:
CENTRALLY ACTING SKELETAL MUSCLE
RELAXANTS

Baclofen
Carisoprodol
Chlorzoxazone
Cyclobenzaprine
Diazepam
Metaxalone
Methocarbamol
Orphenadrine
Tizanidine

Except where noted, the nursing implications summarized below apply to all centrally acting muscle relaxants used to treat muscle spasm.

Preadministration Assessment**Therapeutic Goal**

Relief of signs and symptoms of muscle spasm.

Baseline Data

For patients taking metaxalone and tizanidine, obtain baseline LFTs.

Identifying High-Risk Patients

Avoid *chlorzoxazone*, *metaxalone*, and *tizanidine* in patients with liver disease.

Implementation: Administration**Routes**

Oral. All central skeletal muscle relaxants.

Parenteral. *Methocarbamol* and *diazepam* may be given IM and IV as well as PO.

Dosage

See Table 25-1.

**Implementation: Measures to Enhance
Therapeutic Effects**

The treatment plan should include appropriate physical measures (eg, immobilization of the affected muscle, application of cold compresses, whirlpool baths, and physical therapy).

Ongoing Evaluation and Interventions**Minimizing Adverse Effects**

CNS Depression. All central muscle relaxants cause CNS depression. Inform patients about possible depressant effects (drowsiness, dizziness, lightheadedness, fatigue) and advise them to avoid driving and other hazardous activities if significant impairment occurs.

Hepatic Toxicity. *Metaxalone* and *tizanidine* can cause liver damage. Obtain LFTs before treatment and periodically thereafter. If liver damage develops, discontinue treatment. Avoid these drugs in patients with pre-existing liver disease.

Chlorzoxazone can cause hepatitis and potentially fatal hepatic necrosis. The drug should not be used.

Minimizing Adverse Interactions

CNS Depressants. Caution patients to avoid CNS depressants (eg, alcohol, benzodiazepines, opioids, antihistamines) because these drugs will intensify the depressant effects of muscle relaxants.

Avoiding Withdrawal Reactions

Central muscle relaxants can cause physical dependence. To avoid an abstinence syndrome, withdraw gradually. Warn the patient against abrupt discontinuation of treatment.

BACLOFEN**Preadministration Assessment****Therapeutic Goal**

Relief of signs and symptoms of spasticity.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Baseline Data

Assess for spasm, rigidity, pain, range of motion, and dexterity. Obtain baseline LFTs.

Implementation: Administration

Routes

Oral, intrathecal.

Administration

Patients with muscle spasm may be unable to self-medicate. Provide assistance if needed.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor for reductions in rigidity, muscle spasm, and pain and for improvements in dexterity and range of motion.

Minimizing Adverse Effects

CNS Depression. Baclofen is a CNS depressant. Inform patients about possible depressant effects (drowsiness, dizziness, lightheadedness, fatigue) and advise them to avoid driving and other hazardous activities if significant impairment occurs.

Minimizing Adverse Interactions

CNS Depressants. Caution patients to avoid CNS depressants (eg, alcohol, benzodiazepines, opioids, antihistamines) because these drugs will intensify the depressant effects of baclofen.

Avoiding Withdrawal Reactions

Oral Baclofen. Abrupt withdrawal can cause visual hallucinations, paranoid ideation, and seizures. Caution the patient against abrupt discontinuation of treatment.

Intrathecal Baclofen. Abrupt discontinuation can cause multiple adverse effects, including rhabdomyolysis, multiple organ system failure, and death. Make sure the infusion system is programmed properly and monitored with care.

DANTROLENE

The nursing implications summarized here apply only to the use of dantrolene for spasticity.

Preadministration Assessment

Therapeutic Goal

Relief of signs and symptoms of spasticity.

Baseline Data

Assess for spasm, rigidity, pain, range of motion, and dexterity. Obtain baseline LFTs.

Identifying High-Risk Patients

Dantrolene is *contraindicated* for patients with active liver disease (eg, cirrhosis, hepatitis).

Implementation: Administration

Route

Oral.

Administration

Patients with muscle spasm may be unable to self-medicate. Provide assistance if needed.

Ongoing Evaluation and Interventions

Summary of Monitoring

Therapeutic Effects. Monitor for reductions in rigidity, spasm, and pain and for improvements in dexterity and range of motion.

Adverse Effects. Monitor LFTs and assess for reduced muscle strength.

Minimizing Adverse Effects

CNS Depression. Dantrolene is a CNS depressant. Inform patients about possible depressant effects (drowsiness, dizziness, lightheadedness, fatigue) and advise them to avoid driving and other hazardous activities if significant impairment occurs.

Hepatic Toxicity. Dantrolene is hepatotoxic. Assess liver function at baseline and periodically thereafter. If signs of liver dysfunction develop, withdraw dantrolene. Inform patients about signs of liver dysfunction (eg, jaundice, abdominal pain, malaise) and instruct them to seek medical attention if these develop.

Muscle Weakness. Dantrolene can decrease muscle strength. Evaluate muscle function to ensure that benefits of therapy (decreased spasticity) are not outweighed by reductions in strength.

Minimizing Adverse Interactions

CNS Depressants. Warn patients to avoid CNS depressants (eg, alcohol, benzodiazepines, opioids, antihistamines), because these drugs will intensify depressant effects of dantrolene.

DIAZEPAM

Nursing implications for diazepam and the other benzodiazepines are summarized in Chapter 34 (Sedative-Hypnotic Drugs).

*Patient education information is highlighted as blue text.

Basic Pharmacology of the Local Anesthetics

Classification

Mechanism of Action

Selectivity of Anesthetic Effects

Time Course of Local Anesthesia

Use with Vasoconstrictors

Fate in the Body

Adverse Effects

Properties of Individual Local Anesthetics

Procaine

Lidocaine

Cocaine

Other Local Anesthetics

Clinical Use of Local Anesthetics

Topical Administration

Administration by Injection

Local anesthetics are drugs that suppress pain by blocking impulse conduction along axons. Conduction is blocked only in neurons located near the site of administration. The great advantage of local anesthesia, compared with inhalation anesthesia, is that pain can be suppressed without causing generalized depression of the entire nervous system. Hence, local anesthetics carry much less risk than do general anesthetics.

We begin the chapter by considering the pharmacology of the local anesthetics as a group. After that, we discuss three prototypic agents: procaine, lidocaine, and cocaine. We conclude by discussing specific routes of anesthetic administration.

BASIC PHARMACOLOGY OF THE LOCAL ANESTHETICS

Classification

There are two major groups of local anesthetics: *esters* and *amides*. As shown in Figure 26-1, the ester-type anesthetics, represented by *procaine* [Novocain], contain an ester linkage in their structure. In contrast, the amide-type agents, represented by *lidocaine* [Xylocaine], contain an amide linkage. The ester-type agents and amide-type agents differ in two important ways: (1) method of inactivation and (2) promotion of allergic responses. Contrasts between the esters and amides are summarized in Table 26-1.

Mechanism of Action

Local anesthetics stop axonal conduction by *blocking sodium channels* in the axonal membrane. Recall that propagation of an action potential requires movement of sodium ions from outside the axon to the inside. This influx takes place through specialized sodium channels. By blocking axonal sodium channels, local anesthetics prevent sodium entry, and thereby block conduction.

Selectivity of Anesthetic Effects

Local anesthetics are nonselective modifiers of neuronal function. That is, they will block action potentials in all neurons to which they have access. The only way we can achieve selectivity is by delivering the anesthetic to a limited area.

Although local anesthetics can block traffic in all neurons, blockade develops more rapidly in some neurons than in others. Specifically, small, nonmyelinated neurons are blocked more rapidly than large, myelinated neurons. Because of this differential sensitivity, some sensations are blocked sooner than others. Specifically, perception of pain is lost first, followed in order by perception of cold, warmth, touch, and deep pressure.

Be aware that the effects of local anesthetics are not limited to sensory neurons: These drugs also block conduction in motor neurons, which is why your face looks funny when you leave the dentist.

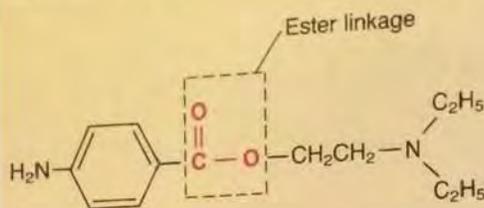
Time Course of Local Anesthesia

Ideally, local anesthesia would begin promptly and would persist no longer (or shorter) than needed. Unfortunately, although onset of anesthesia is usually rapid (see Tables 26-2 and 26-3 below), duration of anesthesia is often less than ideal. In some cases, anesthesia persists longer than needed. In others, repeated administration is required to maintain anesthesia of sufficient duration.

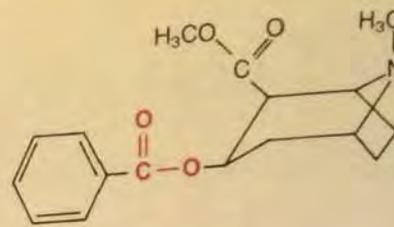
Onset of local anesthesia is determined largely by the molecular properties of the anesthetic. Before anesthesia can occur, the anesthetic must diffuse from its site of administration to its sites of action within the axon membrane. Anesthesia is delayed until this movement has occurred. The ability of an anesthetic to penetrate the axon membrane is determined by three properties: *molecular size*, *lipid solubility*, and *degree of ionization at tissue pH*. Anesthetics of small size, high lipid solubility, and low ionization cross the axon membrane rapidly. In contrast, anesthetics of large size, low lipid solubility, and high ionization cross slowly. Obviously, anesthetics that penetrate the axon most rapidly have the fastest onset.

Termination of local anesthesia occurs as molecules of anesthetic diffuse out of neurons and are carried away in the blood. The same factors that determine onset of anesthesia (molecular size, lipid solubility, degree of ionization) also help determine

ESTER-TYPE LOCAL ANESTHETICS

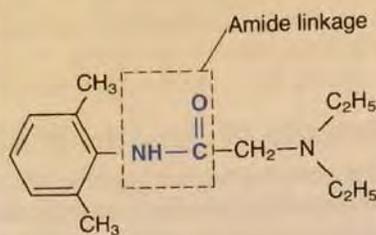


Procaine

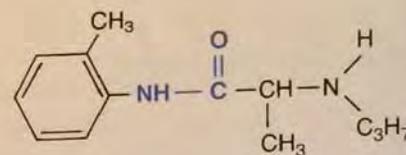


Cocaine

AMIDE-TYPE LOCAL ANESTHETICS



Lidocaine



Prilocaine

Figure 26-1 ■ Structural formulas of representative local anesthetics.

TABLE 26-1 ■ Contrasts Between Ester and Amide Local Anesthetics

Property	Ester-type Anesthetics	Amide-type Anesthetics
Characteristic Chemistry	Ester bond	Amide bond
Representative Agent	Procaine	Lidocaine
Incidence of Allergic Reactions	Low	Very low
Method of Metabolism	Plasma esterases	Hepatic enzymes

duration. In addition, *regional blood flow* is an important determinant of how long anesthesia will last. In areas where blood flow is high, anesthetic is carried away quickly, and hence effects terminate with relative haste. In regions where blood flow is low, anesthesia is more prolonged.

Use with Vasoconstrictors

Local anesthetics are frequently administered in combination with a vasoconstrictor, usually *epinephrine*. The vasoconstrictor decreases local blood flow and thereby delays systemic absorption of the anesthetic. Delaying absorption has two benefits: It *prolongs anesthesia* and *reduces the risk of toxicity*. Why is toxicity reduced? First, because absorption is slowed, we can use less anesthetic. Second, by slowing absorption, we can establish a more favorable balance between the rate of entry of anesthetic into circulation and the rate of its conversion into inactive metabolites.

It should be noted that absorption of the vasoconstrictor itself can result in systemic toxicity (eg, palpitations, tachy-

cardia, nervousness, hypertension). If adrenergic stimulation from absorption of epinephrine is excessive, symptoms can be controlled with alpha- and beta-adrenergic antagonists.

Fate in the Body

Absorption and Distribution. Although administered for local effects, local anesthetics do get absorbed into the blood and become distributed to all parts of the body. The rate of absorption is determined largely by blood flow to the site of administration.

Metabolism. The process by which a local anesthetic is metabolized depends on the class—ester or amide—to which it belongs. *Ester-type* local anesthetics are metabolized in the blood by enzymes known as *esterases*. In contrast, *amide-type* anesthetics are metabolized by enzymes in the *liver*. For both types of anesthetic, metabolism results in inactivation.

The balance between rate of absorption and rate of metabolism is clinically significant. If a local anesthetic is absorbed more slowly than it is metabolized, its level in blood will remain low, and hence systemic reactions will be minimal. Conversely, if absorption outpaces metabolism, plasma drug levels will rise, and the risk of systemic toxicity will increase.

Adverse Effects

Adverse effects can occur locally or distant from the site of administration. Local effects are less common.

Central Nervous System. When absorbed in sufficient amounts, local anesthetics cause central nervous system

(CNS) excitation followed by depression. During the excitation phase, *seizures* may occur. If needed, excessive excitation can be managed with an IV benzodiazepine (diazepam or midazolam) or with IV thiopental (a rapid-acting barbiturate). Depressant effects range from *drowsiness* to *unconsciousness* to *coma*. Death can occur secondary to *depression of respiration*. If respiratory depression is prominent, mechanical ventilation with oxygen is indicated.

Cardiovascular System. When absorbed in sufficient amounts, local anesthetics can affect the heart and blood vessels. In the heart, these drugs suppress excitability in the myocardium and conducting system, and thereby can cause *bradycardia*, *heart block*, *reduced contractile force*, and *even cardiac arrest*. In blood vessels, anesthetics relax vascular smooth muscle; the resultant vasodilation can cause *hypotension*. As discussed in Chapter 49 (Antidysrhythmic Drugs), the cardiosuppressant actions of one local anesthetic—lidocaine—are exploited to treat dysrhythmias.

Allergic Reactions. An array of hypersensitivity reactions, ranging from *allergic dermatitis* to *anaphylaxis*, can be triggered by local anesthetics. These reactions, which are relatively uncommon, are much more likely with the *ester-type* anesthetics (eg, procaine) than with the amides. Patients allergic to one ester-type anesthetic are likely to be allergic to all other ester-type agents. Fortunately, cross-hypersensitivity between the esters and amides has not been observed. Hence, the amides can be used when allergies contraindicate use of ester-type anesthetics. Because they are unlikely to cause hypersensitivity reactions, the amide-type anesthetics have largely replaced the ester-type agents when administration by injection is required.

Use in Labor and Delivery. Local anesthetics can depress uterine contractility and maternal expulsion effort. Both actions can *prolong labor*. Also, local anesthetics can cross the placenta, causing *bradycardia* and *CNS depression* in the neonate.

Methemoglobinemia. Topical *benzocaine* can cause methemoglobinemia, a blood disorder in which hemoglobin is modified such that it cannot release oxygen to tissues. If enough hemoglobin is converted to methemoglobin, death can result. Methemoglobinemia has been associated with benzocaine liquids, sprays, and gels. Most cases were in children under 2 years old treated with benzocaine gel for teething pain. Owing to the risk of methemoglobinemia, topical benzocaine should not be used in children under the age of 2 years without the advice of a healthcare professional, and should be used with caution in older children and adults when applied to mucous membranes of the mouth.

PROPERTIES OF INDIVIDUAL LOCAL ANESTHETICS

Procaine

Procaine [Novocain], introduced in 1905, is the prototype of the ester-type local anesthetics. The drug is not effective topically, and hence must be given by injection. Administration in combination with epinephrine delays absorption. Although procaine is readily absorbed, systemic toxicity is rare. Why? Because plasma esterases rapidly convert the drug to inactive, nontoxic products. Being an ester-type anesthetic, procaine poses a greater risk of allergic reactions than do the amide-

type anesthetics. Individuals allergic to procaine should be considered allergic to all other ester-type anesthetics, but not to the amides.

For many years, procaine was the local anesthetic most preferred for use by injection. However, with the development of newer agents, use of procaine has sharply declined. Once popular in dentistry, procaine is rarely employed in that setting today.

Preparations. Procaine hydrochloride [Novocain] is available in solution for administration by injection. Epinephrine (at a final concentration of 1:100,000 or 1:200,000) may be combined with procaine to delay absorption.

Lidocaine

Lidocaine, introduced in 1948, is the prototype of the amide-type agents. One of today's most widely used local anesthetics, lidocaine can be administered topically and by injection. Anesthesia with lidocaine is more rapid, more intense, and more prolonged than with an equal dose of procaine. Effects can be extended by coadministration of epinephrine. Allergic reactions are rare, and individuals allergic to ester-type anesthetics are not cross-allergic to lidocaine. If plasma levels of lidocaine climb too high, CNS and cardiovascular toxicity can result. Inactivation is by hepatic metabolism.

In addition to its use in local anesthesia, lidocaine is employed to treat dysrhythmias (see Chapter 49). Control of dysrhythmias results from suppression of cardiac excitability secondary to blockade of cardiac sodium channels.

Preparations. Lidocaine hydrochloride [Xylocaine, others] is available in several formulations (cream, ointment, jelly, solution, aerosol, patch) for topical administration. Lidocaine for injection is available in concentrations ranging from 0.5% to 5%. Some injectable preparations contain epinephrine (1:50,000, 1:100,000, or 1:200,000).

Cocaine

Cocaine was our first local anesthetic. Clinical use was initiated in 1884 by Sigmund Freud and Karl Koller. Freud described the physiologic effects of cocaine while Koller focused on the drug's anesthetic actions. As you can see from its structure (see Fig. 26-1), cocaine is an ester-type anesthetic. In addition to causing local anesthesia, cocaine has pronounced effects on the sympathetic and central nervous systems. These sympathetic and CNS effects are due largely to blocking the reuptake of norepinephrine by adrenergic neurons.

Anesthetic Use. Cocaine is an excellent local anesthetic. Administration is topical. The drug is employed for anesthesia of the ear, nose, and throat. Anesthesia develops rapidly and persists for about an hour. Unlike other local anesthetics, cocaine causes intense vasoconstriction (by blocking norepinephrine uptake at sympathetic nerve terminals on blood vessels). Accordingly, the drug should not be given in combination with epinephrine or any other vasoconstrictor. Despite its ability to constrict blood vessels, cocaine is readily absorbed following application to mucous membranes. Significant effects on the brain and heart can result. The drug is inactivated by plasma esterases and liver enzymes.

CNS Effects. Cocaine produces generalized CNS stimulation. Moderate doses cause euphoria, loquaciousness, reduced fatigue, and increased sociability and alertness. Excessive doses can cause seizures. Excitation is followed by CNS depression. Respiratory arrest and death can result.

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In addition to its use in local anesthesia, lidocaine is employed to treat dysrhythmias (see Chapter 49). Control of dysrhythmias results from suppression of cardiac excitability secondary to blockade of cardiac sodium channels.

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Anesthetic Use. Cocaine is an excellent local anesthetic. Administration is topical. The drug is employed for anesthesia of the ear, nose, and throat. Anesthesia develops rapidly and persists for about an hour. Unlike other local anesthetics, cocaine causes intense vasoconstriction (by blocking norepinephrine uptake at sympathetic nerve terminals on blood vessels). Accordingly, the drug should not be given in combination with epinephrine or any other vasoconstrictor. Despite its ability to constrict blood vessels, cocaine is readily absorbed following application to mucous membranes. Significant effects on the brain and heart can result. The drug is inactivated by plasma esterases and liver enzymes.

CNS Effects. Cocaine produces generalized CNS stimulation. Moderate doses cause euphoria, loquaciousness, reduced fatigue, and increased sociability and alertness. Excessive doses can cause seizures. Excitation is followed by CNS depression. Respiratory arrest and death can result.

Although cocaine does not seem to cause substantial physical dependence, psychologic dependence can be profound. The drug is subject to widespread abuse and is classified under Schedule II of the Controlled Substances Act. Cocaine abuse is discussed in Chapter 40.

Cardiovascular Effects. Cocaine stimulates the heart and causes vasoconstriction. These effects result from (1) central stimulation of the sympathetic nervous system and (2) blockade of norepinephrine uptake in the periphery. Stimulation of the heart can produce *tachycardia* and potentially fatal *dysrhythmias*. Vasoconstriction can cause *hypertension*. Cocaine presents an especially serious risk to individuals with cardiovascular disease (eg, hypertension, dysrhythmias, angina pectoris).

When used for local anesthesia, cocaine should not be combined with epinephrine. Why? Because the combination would increase the risk of cardiovascular toxicity. Furthermore, since a vasoconstrictor would not significantly retard cocaine absorption, the combination would be irrational as well as dangerous.

Preparations and Administration. Cocaine hydrochloride is available as a powder (5 and 25 gm) and in solution (4% and 10%). Administration is topical. For application to the ear, nose, or throat, a 4% solution is usually employed. The drug must be dispensed in accord with the Controlled Substances Act.

Other Local Anesthetics

In addition to the drugs discussed above, several other local anesthetics are available. These agents differ with respect to indications, route of administration, mode of elimination, duration of action, and toxicity.

The local anesthetics can be grouped according to route of administration: topical versus injection. (Very few agents are administered by both routes. Why? Primarily because the drugs that are suitable for topical application are usually too toxic for parenteral use.) Table 26-2 lists the topically administered local anesthetics along with trade names and time course of action. Table 26-3 presents equivalent information for the injectable agents.

CLINICAL USE OF LOCAL ANESTHETICS

Local anesthetics may be administered *topically* (for surface anesthesia) and *by injection* (for infiltration anesthesia, nerve block anesthesia, intravenous regional anesthesia, epidural anesthesia, and spinal anesthesia). The uses and hazards of these anesthesia techniques are discussed below.

Topical Administration

Surface anesthesia is accomplished by applying the anesthetic directly to the skin or a mucous membrane. The agents employed most commonly are *lidocaine*, *tetracaine*, and *cocaine*.

Therapeutic Uses. Local anesthetics are applied to the *skin* to relieve pain, itching, and soreness of various causes, including infection, thermal burns, sunburn, diaper rash, wounds, bruises, abrasions, plant poisoning, and insect bites. Application may also be made to *mucous membranes* of the nose, mouth, pharynx, larynx, trachea, bronchi, vagina, and urethra. In addition, local anesthetics may be used to relieve discomfort associated with hemorrhoids, anal fissures, and pruritus ani.

Systemic Toxicity. Topical anesthetics applied to the skin can be absorbed in amounts sufficient to produce serious or even life-threatening effects. Cardiac toxicity can result in bradycardia, heart block, or cardiac arrest. CNS toxicity can result in seizures, respiratory depression, and coma. Obviously, the risk of toxicity increases with the amount absorbed, which is determined primarily by (1) the amount applied, (2) skin condition, and (3) skin temperature. Accordingly, to minimize the amount absorbed, and thereby minimize risk, patients should:

- Apply the smallest amount needed.
- Avoid application to large areas.
- Avoid application to broken or irritated skin.
- Avoid strenuous exercise, wrapping the site, and heating the site, all of which can accelerate absorption by increasing skin temperature.

TABLE 26-2 ■ Topical Local Anesthetics: Trade Names, Indications, and Time Course of Action

Chemical Class	Generic Name	Trade Name	Indications		Time Course of Action*	
			Skin	Mucous Membranes	Peak Effect (min)	Duration (min)
Amides	Dibucaine	Nupercainal	✓		Less than 5	15-45
	Lidocaine [†]	Xylocaine, Lidoderm, others	✓	✓	2-5	15-45
Esters	Benzocaine	Many names	✓	✓	Less than 5	15-45
	Cocaine	Generic only	✓	✓	1-5	30-60
	Tetracaine [‡]	None [‡]	✓	✓	3-8	30-60
Others	Dyclonine	Sucrets (spray)		✓	Less than 10	Less than 60
	Pramoxine	Tronothane, others	✓		3-5	—

*Based primarily on application to mucous membranes.

[†]Also administered by injection.

[‡]For application to the skin, tetracaine is available only in combination products, such as Cetacaine.

TABLE 26-3 ■ Injectable Local Anesthetics: Trade Names and Time Course of Action

Chemical Class	Generic Name	Trade Name	Time Course of Action*	
			Onset (min)	Duration (hr)
Amides	Lidocaine [†]	Xylocaine	Less than 2	0.5–1
	Bupivacaine	Marcaine, Sensorcaine	5	2–4
	Mepivacaine	Carbocaine, Polocaine	3–5	0.75–1.5
	Prilocaine	Citanest	Less than 2	1 or more
	Ropivacaine	Naropin	10–30 [‡]	0.5–6 [‡]
Esters [‡]	Procaine	Novocain	2–5	0.25–1
	Chloroprocaine	Nesacaine	6–12	0.5
	Tetracaine [†]	Pontocaine	15 or less	2–3

*Values are for infiltration anesthesia in the absence of epinephrine (epinephrine prolongs duration two- to threefold).

[†]Also administered topically.

[‡]Values are for epidural administration (without epinephrine).

[§]Because of the risk of allergic reactions, the ester anesthetics are rarely administered by injection.

Administration by Injection

Injection of local anesthetics carries significant risk and requires special skills. Accordingly, injections are usually performed by an anesthesiologist. Because severe systemic reactions may occur, equipment for resuscitation should be immediately available. Also, an IV line should be in place to permit rapid treatment of toxicity. Inadvertent injection into an artery or vein can cause severe toxicity. To ensure the needle is not in a blood vessel, it should be aspirated prior to injection. Following administration, the patient should be monitored for cardiovascular status, respiratory function, and state of consciousness. To reduce the risk of toxicity, local anesthetics should be administered in the lowest effective dose.

Infiltration Anesthesia

Infiltration anesthesia is achieved by injecting a local anesthetic directly into the immediate area of surgery or manipulation. Anesthesia can be prolonged by combining the anesthetic with epinephrine. However, epinephrine should not be used in areas supplied by end arteries (toes, fingers, nose, ears, penis), because restriction of blood flow at these sites may result in gangrene. The agents employed most frequently for infiltration anesthesia are *lidocaine* and *bupivacaine*.

Nerve Block Anesthesia

Nerve block anesthesia is achieved by injecting a local anesthetic into or near nerves that supply the surgical field, but at a site distant from the field itself. This technique has the advantage of producing anesthesia with doses that are smaller than those needed for infiltration anesthesia. Drug selection is based on required duration of anesthesia. For shorter procedures, *lidocaine* or *mepivacaine* might be used. For longer procedures, *bupivacaine* would be appropriate.

Intravenous Regional Anesthesia

Intravenous regional anesthesia is employed to anesthetize the extremities—hands, feet, arms, and lower legs, but not the entire leg (because too much anesthesia would be needed). Anesthesia is produced by injection into a distal vein of an arm or leg. Prior to giving the anesthetic, blood is removed from the limb (by gravity or by application of an Esmarch bandage), and a tourniquet is applied to the limb (proximal to the site of anesthetic injection) to prevent anesthetic from entering the systemic circulation. To ensure complete blockade of arterial flow throughout the procedure, a double tourniquet is used. Following injection, the anesthetic diffuses out of the vasculature and

becomes evenly distributed to all areas of the occluded limb. When the tourniquet is loosened at the end of surgery, about 15% to 30% of administered anesthetic is released into the systemic circulation. *Lidocaine*—without epinephrine—is the preferred agent for this type of anesthesia.

Epidural Anesthesia

Epidural anesthesia is achieved by injecting a local anesthetic into the epidural space (ie, within the spinal column but outside the dura mater). A catheter placed in the epidural space allows administration by bolus or by continuous infusion. Following administration, diffusion of anesthetic across the dura into the subarachnoid space blocks conduction in nerve roots and in the spinal cord itself. Diffusion through intervertebral foramina blocks nerves located in the paravertebral region. With epidural administration, anesthetic can reach the systemic circulation in significant amounts. As a result, when the technique is used during delivery, neonatal depression may result. *Lidocaine* and *bupivacaine* are popular drugs for epidural anesthesia. Because of the risk of death from cardiac arrest, the concentrated (0.75%) solution of bupivacaine must not be used in obstetric patients.

Spinal (Subarachnoid) Anesthesia

Technique. Spinal anesthesia is produced by injecting local anesthetic into the subarachnoid space. Injection is made in the lumbar region below the termination of the cord. Spread of anesthetic within the subarachnoid space determines the level of anesthesia achieved. Movement of anesthetic within the subarachnoid space is determined by two factors: (1) the density of the anesthetic solution and (2) the position of the patient. Anesthetics employed most commonly are *bupivacaine*, *lidocaine*, and *tetracaine*. All must be free of preservatives.

Adverse Effects. The most significant adverse effect of spinal anesthesia is hypotension. Blood pressure is reduced by venous dilation secondary to blockade of sympathetic nerves. (Loss of venous tone decreases the return of blood to the heart, causing a reduction in cardiac output and a corresponding fall in blood pressure.) Loss of venous tone can be compensated for by placing the patient in a 10- to 15-degree head-down position, which promotes venous return to the heart. If blood pressure cannot be restored through head-down positioning, drugs may be indicated; ephedrine and phenylephrine have been employed to promote vasoconstriction and enhance cardiac performance.

Autonomic blockade may disrupt function of the intestinal and urinary tracts, causing fecal incontinence and either urinary incontinence or urinary retention. The prescriber should be notified if the patient fails to void within 8 hours of the end of surgery.

Spinal anesthesia frequently causes headache. These “spinal” headaches are posture dependent and can be relieved by having the patient assume a supine position.

KEY POINTS

- Local anesthetics stop nerve conduction by blocking sodium channels in the axon membrane.
- Small, nonmyelinated neurons are blocked more rapidly than large, myelinated neurons.
- There are two classes of local anesthetics: ester-type anesthetics and amide-type anesthetics.
- Ester-type anesthetics (eg, procaine) occasionally cause allergic reactions and are inactivated by esterases in the blood.
- Amide-type anesthetics (eg, lidocaine) rarely cause allergic reactions and are inactivated by enzymes in the liver.
- Onset of anesthesia occurs most rapidly with anesthetics that are small, lipid soluble, and nonionized at physiologic pH.
- Termination of local anesthesia is determined in large part by regional blood flow. Hence, coadministration of epinephrine, a vasoconstrictor, will prolong anesthesia.
- Local anesthetics can be absorbed in amounts sufficient to cause systemic toxicity. Principal concerns are cardiac dysrhythmias and CNS effects (seizures, unconsciousness, coma). Death can occur.
- The risk of systemic toxicity from topical anesthetics applied to the *skin* can be reduced by (1) using the smallest amount needed, (2) avoiding application to large areas, (3) avoiding application to broken or irritated skin, and (4) avoiding strenuous exercise and use of dressings or heating pads (which can increase absorption by increasing skin temperature).

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Summary of Major Nursing Implications*

TOPICAL LOCAL ANESTHETICS

Benzocaine
Cocaine
Dibucaine
Dyclonine
Lidocaine
Pramoxine
Tetracaine

Preadministration Assessment

Therapeutic Goal

Reduction of discomfort associated with local disorders of the skin and mucous membranes.

Identifying High-Risk Patients

Ester-type local anesthetics are *contraindicated* for patients with a history of serious allergic reactions to these drugs. Avoid topical *benzocaine* in children under the age of 2 years.

Implementation: Administration

Routes

Topical application to skin and mucous membranes.

Administration

Apply in the lowest effective dosage to the smallest area required. If possible, avoid application to skin that is abraded or otherwise injured. Wear gloves when applying the anesthetic.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Systemic Toxicity. Absorption into the general circulation can cause systemic toxicity. Effects on the heart (brady-

cardia, atrioventricular [AV] heart block, cardiac arrest) and CNS (excitation, possibly including convulsions, followed by depression) are of greatest concern. Monitor blood pressure, pulse rate, respiratory rate, and state of consciousness. Have facilities for cardiopulmonary resuscitation available.

The risk of systemic toxicity is determined by the extent of absorption. To minimize absorption, apply topical anesthetics to the smallest surface area needed and, when possible, avoid application to injured skin.

Topical benzocaine can cause methemoglobinemia. Death can result. **Warn parents to avoid topical benzocaine in children under the age of 2 years, unless a healthcare professional says it's OK.** For older children and adults, exercise caution when topical benzocaine is applied to mucous membranes of the mouth.

Allergic Reactions. Severe allergic reactions are rare but can occur. Allergic reactions are most likely with ester-type anesthetics. Avoid ester-type agents in patients with a history of allergy to these drugs.

INJECTED LOCAL ANESTHETICS

Bupivacaine
Chlorprocaine
Lidocaine
Mepivacaine
Prilocaine
Procaine
Ropivacaine
Tetracaine

Preadministration Assessment

Therapeutic Goal

Production of local anesthesia for surgical, dental, and obstetric procedures.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Identifying High-Risk Patients

Ester-type local anesthetics are *contraindicated* for patients with a history of serious allergic reactions to these drugs.

Implementation: Administration

Preparation of the Patient

The nurse may be responsible for preparing the patient to receive an injectable local anesthetic. Preparation includes cleansing the injection site, shaving the site when indicated, and placing the patient in a position appropriate to receive the injection. Children, elderly patients, and uncooperative patients may require restraint prior to injection by some routes.

Administration

Injection of local anesthetics is performed by clinicians with special training in their use (physicians, dentists, nurse anesthetists).

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Systemic Reactions. Absorption into the general circulation can cause systemic toxicity. Effects on the CNS and heart are of greatest concern. CNS toxicity manifests as a brief period of excitement, possibly including convulsions,

followed by CNS depression, which can result in respiratory depression. Cardiotoxicity can manifest as bradycardia, AV heart block, and cardiac arrest. Monitor blood pressure, pulse rate, respiratory rate, and state of consciousness. Have facilities for cardiopulmonary resuscitation available. Manage CNS excitation with IV diazepam or IV thiopental.

Allergic Reactions. Severe allergic reactions are rare but can occur. These are most likely with ester-type anesthetics. Avoid ester-type agents in patients with a history of allergy to these drugs.

Labor and Delivery. Use of local anesthetics during delivery can cause bradycardia and CNS depression in the newborn. Monitor cardiac status. Avoid concentrated (0.75%) bupivacaine.

Self-Inflicted Injury. Since anesthetics eliminate pain, and since pain warns us about injury, patients recovering from anesthesia must be protected from inadvertent harm until the anesthetic wears off. **Caution the patient against activities that might result in unintentional harm.**

Spinal Headache and Urinary Retention. Patients recovering from spinal anesthesia may experience headache and urinary retention. Headache is posture dependent and can be minimized by having the patient remain supine for about 12 hours. Notify the prescriber if the patient fails to void within 8 hours.

*Patient education information is highlighted as **blue text**.

INHALATION ANESTHETICS**Basic Pharmacology**

Properties of an Ideal Inhalation Anesthetic

Balanced Anesthesia

Molecular Mechanism of Action

Minimum Alveolar Concentration

Pharmacokinetics

Adverse Effects

Drug Interactions

Adjuncts to Inhalation Anesthesia

Dosage and Administration

Classification of Inhalation Anesthetics

Properties of Individual Inhalation Anesthetics

Halothane

Isoflurane

Enflurane

Desflurane

Sevoflurane

Nitrous Oxide

Obsolete Inhalation Anesthetics

INTRAVENOUS ANESTHETICS

Short-Acting Barbiturates (Thiobarbiturates)

Benzodiazepines

Propofol

Fospropofol

Etomidate

Ketamine

Neuroleptic-Opioid Combination: Droperidol Plus Fentanyl

General anesthetics are drugs that produce unconsciousness and a lack of responsiveness to all painful stimuli. In contrast, *local anesthetics* do not reduce consciousness, and they blunt sensation only in a limited area (see Chapter 26).

General anesthetics can be divided into two groups: (1) inhalation anesthetics and (2) intravenous anesthetics. The inhalation anesthetics are the main focus of this chapter.

When considering the anesthetics, we need to distinguish between the terms *analgesia* and *anesthesia*. Analgesia refers specifically to loss of sensibility to pain. In contrast, anesthesia refers not only to loss of pain but to loss of all other sensations (eg, touch, temperature, taste), and to loss of consciousness as well. Hence, while analgesics (eg, aspirin, morphine) can selectively reduce pain without affecting other sensory modalities and without reducing consciousness, the general anesthetics have no such selectivity: During general anesthesia, all sensation is lost, and consciousness is lost too.

The development of general anesthetics has had an incalculable impact on the surgeon's art. The first general anesthetic—ether—was introduced by Dr. William T. Morton in 1846. Prior to this, surgery was a brutal and exquisitely painful ordeal, undertaken only in the most desperate circumstances. Immobilization of the surgical field was accomplished with the aid of strong men and straps. Survival of the patient was determined by the surgeon's speed—not his finesse. With the advent of general anesthesia, all of this changed. General anesthesia produced a patient who slept through surgery and experienced no pain. These changes allowed surgeons to develop the lengthy and intricate procedures that are routine today. Such procedures were unthinkable before general anesthetics became available.

In addition to their use in surgery, general anesthetics are used to facilitate other procedures, including endoscopy, urologic procedures, radiation therapy, electroconvulsive therapy, transbronchial biopsy, and various cardiologic procedures.

INHALATION ANESTHETICS**BASIC PHARMACOLOGY**

In this section, we consider the inhalation anesthetics as a group. Our focus is on properties of an ideal anesthetic, pharmacokinetics of inhalation anesthetics, adverse effects of the inhalation anesthetics, and drugs employed as adjuncts to anesthesia.

Properties of an Ideal Inhalation Anesthetic

An ideal inhalation anesthetic would produce unconsciousness, analgesia, muscle relaxation, and amnesia. Furthermore, induction of anesthesia would be brief and pleasant, as would the process of emergence. Depth of anesthesia could be raised or lowered with ease. Adverse effects would be minimal, and the margin of safety would be large. As you might guess, the ideal inhalation anesthetic does not exist: No single agent has all of these qualities.

Balanced Anesthesia

The term *balanced anesthesia* refers to the use of a combination of drugs to accomplish what we cannot achieve with an inhalation anesthetic alone. Put another way, balanced anesthesia is a technique employed to compensate for the lack of an ideal anesthetic. Drugs are combined in balanced anesthesia to ensure that induction is smooth and rapid, and that analgesia and muscle relaxation are adequate. The agents used most commonly to achieve these goals are (1) propofol and

short-acting barbiturates (for induction of anesthesia), (2) neuromuscular blocking agents (for muscle relaxation), and (3) opioids and nitrous oxide (for analgesia). The primary benefit of combining drugs to achieve surgical anesthesia is that doing so permits full general anesthesia at doses of the inhalation anesthetic that are lower (safer) than those that would be required if surgical anesthesia were attempted using an inhalation anesthetic alone.

Molecular Mechanism of Action

Our understanding of how inhalation anesthetics act has changed dramatically. In the past, we believed that anesthetics worked through nonspecific effects on neuronal membranes. Today, we believe they work through selective alteration of synaptic transmission. However, despite recent advances, we still don't know with certainty just how these drugs work.

More than 100 years ago, scientists postulated that inhalation anesthetics produced their effects through nonspecific interactions with lipid components of the neuronal cell membrane. This long-standing theory was based on the observation that there was a direct correlation between the potency of an anesthetic and its lipid solubility. That is, the more readily an anesthetic could dissolve in the lipid matrix of the neuronal membrane, the more readily that agent could produce anesthesia. Hence the theory that anesthetics dissolve into neuronal membranes, disrupt their structure, and thereby suppress axonal conduction and possibly synaptic transmission. However, this theory was called into question by an important observation: Enantiomers of the same anesthetic have different actions. Recall that enantiomers are simply mirror-image molecules that have identical atomic components, and hence have identical physical properties, including lipid solubility. Therefore, since enantiomers have the same ability to penetrate the axonal membrane, but do not have the same ability to produce anesthesia, a property other than lipid solubility must underlie anesthetic actions.

Current data indicate that inhalation anesthetics work by *enhancing transmission at inhibitory synapses* and by *depressing transmission at excitatory synapses*. Except for nitrous oxide, all of the agents used today enhance activation of receptors for gamma-aminobutyric acid (GABA), the principal inhibitory transmitter in the central nervous system (CNS). As a result, these drugs promote generalized inhibition of CNS function. It should be noted that anesthetics do not acti-

vate GABA receptors directly. Rather, by binding with the GABA receptor, they increase receptor sensitivity to activation by GABA itself. How does nitrous oxide work? Probably by blocking the actions of *N*-methyl-D-aspartate (NMDA), an excitatory neurotransmitter. Nitrous oxide appears to bind with the NMDA receptor and thereby prevent receptor activation by NMDA itself.

Minimum Alveolar Concentration

The minimum alveolar concentration (MAC), also known as the median alveolar concentration, is an index of inhalation anesthetic potency. The MAC is defined as *the minimum concentration of drug in the alveolar air that will produce immobility in 50% of patients exposed to a painful stimulus*. Note that, by this definition, a *low* MAC indicates *high* anesthetic potency.

From a clinical perspective, knowledge of the MAC of an anesthetic is of great practical value: The MAC tells us approximately how much anesthetic the inspired air must contain to produce anesthesia. A low MAC indicates that the inspired air need contain only low concentrations of the anesthetic to produce surgical anesthesia. The opposite is true for drugs with a high MAC. Fortunately, most inhalation anesthetics have low MACs (Table 27-1). However, one important agent—nitrous oxide—has a very high MAC. The MAC is so high, in fact, that surgical anesthesia cannot be achieved using nitrous oxide alone.

Please note that, to produce general anesthesia in *all* patients, the inspired anesthetic concentration should be 1.2 to 1.5 times the MAC. Why? Because if the concentration were simply equal to the MAC, 50% of patients would receive less than they need.

Pharmacokinetics

Uptake and Distribution

To produce therapeutic effects, an inhalation anesthetic must reach a CNS concentration sufficient to suppress neuronal excitability. The principal determinants of anesthetic concentration are (1) uptake from the lungs and (2) distribution to the CNS and other tissues. The kinetics of anesthetic uptake and distribution are complex, and we will not try to cover them in depth.

Uptake. A major determinant of anesthetic uptake is the concentration of anesthetic in the inspired air: The greater the

TABLE 27-1 • Properties of the Major Inhalation Anesthetics

Drug	MAC* (%)	Analgesic Effect	Effect on Blood Pressure	Effect on Respiration	Muscle Relaxant Effect	Extent of Metabolism	Compatible with Epinephrine
Nitrous oxide	105	++++	→	→	0	0	Yes
Halothane†	0.75	++	↓	↓↓	+	20%	No
Desflurane	4.58	++	↓	↓↓	++	0.02%	Yes
Enflurane	1.68	++	↓	↓↓	++	2.4%	Yes‡
Isolfurane	1.15	++	↓	↓↓	++	0.2%	Yes
Sevoflurane	1.71	++	↓	↓↓	++	3%	Yes

*Minimum alveolar concentration.

†No longer used in the United States and Canada.

‡Enflurane sensitizes the myocardium to catecholamines, but less so than halothane.

anesthetic concentration, the more rapid uptake will be. Other factors that influence uptake are pulmonary ventilation, solubility of the anesthetic in blood, and blood flow through the lungs. An increase in any of these will increase the speed of uptake.

Distribution. Distribution to specific tissues is determined largely by regional blood flow. Anesthetic levels rise rapidly in the brain, kidney, heart, and liver—tissues that receive the largest fraction of the cardiac output. Anesthetic levels in these tissues equilibrate with those in blood 5 to 15 minutes after inhalation starts. In skin and skeletal muscle—tissues with an intermediate blood flow—equilibration occurs more slowly. The most poorly perfused tissues—fat, bone, ligaments, and cartilage—are the last to equilibrate with anesthetic levels in the blood.

Elimination

Export in the Expired Breath. Inhalation anesthetics are eliminated almost entirely via the lungs; hepatic metabolism is minimal. The same factors that determine anesthetic uptake (pulmonary ventilation, blood flow to the lungs, anesthetic solubility in blood and tissues) also determine the rate of elimination. Since blood flow to the brain is high, anesthetic levels in the brain drop rapidly when administration is stopped. Anesthetic levels in tissues that have a lower blood flow decline more slowly. Because anesthetic levels in the CNS decline more rapidly than levels in other tissues, patients can awaken from anesthesia long before all anesthetic has left the body.

Metabolism. Most inhalation anesthetics undergo very little metabolism. Hence, metabolism does not influence the time course of anesthesia. However, since some metabolites can be toxic, metabolism is nonetheless clinically relevant.

Adverse Effects

The adverse effects discussed here apply to the inhalation anesthetics as a group. Not all of these effects are seen with every anesthetic.

Respiratory and Cardiac Depression. Depression of respiratory and cardiac function is a concern with virtually all inhalation anesthetics. Doses only 2 to 4 times greater than those needed for surgical anesthesia are sufficient to cause potentially lethal depression of pulmonary and cardiac function. To compensate for respiratory depression, and to maintain a steady rate of administration, almost all patients require mechanical support of ventilation.

Sensitization of the Heart to Catecholamines. Some anesthetics—most notably *halothane*—can increase the sensitivity of the heart to stimulation by catecholamines (eg, norepinephrine, epinephrine). While in this sensitized state, the heart may develop dysrhythmias in response to catecholamines. Exposure to catecholamines may result from two causes: (1) release of endogenous catecholamines (in response to pain or other stimuli of the sympathetic nervous system), and (2) topical application of catecholamines to control bleeding in the surgical field.

Malignant Hyperthermia. Malignant hyperthermia is a rare but potentially fatal reaction that can be triggered by all inhalation anesthetics (except nitrous oxide). Predisposition to the reaction is genetic. Malignant hyperthermia is characterized by muscle rigidity and a profound elevation of

temperature—sometimes to as high as 43°C (109°F). Left untreated, the reaction can rapidly prove fatal. The risk of malignant hyperthermia is greatest when an inhalation anesthetic is combined with *succinylcholine*, a neuromuscular blocker that also can trigger the reaction. Diagnosis and management of malignant hyperthermia are discussed in Chapter 16.

Aspiration of Gastric Contents. During the state of anesthesia, reflexes that normally prevent aspiration of gastric contents into the lungs are abolished. Aspiration of gastric fluids can cause bronchospasm and pneumonia. Use of an endotracheal tube isolates the trachea and can thereby help prevent these complications.

Hepatotoxicity. Rarely, patients receiving inhalation anesthesia develop serious liver dysfunction. The risk is about equal with all anesthetics.

Toxicity to Operating Room Personnel. Chronic exposure to low levels of anesthetics may harm operating room personnel. Suspected reactions include headache, reduced alertness, and spontaneous abortion. Risk can be reduced by venting anesthetic gases from the operating room.

Drug Interactions

Several classes of drugs—analgesics, CNS depressants, CNS stimulants—can influence the amount of anesthetic required to produce anesthesia. Opioid analgesics allow a reduction in anesthetic dosage. Why? Because, when opioids are present, analgesia needn't be produced by the anesthetic alone. Similarly, because CNS depressants (barbiturates, benzodiazepines, alcohol) add to the depressant effects of anesthetics, concurrent use of CNS depressants lowers the required dose of anesthetic. Conversely, concurrent use of CNS stimulants (amphetamines, cocaine) increases the required dose of anesthetic.

Adjuncts to Inhalation Anesthesia

Adjunctive drugs are employed to complement the beneficial effects of inhalation anesthetics and to counteract their adverse effects. Some adjunctive agents are administered before surgery, some during, and some after.

Preanesthetic Medications

Preanesthetic medications are administered for three main purposes: (1) reducing anxiety, (2) producing perioperative amnesia, and (3) relieving preoperative and postoperative pain. In addition, preanesthetic medications may be used to suppress certain adverse responses: excessive salivation, excessive bronchial secretion, coughing, bradycardia, and vomiting.

Benzodiazepines. Benzodiazepines are given preoperatively to reduce anxiety and promote amnesia. When administered properly, these drugs produce sedation with little or no respiratory depression. Intravenous midazolam [Versed] is used most often.

Opioids. Opioids (eg, morphine, fentanyl) are administered to relieve preoperative and postoperative pain. These drugs may also help by suppressing cough.

Opioids can have adverse effects. Because they depress the CNS, opioids can delay awakening after surgery. Effects on the bowel and urinary tract may result in postoperative consti-

pation and urinary retention. Stimulation of the chemoreceptor trigger zone promotes vomiting. Opioid-induced respiratory depression adds with anesthetic-induced respiratory depression, thereby increasing the risk of postoperative respiratory distress.

Alpha₂-Adrenergic Agonists. Two alpha₂ agonists—clonidine and dexmedetomidine—are employed as adjuncts to anesthesia. Both produce their effects through actions in the CNS.

Clonidine is used for hypertension and pain reduction. When administered prior to surgery, the drug reduces anxiety and causes sedation. In addition, it permits a reduction in anesthetic and analgesic dosages. Analgesic properties of clonidine are discussed further in Chapter 28; antihypertensive properties are discussed in Chapters 19 and 47. The formulation used for analgesia is marketed under the trade name *Duraclon*; the formulation for hypertension is marketed as *Catapres*.

Dexmedetomidine [Precedex] is a highly selective alpha₂-adrenergic agonist currently approved only for short-term sedation in critically ill patients. However, the drug is also used for other purposes, including enhancement of sedation and analgesia in patients undergoing anesthesia. The pharmacology of dexmedetomidine is discussed further in Chapter 28.

Anticholinergic Drugs. Anticholinergic drugs (eg, atropine) may be given to decrease the risk of bradycardia during surgery. Surgical manipulations can trigger parasympathetic reflexes, which in turn can produce profound vagal slowing of the heart. Pretreatment with a cholinergic antagonist prevents bradycardia from this cause.

At one time, anticholinergic drugs were needed to prevent excessive bronchial secretions associated with anesthesia. Older anesthetic agents (eg, ether) irritate the respiratory tract, and thereby cause profuse bronchial secretions. Cholinergic blockers were given to suppress this response. Since the inhalation anesthetics used today are much less irritating, bronchial secretions are minimal. Consequently, although anticholinergic agents are still employed as adjuncts to anesthesia, their purpose is no longer to suppress bronchial secretions (although they may still help by suppressing salivation).

Neuromuscular Blocking Agents

Most surgical procedures require skeletal muscle relaxation, a state achieved with neuromuscular blockers (eg, succinylcholine, pancuronium). By using these drugs, we can reduce the dose of general anesthetic. Why? Because we don't need the

very high doses of anesthetic that would be required if we tried to produce muscle relaxation with the anesthetic alone.

Muscle relaxants can have adverse effects. Neuromuscular blocking agents prevent contraction of all skeletal muscles, including the diaphragm and other muscles of respiration. Accordingly, patients require mechanical support of ventilation during surgery. Patients recovering from anesthesia may have reduced respiratory capacity owing to residual neuromuscular blockade. Accordingly, respiration must be monitored until recovery is complete.

It is important to appreciate that neuromuscular blockers produce a state of total flaccid paralysis. In this condition, a patient could be fully awake while seeming asleep. Incidents in which paralyzed patients have been awake during surgery, but unable to communicate their agony, are all too common: Every year in the United States, of the 21 million people who undergo anesthesia, an estimated 2000 to 4000 wake up during the procedure. Because neuromuscular blockade can obscure depth of anesthesia, and because failure to maintain adequate anesthesia can result in true horror, the clinician administering anesthesia must be especially watchful to ensure that the anesthetic dosage is adequate.

Postanesthetic Medications

Analgesics. Analgesics are needed to control postoperative pain. If pain is severe, opioids are indicated. For mild pain, aspirin-like drugs may suffice.

Antiemetics. Patients recovering from anesthesia often experience nausea and vomiting. This can be suppressed with antiemetics. Among the most effective is *ondansetron* [Zofran], a drug developed to suppress nausea and vomiting in patients undergoing cancer chemotherapy. Other commonly used antiemetics are *promethazine* and *droperidol*.

Muscarinic Agonists. Abdominal distention (from atony of the bowel) and urinary retention are potential postoperative complications. Both conditions can be relieved through activation of muscarinic receptors. The muscarinic agonist employed most often is *bethanechol*.

Dosage and Administration

Administration of inhalation anesthetics is performed only by anesthesiologists (physicians) and anesthetists (nurses). Clinicians who lack the training of these specialists have no authority to administer anesthesia. Since knowledge of anesthetic dosage and administration is the responsibility of specialists, and since this text is designed for beginning students, details on dosage and administration are not presented. If you need this information, consult a textbook of anesthesiology.

Classification of Inhalation Anesthetics

Inhalation anesthetics fall into two basic categories: *gases* and *volatile liquids*. The gases, as their name implies, exist in a gaseous state at atmospheric pressure. The volatile liquids exist in a liquid state at atmospheric pressure, but can be easily volatilized (converted to a vapor) for administration by inhalation. The inhalation anesthetics in current use are listed in Table 27-2. The volatile liquids—halothane, enflurane, isoflurane, desflurane, and sevoflurane—are similar to one another in structure and function. The only gas in current use is nitrous oxide.

TABLE 27-2 ■ Classification of the Inhalation Anesthetics

Class	Anesthetic	
	Generic Name	Trade Name
Volatile Liquids	Halothane*	Fluothane
	Enflurane	Ethrane
	Isoflurane	Forane
	Desflurane	Suprane
	Sevoflurane	Ultane
Gases	Nitrous oxide	

*No longer used in the United States or Canada.

PROPERTIES OF INDIVIDUAL INHALATION ANESTHETICS

Halothane

Halothane is the prototype of the volatile inhalation anesthetics. The drug was introduced in 1956, and for decades has been the standard against which newer volatile liquids are judged. Although halothane is no longer available (it was recently withdrawn owing to concerns about liver toxicity), we will continue to use it as our prototype. Why? Because halothane embodies properties that typify the inhalation anesthetics, and hence the drug remains a valuable example for teaching and learning.

Anesthetic Properties

Halothane is an effective anesthetic. For some procedures, anesthesia may be produced with halothane alone. Other procedures require adjunctive drugs.

Potency. Halothane is a high-potency anesthetic, and hence has a low MAC (0.75%), indicating that unconsciousness can be produced when the drug's concentration in alveolar air is only 0.75%.

Time Course. Induction of anesthesia is smooth and relatively rapid. However, although halothane can act quickly, in actual practice, induction is usually produced with thiopental, a rapid-acting barbiturate. Once the patient is unconscious, depth of anesthesia can be raised or lowered with ease. Patients awaken about 1 hour after ceasing halothane inhalation.

Analgesia. Halothane is a weak analgesic. Consequently, when the drug is used for surgical anesthesia, coadministration of a strong analgesic is usually required. The analgesics most commonly employed are opioids (eg, morphine) and nitrous oxide.

Muscle Relaxation. Although halothane has muscle-relaxant actions, the degree of relaxation is generally inadequate for surgery. Accordingly, concurrent use of a neuromuscular blocking agent (eg, pancuronium) is usually required. Although relaxation of skeletal muscle is only moderate, halothane does promote significant relaxation of uterine smooth muscle. Consequently, when used in obstetrics, halothane may inhibit uterine contractions, thereby delaying delivery and possibly increasing postpartum bleeding.

Adverse Effects

Hypotension. Halothane causes a dose-dependent reduction in blood pressure. Doses only twice those needed for surgical anesthesia can produce complete circulatory failure and death. Halothane promotes hypotension by two mechanisms. First, the drug depresses myocardial contractility, and can thereby reduce cardiac output by 20% to 50%. Second, halothane increases vagal tone, which slows heart rate and thereby reduces cardiac output even further.

Respiratory Depression. Halothane produces significant depression of respiration. To ensure adequate oxygenation, two measures are implemented: (1) mechanical or manual ventilatory support and (2) enrichment of the inspired gas mixture with oxygen.

Promotion of Dysrhythmias. Halothane promotes dysrhythmias in two ways. First, the drug sensitizes the myocardium to catecholamines. Second, it prolongs the QT interval (see discussion of QT interval drugs in Chapter 7). To reduce the risk of dysrhythmias, epinephrine and other catechol-

amines should be used with caution. Also, caution is required in patients with existing QT prolongation and in those taking other drugs known to cause QT prolongation.

Malignant Hyperthermia. Genetically predisposed patients may experience malignant hyperthermia. Accordingly, patients with a personal or familial history of malignant hyperthermia should not receive halothane, unless there is no other option. If halothane is employed, it must not be combined with succinylcholine, which would further increase the risk of malignant hyperthermia.

Hepatotoxicity. Rarely, halothane produces hepatitis, sometimes progressing to massive hepatic necrosis and death. The incidence of fulminant hepatic failure is 1 in 30,000. Hepatotoxicity is thought to result from an autoimmune process triggered by metabolites of halothane that have formed complexes with liver proteins. Owing to concerns about liver damage, halothane has been voluntarily withdrawn in the United States and Canada.

Other Adverse Effects. Postoperative nausea and vomiting may occur, but these reactions are less common with halothane than with older anesthetics (eg, ether). By decreasing blood flow to the kidney, halothane can cause a substantial decrease in urine output.

Elimination

The majority (60% to 80%) of an administered dose is eliminated intact in the exhaled breath. Hepatic metabolism accounts for about 20% of elimination. However, as you can see from Table 27-1, the percent metabolized is much higher than with any other inhalation agent.

Isoflurane

Isoflurane [Forane] is widely used. The drug is potent (MAC = 1.15%) and has properties much like those of halothane. Induction of anesthesia is smooth and rapid, depth of anesthesia can be adjusted with speed and ease, and patients emerge from anesthesia rapidly. Like other volatile liquids, isoflurane causes respiratory depression and hypotension. With isoflurane, hypotension results from vasodilation rather than from reduced cardiac output. Isoflurane is a better muscle relaxant than halothane, but nonetheless is usually employed with a neuromuscular blocker. Like halothane, isoflurane suppresses uterine contractions. In contrast to halothane, isoflurane is not associated with renal or hepatic toxicity. Isoflurane is eliminated almost entirely in the expired breath; only 0.2% undergoes metabolism.

The cardiac actions of isoflurane differ significantly from those of halothane. Unlike halothane, isoflurane does not cause myocardial depression. Hence, cardiac output is not decreased. Furthermore, isoflurane does not sensitize the myocardium to catecholamines. Hence, patients can be given epinephrine and other catecholamines with little fear of precipitating a dysrhythmia. Finally, isoflurane is not associated with QT prolongation.

Enflurane

Enflurane [Ethrane] has pharmacologic properties very similar to those of halothane. Enflurane was introduced in 1973 and became quite popular. However, with the introduction of newer agents with preferable kinetics and fewer risks, use of enflurane has declined.

Comparison of enflurane with halothane reveals important similarities and a few significant differences. Both anesthetics are very potent: the MAC of enflurane is 1.68%, compared with 0.75% for halothane. As with halo-

thane, induction of anesthesia is smooth and rapid, and depth of anesthesia can be changed quickly and easily. Like halothane, enflurane produces substantial depression of respiration. Accordingly, patients are likely to need ventilatory support; the concentration of inspired oxygen should be at least 35%. Muscle relaxation induced by enflurane is greater than with halothane. However, despite this action, a neuromuscular blocker is usually employed (to permit a reduction of enflurane dosage). Like halothane, enflurane can suppress uterine contractions, thereby impeding labor. Significantly, sensitization of the myocardium to catecholamines is less than with halothane. As a result, patients can be given catecholamines with relative safety. High doses of enflurane can induce seizures, a response not seen with halothane. Obviously, enflurane should be avoided in patients with a history of seizure disorders. Like halothane, enflurane is eliminated primarily in the exhaled breath as the intact parent compound. About 2% is eliminated by hepatic metabolism.

Desflurane

Desflurane [Suprane] is nearly identical in structure to isoflurane. Induction occurs more rapidly than with any other volatile anesthetic; depth of anesthesia can be changed quickly; and recovery occurs only minutes after ceasing administration. Desflurane is indicated for *maintenance* of anesthesia in adults and children and for *induction* of anesthesia in adults. The drug is not approved for induction in children and infants owing to a high incidence of respiratory difficulties (laryngospasm, apnea, increased secretions), which are caused by the drug's pungency. Like isoflurane, desflurane can cause respiratory depression and hypotension secondary to vasodilation. During induction, or in response to an abrupt increase in desflurane blood levels, heart rate and blood pressure may increase, causing tachycardia and hypertension. Postoperative nausea and vomiting are possible. Malignant hypertension has occurred in experimental animals. Desflurane undergoes even less metabolism than isoflurane. Hence, the risk of postoperative organ injury is probably low.

Sevoflurane

Sevoflurane [Ultane, Sevorane⁺] is similar to desflurane. The drug is approved for induction and maintenance of anesthesia in adults and children. As with desflurane, induction is rapid, depth of anesthesia can be adjusted easily, and recovery occurs minutes after ceasing inhalation. Because onset and recovery occur quickly, sevoflurane is widely used for outpatient procedures. In contrast to desflurane, sevoflurane has a pleasant odor and is not a respiratory irritant. Accordingly, the drug is suitable for mask induction in children. Sevoflurane has a MAC of 1.71% and is eliminated primarily in the exhaled breath; about 3% gets metabolized. Adverse effects are minimal. The most common problem is postoperative nausea and vomiting. In contrast to desflurane, sevoflurane does not cause tachycardia or hypertension. Occasionally, sevoflurane produces extreme heat and even fire in the administration apparatus, usually when the CO₂ adsorbent in the apparatus has become desiccated.

Nitrous Oxide

Nitrous oxide (aka "laughing gas") differs from the volatile liquid anesthetics with respect to pharmacologic properties and uses. Pharmacologically, nitrous oxide is unique in two ways: (1) it has very low *anesthetic* potency, whereas the anesthetic potency of the other inhalation agents is high, and (2) it has very high *analgesic* potency, whereas the analgesic potency of other inhalation agents is low. Because of these properties, nitrous oxide has a unique pattern of use: owing to its low anesthetic potency, nitrous oxide is never employed as a primary anesthetic. However, owing to its high analgesic potency, nitrous oxide is frequently combined with other inhalation agents to enhance analgesia.

Because nitrous oxide has such low anesthetic potency, it is *virtually impossible to produce surgical anesthesia employing nitrous oxide alone*. The MAC of nitrous oxide is very high—greater than 100%. This tells us that, even if it were possible to administer 100% nitrous oxide (ie, inspired gas that contains only nitrous oxide and no oxygen), this would still be insufficient to produce surgical anesthesia. Because practical considerations (ie, the need to administer at least 30% oxygen) limit the maximum usable concentra-

tion of nitrous oxide to 70%, and because much higher concentrations are needed to produce surgical anesthesia, it is clear that full anesthesia cannot be achieved with nitrous oxide alone.

Despite its low anesthetic potency, nitrous oxide is one of our most widely used inhalation agents: *Many patients undergoing general anesthesia receive nitrous oxide to supplement the analgesic effects of the primary anesthetic*. As indicated in Table 27-1, the analgesic effects of nitrous oxide are substantially greater than those of the other inhalation agents. In fact, nitrous oxide is such a potent analgesic that inhaling 20% nitrous oxide can produce pain relief equivalent to that of morphine. The advantage of providing analgesia with nitrous oxide, rather than relying entirely on the primary anesthetic, is that the dosage of the primary anesthetic can be significantly decreased—usually by 50% or more. As a result, respiratory and cardiac depression are reduced, and emergence from anesthesia is accelerated. When employed in combination with other inhalation anesthetics, nitrous oxide is administered at a concentration of 70%.

At therapeutic concentrations, nitrous oxide has no serious adverse effects. The drug is not toxic to the CNS, and does not cause cardiovascular or respiratory depression. Furthermore, the drug is not likely to precipitate malignant hyperthermia. The major concern with nitrous oxide is postoperative *nausea* and *vomiting*, which occur more often with this agent than with any other inhalation anesthetic.

In certain settings, nitrous oxide can be used alone—but only for *analgesia*, not anesthesia. Nitrous oxide alone is used for analgesia in dentistry and during delivery.

Obsolete Inhalation Anesthetics

Several once-popular anesthetics are now obsolete. Five of these agents—*ethylene*, *cyclopropane*, *diethyl ether (ether)*, *vinyl ether*, and *ethyl chloride*—are gases. They were abandoned because they are explosive and because they offer no advantages over newer, less hazardous anesthetics. Only two volatile liquids—*methoxyflurane* and *halothane*—have been discontinued. The reasons are kidney damage (with methoxyflurane) and liver damage (with halothane).

INTRAVENOUS ANESTHETICS

Intravenous anesthetics may be used alone or to supplement the effects of inhalation agents. When combined with an inhalation anesthetic, IV agents offer two potential benefits: (1) they permit dosage of the inhalation agent to be reduced and (2) they produce effects that cannot be achieved with an inhalation agent alone. Three of the drug families discussed in this section—opioids, barbiturates, and benzodiazepines—are considered at length in other chapters. Accordingly, discussion here is limited to their use in anesthesia.

Short-Acting Barbiturates (Thiobarbiturates)

Short-acting barbiturates, administered intravenously, are employed for *induction of anesthesia*. Two agents are available: *thiopental sodium* [Pentothal] and *methohexital sodium* [Brevital].

Thiopental. Thiopental [Pentothal] was the first short-acting barbiturate and is the prototype for the group. This drug acts rapidly to produce unconsciousness. Analgesic and muscle-relaxant effects are weak.

Thiopental is a mainstay of anesthesia induction. Compared with other induction agents, thiopental causes a smaller drop in blood pressure, and hence is preferred for geriatric, cardiovascular, and neurosurgical patients. In addition, thiopental is the drug of choice for induction during cesarean delivery.

Thiopental has a rapid onset and short duration. Unconsciousness occurs 10 to 20 seconds after IV injection. If thiopental is not followed by inhalation anesthesia, the patient will wake up in about 10 minutes.

The time course of anesthesia is determined by thiopental's pattern of distribution. Thiopental is highly lipid soluble, and therefore enters the brain rapidly to begin its effects. Anesthesia is terminated as thiopental undergoes redistribution from the brain and blood to other tissues. Practically no metabolism of the drug takes place between giving the injection and the time of waking.

Like most of the inhalation anesthetics, thiopental causes cardiovascular and respiratory depression. If administered too rapidly, the drug may cause apnea.

In addition to its medical use, thiopental is part of a three-drug regimen used for capital punishment. Thiopental is given first to induce rapid unconsciousness. Pancuronium, a muscle relaxant, is given next to cause paralysis. And then potassium chloride is given to stop the heart.

Despite its medical importance, thiopental is in short supply. In 2009, Hospira, the only FDA-approved source, stopped making the drug. Furthermore, importing thiopental is difficult. Why? Because many countries object to capital punishment, and hence do not allow export of thiopental to the United States, owing to concerns that some of the drug might be diverted for executions.

Benzodiazepines

When administered in large doses, benzodiazepines produce unconsciousness and amnesia. Because of this ability, IV benzodiazepines are occasionally given to induce anesthesia. However, short-acting barbiturates are generally preferred. Three benzodiazepines—*diazepam*, *lorazepam*, and *midazolam*—are administered IV for induction. Diazepam is the prototype for the group. The basic pharmacology of the benzodiazepines is discussed in Chapter 34.

Diazepam. Induction with IV diazepam [Valium] occurs more slowly than with barbiturates. Unconsciousness develops in about 1 minute. Diazepam causes very little muscle relaxation and no analgesia. Cardiovascular and respiratory depression are usually only moderate. However, on occasion respiratory depression is severe. Therefore, whenever diazepam is administered IV, facilities for respiratory support must be immediately available.

Midazolam. Intravenous midazolam [Versed] may be used for *induction of anesthesia* and to produce *conscious sedation*. When used for induction, midazolam is usually combined with a short-acting barbiturate. Unconsciousness develops in 80 seconds.

Conscious sedation can be produced by combining midazolam with an opioid analgesic (eg, morphine, fentanyl). The state is characterized by sedation, analgesia, amnesia, and lack of anxiety. The patient is unperturbed and passive, but responsive to commands, such as "open your eyes." Conscious sedation persists for an hour or so and is suitable for minor surgeries and endoscopic procedures.

Midazolam can cause dangerous cardiorespiratory effects, including respiratory depression and respiratory and cardiac arrest. Accordingly, the drug should be used only in a setting that permits constant monitoring of cardiac and respiratory status. Facilities for resuscitation must be immediately available. The risk of adverse effects can be minimized by injecting midazolam slowly (over 2 or more minutes) and by waiting another 2 or more minutes for full effects to develop before dosing again.

Propofol

Actions and Uses. Propofol [Diprivan] was approved in 1989, and is now our most widely used IV anesthetic. About 90% of patients who undergo anesthesia receive the drug. Propofol is indicated for induction and maintenance of general anesthesia as part of a balanced anesthesia technique. In addition, the drug can be used to sedate patients undergoing mechanical ventilation, radiation therapy, and diagnostic procedures (eg, endoscopy, magnetic resonance imaging). How does propofol work? It promotes release of GABA, the major inhibitory neurotransmitter in the brain. The result is generalized CNS depression. Propofol has no analgesic actions. Like thiopental, propofol has a rapid onset and ultra short duration. Unconsciousness develops in less than 60 seconds after IV injection, but lasts only 3 to 5 minutes. As with thiopental, redistribution from the brain to other tissues explains the speed of awakening. For extended sedation, a continuous, low-dose infusion is used, not to exceed 4 mg/kg/hr.

Adverse Effects. Propofol can cause profound *respiratory depression* (including apnea) and *hypotension*. The drug has a relatively narrow therapeutic range and can cause death from respiratory arrest. To reduce risk, propofol should be used with caution in elderly patients, hypovolemic patients, and patients with compromised cardiac function. With all patients, facilities for respiratory support should be immediately available.

Propofol poses a high risk of *bacterial infection*. The reason? Propofol is not water soluble, and hence must be formulated in a lipid-based medium, which is ideal for bacterial growth. In surgical patients, use of preparations that have become contaminated after opening has caused sepsis and death. To minimize the risk of infection, propofol solutions and opened vials should be discarded within 6 hours. Unopened vials should be stored at 22°C (72°F).

Propofol can cause transient pain at the site of IV injection. This can be minimized by using a large vein and by injecting IV lidocaine (a local anesthetic) at the site just prior to injecting propofol.

Rarely, prolonged, high-dose infusion leads to *propofol infusion syndrome*, characterized by metabolic acidosis, cardiac failure, renal failure, and rhabdomyolysis. Deaths have occurred. Traumatic brain injury and young age are major risk factors. Risk can be minimized by using a low-dose infusion (no more than 4 mg/kg/hr), and by daily monitoring of plasma creatine phosphokinase (CPK), a marker for skeletal and cardiac muscle injury. If CPK rises above 5000 units/L, the propofol infusion should stop immediately.

Abuse. Although not regulated as a controlled substance, propofol is subject to abuse, primarily by anesthesiologists, nurse anesthetists, and other medical professionals, all of whom have easy access to the drug. Why is access easy? First,

propofol is widely available in operating rooms, endoscopy suites, and physicians' offices. And second, because propofol is not a controlled substance, supplies are not closely monitored.

The appeal of propofol is unique. As a rule, clinicians don't use the drug to produce a "high." Rather, they use it to produce instantaneous (but brief) sleep, after which they wake up feeling refreshed. When patients awake after getting propofol, they are often talkative, and report feeling elated and even euphoric. Animal studies show a profound effect on the brain's reward center.

Unfortunately, although propofol can make us feel good, it can also kill: Because propofol has a low therapeutic index, death from overdose is not uncommon. In 2009, propofol made the headlines as the cause of death for pop singer Michael Jackson.

Despite its clear potential for abuse, and despite a recommendation from the American Society of Anesthesiology, propofol remains unregulated under the Controlled Substances Act. The principal reason, apparently, is that propofol is not readily available to the general public, and hence regulation is seen as unnecessary.

Fospropofol

Fospropofol [Lusedra] is an IV prodrug that undergoes conversion to propofol in the liver. Accordingly, effects of fospropofol are much like those of propofol itself, although the time course of effects is different. Specifically, following an IV bolus injection, onset of sedation is slower with fospropofol (4 minutes vs. less than 1 minute) and duration of sedation is longer (20 to 30 minutes vs. 3 to 5 minutes). In addition, peak plasma levels of propofol are lower following injection of fospropofol than they are following injection of propofol itself. Like propofol, fospropofol is indicated for sedation in adults undergoing diagnostic or therapeutic procedures (eg, GI endoscopy, colonoscopy, bronchoscopy). Because the effects of fospropofol are prolonged, some procedures can be performed with just a single injection. Compared with propofol, fospropofol poses a much lower risk of bacteremia. Why? Because, unlike propofol, fospropofol is water soluble, and hence is not formulated in a lipid-based medium. When it was first released, fospropofol was not regulated as a controlled substance. However, in 2009, it was reclassified as a schedule IV drug, in recognition of its potential for abuse. Adult dosing consists of an initial IV bolus (6.5 mg/kg) followed by additional doses (1.6 mg/kg) as needed. Supplemental oxygen should be administered to all patients.

Etomidate

Etomidate [Amidate] is a potent hypnotic agent used for induction of surgical anesthesia. Unconsciousness develops rapidly and lasts about 5 minutes. The drug has no analgesic actions. Adverse effects associated with single injections include transient apnea, venous pain at the injection site, and suppression of plasma cortisol levels for 6 to 8 hours. Repeated administration can cause hypotension, oliguria, electrolyte disturbances, and a high incidence (up to 20%) of postoperative nausea and vomiting. Cardiovascular effects are less common with barbiturates, and hence the drug is preferred for patients with cardiovascular disorders.

Ketamine

Anesthetic Effects. Ketamine [Ketalar] produces a state known as *dissociative anesthesia* in which the patient feels dissociated from his or her environment. In addition, the drug causes sedation, immobility, analgesia, and amnesia; respon-

siveness to pain is lost. Induction is rapid and emergence begins within 10 to 15 minutes. Full recovery, however, may take several hours.

Adverse Psychologic Reactions. During recovery from ketamine, about 12% of patients experience unpleasant psychologic reactions, including hallucinations, disturbing dreams, and delirium. These emergence reactions usually fade in a few hours, although they sometimes last up to 24 hours. To minimize these reactions, the patient should be kept in a soothing, stimulus-free environment until recovery is complete. Pre-medication with diazepam or midazolam reduces the risk of an adverse reaction. Emergence reactions are least likely in children under the age of 15 years and in adults over the age of 65. Despite its potential for unpleasant psychologic effects, ketamine has become a popular drug of abuse (see Chapter 40).

Who Should Receive Ketamine. In the past, ketamine was used primarily in children. However, an updated guideline, issued in 2011, now recommends expanding ketamine use to include adults, and babies between 3 and 12 months old.

Therapeutic Uses. Ketamine is especially valuable for anesthesia in patients undergoing minor surgical and diagnostic procedures. The drug is frequently used to facilitate changing of burn dressings. Because of its potential for adverse psychologic effects, ketamine should generally be avoided in patients with a history of psychiatric illness, although the drug has produced rapid relief in patients with intractable depression (see Chapter 32). Owing to its potential for abuse, ketamine is regulated as a Schedule III drug.

Neuroleptic-Opioid Combination: Droperidol Plus Fentanyl

A unique state, known as *neurolept analgesia*, can be produced with a combination of fentanyl, a potent opioid, plus droperidol, a neuroleptic (antipsychotic) agent. In the past, the combination was available premixed under the trade name *Innovar*.

Neurolept analgesia is characterized by quiescence, indifference to surroundings, and insensitivity to pain. The patient appears to be asleep but is not (ie, complete loss of consciousness does not occur). In large part, neurolept analgesia is similar to the dissociative anesthesia produced by ketamine. Neurolept analgesia is employed for diagnostic and minor surgical procedures (eg, bronchoscopy, repeated changing of burn dressings).

Droperidol prolongs the QT interval on the electrocardiogram, indicating that it can cause potentially fatal dysrhythmias. Accordingly, droperidol should be used only when safer drugs are ineffective or intolerable. Droperidol is contraindicated for patients with existing QT prolongation, and should be used with great caution in those at risk of developing QT prolongation. The issue of drug-induced QT prolongation is discussed at length in Chapter 7 (Adverse Drug Reactions and Medication Errors).

Other adverse effects include hypotension and respiratory depression. Respiratory depression can be severe and may persist for hours. Respiratory assistance is usually required. Like other neuroleptics, droperidol blocks receptors for dopamine, and hence should not be given to patients with Parkinson's disease.

For some procedures, the combination of fentanyl plus droperidol is supplemented with nitrous oxide. The state produced by this three-drug regimen is called *neurolept anesthesia*. Neurolept anesthesia produces more analgesia and a greater reduction of consciousness than does *neurolept analgesia*. Neurolept anesthesia can be used for major surgical procedures.

KEY POINTS

- General anesthetics produce unconsciousness and insensitivity to painful stimuli. In contrast, analgesics reduce sensitivity to pain but do not reduce consciousness.
- The term *balanced anesthesia* refers to the use of several drugs to ensure that induction of anesthesia is smooth and rapid and that analgesia and muscle relaxation are adequate.
- The minimum alveolar concentration (MAC) of an inhalation anesthetic is defined as the minimum concentration of drug in alveolar air that will produce immobility in 50% of patients exposed to a painful stimulus. A *low* MAC indicates *high* anesthetic potency!
- Inhalation agents work by enhancing transmission at inhibitory synapses and by inhibiting transmission at excitatory synapses.
- Inhalation anesthetics are eliminated almost entirely in the expired air. As a rule, they undergo minimal hepatic metabolism.
- The principal adverse effects of general anesthetics are depression of respiration and cardiac performance.
- Malignant hyperthermia is a rare, genetically determined, life-threatening reaction to general anesthetics. Co-administration of succinylcholine, a neuromuscular blocker, increases the risk of the reaction.
- By enhancing analgesia, opioids reduce the required dosage of general anesthetic.
- By enhancing muscle relaxation, neuromuscular blockers reduce the required dosage of general anesthetic.
- Nitrous oxide differs from other general anesthetics in two important ways: (1) it has a very high MAC, and therefore cannot be used alone to produce general anesthesia; and (2) it has high analgesic potency, and therefore is frequently combined with other general anesthetics to supplement their analgesic effects.
- Thiopental, a short-acting barbiturate, is a preferred drug for induction of anesthesia.
- Propofol, a rapid-acting agent with an ultrashort duration, is widely used alone (for diagnostic procedures) and combined with an inhalation anesthetic (as a component of balanced anesthesia).
- Ketamine is an IV anesthetic that produces a state known as dissociative anesthesia. Patients recovering from ketamine may experience adverse psychologic reactions.

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Summary of Major Nursing Implications

ALL INHALATION ANESTHETICS

Desflurane
Enflurane
Isoflurane
Nitrous oxide
Sevoflurane

Nursing management of the patient receiving general anesthesia is almost exclusively preoperative and postoperative; intraoperative management is the responsibility of anesthesiologists and anesthesiologists. Accordingly, our summary of anesthesia-related nursing implications is divided into two sections: (1) implications that pertain to the preoperative patient and (2) implications that pertain to the postoperative patient. Intraoperative implications are not considered.

The nursing implications summarized here are limited to ones that are directly related to anesthesia. Nursing implications regarding the overall management of the surgical patient (ie, implications unrelated to anesthesia) are not presented. (Overall nursing management of the surgical patient is discussed fully—and appropriately—in your medical-surgical text.)

Nursing implications for drugs employed as adjuncts to anesthesia (barbiturates, benzodiazepines, anticholinergic agents, opioids, neuromuscular blocking agents) are summarized in other chapters. Only those implications that apply specifically to their adjunctive use are addressed here.

Preoperative Patients: Counseling, Assessment, and Medicating

Counseling

Anxiety is common among patients anticipating surgery; the patient may fear the surgery itself, or may be concerned about the possibility of waking up or experiencing pain during the procedure. Since excessive anxiety can disrupt the smoothness of the surgical course (in addition to being distressing to the patient), you should attempt to dispel preoperative fears. To some extent, fear can be allayed by reassuring the patient that anesthesia will keep him or her asleep for the entire procedure, will prevent pain, and will create amnesia about the experience.

Assessment

Medication History. The patient may be taking drugs that can affect responses to anesthetics. Drugs that act on the respiratory and cardiovascular systems are of particular concern. To decrease the risk of adverse interactions, obtain a thorough history of drug use. *All* drugs—prescription medications, over-the-counter preparations, and illicit agents—should be considered. With illicit drugs (eg, heroin, barbiturates) and with alcohol, it is important to determine both the duration of use and the amount used per day.

Respiratory and Cardiovascular Function. Most general anesthetics produce cardiovascular and respiratory

Summary of Major Nursing Implications*—cont'd

depression in order to evaluate the effects of anesthesia, baseline values for blood pressure, heart rate, and respiration are required. Also, any disease of the cardiovascular and respiratory systems should be noted.

Preoperative Medication

Preoperative medications (eg, benzodiazepines, opioids, anticholinergic agents) are employed to (1) calm the patient, (2) provide analgesia, and (3) counteract adverse effects of general anesthetics. Since preoperative medication can have a significant impact on the overall response to anesthesia, it is important that these drugs be given at an appropriate time—typically 30 to 60 minutes before surgery. Because preoperative medication may produce drowsiness or hypotension, the patient should remain in bed. A calm environment will complement the effect of sedatives.

Postoperative Patients: Ongoing Evaluation and Interventions

When receiving a patient for postoperative care, you should know all of the drugs the patient has received in the hospital (anesthetics and adjunctive medications). In addition, you should know what medications the patient was taking at home, especially drugs for hypertension. With this information, you will be able to anticipate the time course of emergence from anesthesia as well as potential drug-related postoperative complications.

Evaluations and Interventions That Pertain to Specific Organ Systems

Cardiovascular and Respiratory Systems. Anesthetics depress cardiovascular and respiratory function. Monitor vital signs until they return to baseline. Determine blood pressure, pulse rate, and respiration immediately upon receipt of the patient, and repeat monitoring at brief intervals until recovery is complete. During the recovery period, observe the patient for respiratory and cardiovascular distress. Be alert for (1) reductions in blood pressure; (2) altered

cardiac rhythm; and (3) shallow, slow, or noisy breathing. Ensure that the airway remains patent. Have facilities for respiratory support available.

Central Nervous System. Return of CNS function is gradual, and precautions are needed until recovery is complete. When appropriate, employ side rails or straps to avoid accidental falls. Assist ambulation until the patient is able to stand steadily. During the early stage of emergence, the patient may be able to hear, even though he or she may appear unconscious. Accordingly, exercise discretion in what you say.

Gastrointestinal Tract. Bowel function may be compromised by the surgery itself or by the drugs employed as adjuncts to anesthesia (eg, opioids, anticholinergics). Constipation or atony of the bowel may occur. Monitor bowel function. A muscarinic agonist (eg, bethanechol) may be needed to restore peristalsis. Determine bowel sounds before giving oral medications.

Nausea and vomiting are potential postanesthetic reactions. To reduce the risk of aspiration, position the patient with his or her head to the side. Have equipment for suctioning available. Antiemetic medication may be needed.

Urinary Tract. Anesthetics and their adjuncts can disrupt urinary tract function. Anesthetics can decrease urine production by reducing renal blood flow. Opioids and anticholinergic drugs can cause urinary retention. Monitor urine output. If the patient fails to void, follow hospital protocol. Catheterization or medication (eg, bethanechol) may be needed.

Management of Postoperative Pain

As anesthesia wears off, the patient may experience postoperative pain. An opioid may be required. Since respiratory depression from opioids will add to residual respiratory depression from anesthesia, use opioids with caution; balance the need to relieve pain against the need to maintain ventilation.

Opioid (Narcotic) Analgesics, Opioid Antagonists, and Nonopioid Centrally Acting Analgesics

OPIOID ANALGESICS

Introduction to the Opioids

Terminology

Endogenous Opioid Peptides

Opioid Receptors

Classification of Drugs That Act at Opioid Receptors

Basic Pharmacology of the Opioids

Morphine

Other Strong Opioid Agonists

Moderate to Strong Opioid Agonists

Agonist-Antagonist Opioids

Clinical Use of Opioids

Dosing Guidelines

Physical Dependence, Abuse, and Addiction as Clinical Concerns

Patient-Controlled Analgesia

Using Opioids for Specific Kinds of Pain

REMS to Reduce Opioid-Related Morbidity, Mortality, and Abuse

OPIOID ANTAGONISTS

Naloxone

Other Opioid Antagonists

NONOPIOID CENTRALLY ACTING ANALGESICS

Tramadol

Clonidine

Ziconotide

Dexmedetomidine

Analgesics are drugs that relieve pain without causing loss of consciousness. In this chapter, we focus mainly on the opioid analgesics, the most effective pain relievers available. The opioid family, whose name derives from *opium*, includes such widely used agents as morphine, fentanyl, codeine, and oxycodone [OxyContin, others].

opiate is more specific and applies only to compounds present in opium (eg, morphine, codeine).

The term *narcotic* has had so many definitions that it cannot be used with precision. *Narcotic* has been used to mean an analgesic, a central nervous system (CNS) depressant, and any drug capable of causing physical dependence. *Narcotic* has also been employed in a legal context to designate not only the opioids but also such diverse drugs as cocaine, marijuana, and lysergic acid diethylamide (LSD). Because of its more precise definition, *opioid* is clearly preferable to *narcotic* as a label for a discrete family of pharmacologic agents.

Endogenous Opioid Peptides

The body has three families of peptides—*enkephalins*, *endorphins*, and *dynorphins*—that have opioid-like properties. Although we know that endogenous opioid peptides serve as neurotransmitters, neurohormones, and neuromodulators, their precise physiologic role is not fully understood. Endogenous opioid peptides are found in the CNS and in peripheral tissues.

Opioid Receptors

There are three main classes of opioid receptors, designated *mu*, *kappa*, and *delta*. From a pharmacologic perspective, *mu* receptors are the most important. Why? Because opioid analgesics act primarily by activating *mu* receptors, although they also produce weak activation of *kappa* receptors. As a rule, opioid analgesics do not interact with *delta* receptors. In contrast to opioid analgesics, endogenous opioid peptides act through all three opioid receptors, including *delta* receptors. Important responses to activation of *mu* and *kappa* receptors are summarized in Table 28-1.

Mu Receptors. Responses to activation of *mu* receptors include analgesia, respiratory depression, euphoria, and sedation. In addition, *mu* activation is related to physical dependence.

A study in genetically engineered mice underscores the importance of *mu* receptors in drug action. In this study, researchers studied mice that lacked the gene for *mu* receptors. When these mice were given morphine, the drug had no effect. It did not produce analgesia or physical dependence, and it did not reinforce social behaviors that are thought to indicate subjective effects. Hence, at least in mice, *mu* receptors appear both necessary and sufficient to mediate the major actions of opioid drugs.

OPIOID ANALGESICS

INTRODUCTION TO THE OPIOIDS

Terminology

Opioid is a general term defined as any drug, natural or synthetic, that has actions similar to those of morphine. The term

TABLE 28-1 ■ Important Responses to Activation of Mu and Kappa Receptors

Response	Receptor Type	
	Mu	Kappa
Analgesia	✓	✓
Respiratory depression	✓	
Sedation	✓	✓
Euphoria	✓	
Physical dependence	✓	
Decreased GI motility	✓	✓

Kappa Receptors. As with mu receptors, activation of kappa receptors can produce analgesia and sedation. In addition, kappa activation may underlie psychotomimetic effects seen with certain opioids.

Classification of Drugs That Act at Opioid Receptors

Drugs that act at opioid receptors are classified on the basis of how they affect receptor function. At each type of receptor, a drug can act in one of three ways: as an *agonist*, *partial agonist*, or *antagonist*. (Recall from Chapter 5 that a partial agonist is a drug that produces low to moderate receptor activation when administered alone, but will block the actions of a full agonist if the two are given together.) Based on these actions, drugs that bind opioid receptors fall into three major groups: (1) pure opioid agonists, (2) agonist-antagonist opioids, and (3) pure opioid antagonists. The actions of drugs in these groups at mu and kappa receptors are summarized in Table 28-2.

Pure Opioid Agonists. The pure opioid agonists activate mu receptors and kappa receptors. By doing so, the pure agonists can produce analgesia, euphoria, sedation, respiratory depression, physical dependence, constipation, and other effects. As indicated in Table 28-3, the pure agonists can be subdivided into two groups: *strong opioid agonists* and *moderate to strong opioid agonists*. Morphine is the prototype of the strong agonists. Codeine is the prototype of the moderate to strong agonists.

Agonist-Antagonist Opioids. Four agonist-antagonist opioids are available: pentazocine, nalbuphine, butorphanol, and buprenorphine. The actions of these drugs at mu and kappa receptors are summarized in Table 28-2. When administered alone, the agonist-antagonist opioids produce analgesia. However, if given to a patient who is taking a pure opioid agonist, these drugs can *antagonize* analgesia caused by the agonist. Pentazocine [Talwin] is the prototype of the agonist-antagonists.

Pure Opioid Antagonists. The pure opioid antagonists act as antagonists at mu and kappa receptors. These drugs do not produce analgesia or any of the other effects caused by opioid agonists. Their principal use is reversal of respiratory and CNS depression caused by overdose with opioid agonists. In addition, one of these drugs—methylnaltrexone—is used to treat opioid-induced constipation. Naloxone [Narcan] is the prototype of the pure opioid antagonists.

TABLE 28-2 ■ Drug Actions at Mu and Kappa Receptors

Drugs	Receptor Type	
	Mu	Kappa
Pure Opioid Agonists		
Morphine, codeine, meperidine, and other morphine-like drugs	Agonist	Agonist
Agonist-Antagonist Opioids		
Pentazocine, nalbuphine, butorphanol	Antagonist	Agonist
Buprenorphine	Partial agonist	Antagonist
Pure Opioid Antagonists		
Naloxone, naltrexone, others	Antagonist	Antagonist

BASIC PHARMACOLOGY OF THE OPIOIDS

Morphine

Morphine is the prototype of the strong opioid analgesics and remains the standard by which newer opioids are measured. Morphine has multiple pharmacologic effects, including analgesia, sedation, euphoria, respiratory depression, cough suppression, and suppression of bowel motility. The drug is named after Morpheus, the Greek god of dreams.

Source

Morphine is found in the seedpod of the poppy plant, *Papaver somniferum*. The drug is prepared by extraction from opium (the dried juice of the poppy seedpod). In addition to morphine, opium contains two other medicinal compounds: codeine (an analgesic) and papaverine (a smooth muscle relaxant).

Overview of Pharmacologic Actions

Morphine has multiple pharmacologic actions. In addition to relieving pain, the drug causes drowsiness and mental clouding, reduces anxiety, and creates a sense of well-being. Through actions in the CNS and periphery, morphine can cause respiratory depression, constipation, urinary retention, orthostatic hypotension, emesis, miosis, cough suppression, and biliary colic. With prolonged use, the drug produces tolerance and physical dependence.

Individual effects of morphine may be beneficial, detrimental, or both. For example, analgesia is clearly beneficial, whereas respiratory depression and urinary retention are clearly detrimental. Certain other effects, such as sedation and reduced bowel motility, may be beneficial or detrimental, depending on the circumstances of drug use.

Therapeutic Use: Relief of Pain

The principal indication for morphine is relief of moderate to severe pain. The drug can relieve postoperative pain, pain of labor and delivery, and chronic pain caused by cancer and other conditions. In addition, morphine can be used to relieve pain of myocardial infarction and dyspnea associated with left ventricular failure and pulmonary edema—although it is no longer the drug of choice for these disorders. Morphine may also be administered preoperatively for sedation and reduction of anxiety.

Morphine relieves pain without affecting other senses (eg, sight, touch, smell, hearing) and without causing loss of consciousness. The drug is more effective against constant, dull pain than against sharp, intermittent pain. However, even

TABLE 28-3 • Opioid Analgesics: Abuse Liability and Maximal Pain Relief

Drug and Category	CSA* Schedule	Abuse Liability	Maximal Pain Relief
Strong Opioid Agonists			
Alfentanil	II	High	High
Fentanyl	II	High	High
Hydromorphone	II	High	High
Levorphanol	II	High	High
Meperidine	II	High	High
Methadone	II	High	High
Morphine	II	High	High
Oxymorphone	II	High	High
Remifentanyl	II	—	High
Sufentanil	II	High	High
Moderate to Strong Opioid Agonists			
Codeine	II	Moderate	Low
Hydrocodone	III [†]	Moderate	Moderate
Oxycodone	II	Moderate	Moderate to high
Tapentadol	II	Moderate	Moderate to high
Agonist-Antagonist Opioids			
Buprenorphine	V	Low	Moderate to high
Butorphanol	IV	Low	Moderate to high
Nalbuphine	NR [‡]	Low	Moderate to high
Pentazocine	IV	Low	Moderate

*CSA = Controlled Substances Act.

[†]In the United States, hydrocodone is available only in combination with aspirin or acetaminophen. These combination products are classified under Schedule III.

[‡]NR = not regulated under the Controlled Substances Act.

sharp pain can be relieved by large doses. The ability of morphine to cause mental clouding, sedation, euphoria, and anxiety reduction can contribute to relief of pain.

The use of morphine and other opioids to relieve pain is discussed further in this Chapter (under *Clinical Use of Opioids*) and in Chapter 29 (Pain Management in Patients with Cancer).

Mechanism of Analgesic Action. Morphine and other opioid agonists appear to relieve pain by mimicking the actions of endogenous opioid peptides, primarily at mu receptors. This hypothesis is based on the following observations:

- Opioid peptides and morphine-like drugs both produce analgesia when administered to experimental subjects.
- Opioid peptides and morphine-like drugs share structural similarities (Fig. 28-1).
- Opioid peptides and morphine-like drugs bind to the same receptors in the CNS.
- The receptors to which opioid peptides and morphine-like drugs bind are located in regions of the brain and spinal cord associated with perception of pain.
- Subjects rendered tolerant to analgesia from morphine-like drugs show cross-tolerance to analgesia from opioid peptides.
- The analgesic effects of opioid peptides and morphine-like drugs can both be blocked by the same antagonist: naloxone.

From these data we can postulate that (1) opioid peptides serve a physiologic role as modulators of pain perception, and (2) morphine-like drugs produce analgesia by mimicking the actions of endogenous opioid peptides.

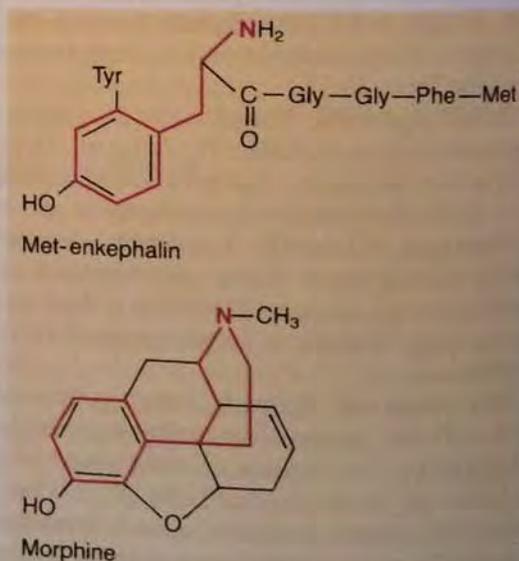


Figure 28-1 • Structural similarity between morphine and met-enkephalin.

In the morphine structural formula, highlighting indicates the part of the molecule thought responsible for interaction with opioid receptors. In the met-enkephalin structural formula, highlighting indicates the region of structural similarity with morphine.

Adverse Effects

Respiratory Depression. Respiratory depression is the most serious adverse effect. At equianalgesic doses, all of the pure opioid agonists depress respiration to the same extent. Death following overdose is almost always from respiratory arrest. Opioids depress respiration primarily through activation of mu receptors, although activation of kappa receptors also contributes.

The time course of respiratory depression varies with route of administration. Depressant effects begin about 7 minutes after IV injection, 30 minutes after IM injection, and up to 90 minutes after subQ injection. With all three routes, significant depression may persist for 4 to 5 hours. When morphine is administered by spinal injection, onset of respiratory depression may be delayed for hours; be alert to this possibility.

With prolonged use of opioids, tolerance develops to respiratory depression. Huge doses that would be lethal to a non-tolerant individual have been taken by opioid addicts without noticeable effect. Similarly, tolerance to respiratory depression develops during long-term clinical use of opioids (eg, in patients with cancer).

When administered at usual therapeutic doses, opioids rarely cause significant respiratory depression. However, although uncommon, substantial respiratory depression can nonetheless occur. Accordingly, respiratory rate should be determined prior to opioid administration. If the rate is 12 breaths per minute or less, the opioid should be withheld and the prescriber notified. Certain patients, including the very young, the elderly, and those with respiratory disease (eg, asthma, emphysema) are especially sensitive to respiratory depression, and hence must be monitored closely. Outpatients should be informed about the risk of respiratory depression and instructed to notify the prescriber if respiratory distress occurs.

Respiratory depression is increased by concurrent use of other drugs with CNS-depressant actions (eg, alcohol, barbiturates, benzodiazepines). Accordingly, these drugs should be avoided. Outpatients should be warned against use of alcohol and all other CNS depressants.

Pronounced respiratory depression can be reversed with naloxone [Narcan], an opioid antagonist (see below). However, dosing must be carefully titrated. Why? Because excessive doses will completely block the analgesic effects of morphine, thereby causing pain to return.

Constipation. Opioids promote constipation through actions in the CNS and GI tract. Specifically, by anticipating mu receptors in the gut, these drugs can suppress propulsive intestinal contractions, intensify nonpropulsive contractions, increase the tone of the anal sphincter, and inhibit secretion of fluids into the intestinal lumen. As a result, constipation can develop after a few days of opioid use. Potential complications of constipation include fecal impaction, bowel perforation, rectal tearing, and hemorrhoids.

Opioid-induced constipation can be managed with a combination of pharmacologic and nonpharmacologic measures. The goal is to produce a soft, formed stool every 1 to 2 days. Principal nondrug measures are physical activity and increased intake of fiber and fluids (for prevention) and enemas (for treatment). Most patients also require *prophylactic drugs*: A stimulant laxative, such as senna, is given to counteract reduced bowel motility; a stool softener, such as docusate [Colace, others] plus polyethylene glycol (an osmotic laxative) can provide additional benefit. If these prophylactic

drugs prove inadequate, the patient may need *rescue therapy* with a strong osmotic laxative, such as lactulose or sodium phosphate. As a last resort, patients may be given *methylal-trexone* [Relistor], an oral drug that blocks mu receptors in the intestine. As discussed later in the chapter, methylal-trexone can't cross the blood-brain barrier, and hence does not reverse opioid-induced analgesia.

Because of their effects on the intestine, opioids are highly effective for treating diarrhea. In fact, antidiarrheal use of these drugs preceded analgesic use by centuries. The impact of opioids on intestinal function is an interesting example of how an effect can be detrimental (constipation) or beneficial (relief of diarrhea) depending on who is taking the medication. Opioids employed specifically to treat diarrhea are discussed in Chapter 80.

Orthostatic Hypotension. Morphine-like drugs lower blood pressure by blunting the baroreceptor reflex and by dilating peripheral arterioles and veins. Peripheral vasodilation results primarily from morphine-induced release of histamine. Hypotension is mild in the recumbent patient but can be significant when the patient stands up. Patients should be informed about symptoms of hypotension (lightheadedness, dizziness) and instructed to sit or lie down if they occur. Also, patients should be informed that hypotension can be minimized by moving slowly when changing from a supine or seated position to an upright position. Patients should be warned against walking if hypotension is substantial. Hospitalized patients may require ambulatory assistance. Hypotensive drugs can exacerbate opioid-induced hypotension.

Urinary Retention. Morphine can cause urinary hesitancy and urinary retention. Three mechanisms are involved. First, morphine increases tone in the bladder sphincter. Second, morphine increases tone in the detrusor muscle, thereby elevating pressure within the bladder, causing a sense of urinary urgency. Third, in addition to its direct effects on the urinary tract, morphine may interfere with voiding by suppressing awareness of bladder stimuli. To reduce discomfort, patients should be encouraged to void every 4 hours. Urinary hesitancy or retention is especially likely in patients with prostatic hypertrophy. Drugs with anticholinergic properties (eg, tricyclic antidepressants, antihistamines) can exacerbate the problem.

Urinary retention should be assessed by monitoring intake and output and by palpating the lower abdomen every 4 to 6 hours for bladder distention. If a change in intake/output ratio develops, or if bladder distention is detected, or if the patient reports difficulty voiding, the prescriber should be notified. Catheterization may be required.

In addition to causing urinary retention, morphine may decrease urine production. How? Largely by decreasing renal blood flow, and partly by promoting release of antidiuretic hormone.

Cough Suppression. Morphine-like drugs act at opioid receptors in the medulla to suppress cough. Suppression of spontaneous cough may lead to accumulation of secretions in the airway. Accordingly, patients should be instructed to actively cough at regular intervals. Lung status should be assessed by auscultation for rales. The ability of opioids to suppress cough is put to clinical use in the form of codeine- and hydrocodone-based cough remedies.

Biliary Colic. Morphine can induce spasm of the common bile duct, causing pressure within the biliary tract to rise dra-

matically. Symptoms range from epigastric distress to biliary colic. In patients with pre-existing biliary colic, morphine may intensify pain rather than relieve pain. Certain opioids (eg, meperidine) cause less smooth muscle spasm than morphine, and hence are less likely to exacerbate biliary colic.

Emesis. Morphine promotes nausea and vomiting through direct stimulation of the chemoreceptor trigger zone of the medulla. Emetic reactions are greatest with the initial dose and then diminish with subsequent doses. Nausea and vomiting are uncommon in recumbent patients, but occur in 15% to 40% of ambulatory patients, suggesting a vestibular component. Nausea and vomiting can be reduced by pretreatment with an antiemetic (eg, prochlorperazine) and by having the patient remain still.

Elevation of Intracranial Pressure. Morphine can elevate intracranial pressure (ICP). The mechanism is indirect: By suppressing respiration, morphine increases the CO₂ content of blood, which dilates the cerebral vasculature, causing ICP to rise. Accordingly, if respiration is maintained at a normal rate, ICP will remain normal too.

Euphoria/Dysphoria. Euphoria is defined as an exaggerated sense of well-being. Morphine often produces euphoria when given to patients in pain. Although euphoria can enhance pain relief, it also contributes to the drug's potential for abuse. Euphoria is caused by activation of mu receptors.

In some individuals, morphine causes *dysphoria* (a sense of anxiety and unease). Dysphoria is uncommon among patients in pain, but may occur when morphine is taken in the absence of pain.

Sedation. When administered to relieve pain, morphine is likely to cause drowsiness and some mental clouding. Although these effects can complement analgesic actions, they can also be detrimental. Outpatients should be warned about CNS depression and advised to avoid hazardous activities (eg, driving) if sedation is significant. Sedation can be minimized by (1) taking smaller doses more often, (2) using opioids that have short half-lives, and (3) giving small doses of a CNS stimulant (methylphenidate or dextroamphetamine) in the morning and early afternoon. A nonamphetamine stimulant—modafinil [Provigil, Alertec] or armodafinil [Nuvigil]—may also be tried.

Miosis. Morphine and other opioids cause pupillary constriction (miosis). In response to toxic doses, the pupils may constrict to "pinpoint" size. Since miosis can impair vision in dim light, room light should be kept bright during waking hours.

Birth Defects. Morphine and other opioids increase in the risk of serious birth defects by two- to threefold, although the absolute risk remains low. In 2011, the Centers for Disease Control and Prevention (CDC) released preliminary data showing that, when opioids are taken just before conception or during early pregnancy, they increase the risk of congenital heart defects, including atrioventricular septal defects, hypoplastic left heart syndrome, and conoventricular septal defects. In addition, opioids increase the risk of spina bifida and gastroschisis (protrusion of the intestine through the abdominal wall near the umbilicus). Clearly, opioids should be avoided prior to and during pregnancy.

Neurotoxicity. Opioid-induced neurotoxicity can cause delirium, agitation, myoclonus, hyperalgesia, and other symptoms. Primary risk factors are renal impairment, pre-existing cognitive impairment, and prolonged, high-dose opioid use.

Management consists of hydration and dose reduction. For patients who must take opioids long term, opioid rotation (periodically switching from one opioid to another) may reduce neurotoxicity development.

Adverse Effects from Prolonged Use. Clinical and preclinical studies indicate that prolonged use of opioids can cause hormonal changes and can alter immune function. Hormonal changes include a progressive decline in cortisol levels, an increase in prolactin levels, and a decrease in levels of luteinizing hormone, follicle-stimulating hormone, testosterone, and estrogen. With prolonged opioid exposure, immune function is suppressed. Are these changes clinically relevant? We don't really know.

Pharmacokinetics

Morphine is administered by several routes: oral, IM, IV, subQ, epidural, and intrathecal. Onset of effects is slower with oral dosing than with parenteral dosing. With three routes—oral, IM, and subQ—analgesia lasts 4 to 5 hours. With two routes—epidural and intrathecal—analgesia may persist up to 24 hours. With oral therapy, duration depends on the formulation. For example, with immediate-release (IR) tablets, effects last 4 to 5 hours, whereas with extended-release (ER) capsules, effects last 24 hours.

In order to relieve pain, morphine must cross the blood-brain barrier and enter the CNS. Because the drug has poor lipid solubility, it does not cross the barrier easily. Consequently, only a small fraction of each dose reaches sites of analgesic action. Since the blood-brain barrier is not well developed in infants, these patients generally require lower doses than do older children and adults.

Morphine is inactivated by hepatic metabolism. When taken by mouth, the drug must pass through the liver on its way to the systemic circulation. Much of an oral dose is inactivated during this first pass through the liver. Consequently, oral doses need to be substantially larger than parenteral doses to achieve equivalent analgesic effects. In patients with liver disease, analgesia and other effects may be intensified and prolonged. Accordingly, it may be necessary to reduce the dosage or lengthen the dosing interval.

Tolerance and Physical Dependence

With continuous use, morphine can cause tolerance and physical dependence. These phenomena, which are generally inseparable, reflect cellular adaptations that occur in response to prolonged opioid exposure.

Tolerance. Tolerance can be defined as a state in which a larger dose is required to produce the same response that could formerly be produced with a smaller dose. Alternatively, tolerance can be defined as a condition in which a particular dose now produces a smaller response than it did when treatment began. Because of tolerance, dosage must be increased to maintain analgesic effects.

Tolerance develops to many—but not all—of morphine's actions. With prolonged treatment, tolerance develops to analgesia, euphoria, and sedation. As a result, with long-term therapy, an increase in dosage may be required to maintain these desirable effects. Fortunately, as tolerance develops to these therapeutic effects, tolerance also develops to respiratory depression. As a result, the high doses needed to control pain in the tolerant individual are not associated with increased respiratory depression.

Very little tolerance develops to *constipation* and *miosis*. Even in highly tolerant addicts, constipation remains a chronic problem, and constricted pupils are characteristic.

Cross-tolerance exists among the opioid agonists (eg, oxycodone, methadone, fentanyl, codeine, heroin). Accordingly, individuals tolerant to one of these agents will be tolerant to all the others. No cross-tolerance exists between opioids and general CNS depressants (eg, barbiturates, ethanol, benzodiazepines, general anesthetics).

Physical Dependence. Physical dependence is defined as a state in which an abstinence syndrome will occur if drug use is abruptly stopped. Opioid dependence results from adaptive cellular changes that occur in response to the continuous presence of these drugs. Although the exact nature of these changes is unknown, it is clear that, once these compensatory changes have taken place, the body requires the continued presence of opioids to function normally. If opioids are withdrawn, an abstinence syndrome usually will follow.

The intensity and duration of the opioid abstinence syndrome depends on two factors: the half-life of the drug being used and the degree of physical dependence. With opioids that have relatively short half-lives (eg, morphine), symptoms of abstinence are intense but brief. In contrast, with opioids that have long half-lives (eg, methadone), symptoms are less intense but more prolonged. With any opioid, the intensity of withdrawal symptoms parallels the degree of physical dependence.

For individuals who are highly dependent, the abstinence syndrome can be extremely unpleasant. Initial reactions include yawning, rhinorrhea, and sweating. Onset occurs about 10 hours after the final dose. These early responses are followed by anorexia, irritability, tremor, and "gooseflesh"—hence the term *cold turkey*. At its peak, the syndrome manifests as violent sneezing, weakness, nausea, vomiting, diarrhea, abdominal cramps, bone and muscle pain, muscle spasm, and kicking movements—hence, "kicking the habit." Giving an opioid at any time during withdrawal rapidly reverses all signs and symptoms. Left untreated, the morphine withdrawal syndrome runs its course in 7 to 10 days. It should be emphasized that, although withdrawal from opioids is unpleasant, the syndrome is rarely dangerous. In contrast, withdrawal from general CNS depressants (eg, barbiturates, alcohol) can be lethal (see Chapter 34).

To minimize the abstinence syndrome, opioids should be withdrawn gradually. When the degree of dependence is moderate, symptoms can be avoided by administering progressively smaller doses over 3 days. When the patient is highly dependent, dosage should be tapered more slowly—over 7 to 10 days. With a proper withdrawal schedule, withdrawal symptoms will resemble those of a mild case of flu—even when the degree of dependence is high.

It is important to note that physical dependence is rarely a complication when opioids are taken *acutely* to treat pain. Hospitalized patients receiving morphine 2 to 3 times a day for up to 2 weeks show no significant signs of dependence. If morphine is withheld from these patients, no significant signs of withdrawal can be detected. The issue of physical dependence as a clinical concern is discussed further later in the chapter.

Infants exposed to opioids *in utero* may be born drug dependent. If the infant is not provided with opioids, an abstinence syndrome will ensue. Signs of withdrawal include ex-

cessive crying, sneezing, tremor, hyperreflexia, fever, and diarrhea. The infant can be weaned from drug dependence by administering dilute paregoric in progressively smaller doses.

Cross-dependence exists among pure opioid agonists. As a result, any pure agonist will prevent withdrawal in a patient who is physically dependent on any other pure agonist.

Abuse Liability

Morphine and the other opioids are subject to abuse, largely because of their ability to cause pleasurable experiences (eg, euphoria, sedation, a sensation in the lower abdomen resembling orgasm). Physical dependence contributes to abuse: Once dependence exists, the ability of opioids to ward off withdrawal serves to reinforce their desirability in the mind of the abuser.

The abuse liability of the opioids is reflected in their classification under the Controlled Substances Act. (The provisions of this act are discussed in Chapter 37.) As shown in Table 28-3, morphine and all other strong opioid agonists are classified under Schedule II. This classification reflects a moderate to high abuse liability. The agonist-antagonist opioids have a lower abuse liability and hence are classified under Schedule IV (butorphanol, pentazocine) or Schedule V (buprenorphine), or have no classification at all (nalbuphine). Healthcare personnel who prescribe, dispense, and administer opioids must adhere to the procedures set forth in the Controlled Substances Act.

Fortunately, abuse is rare when opioids are employed to treat pain. The issue of abuse as a clinical concern is addressed in depth later in the chapter.

Precautions

Some patients are more likely than others to experience adverse effects. Common sense dictates that opioids be used with special caution in these people. Conditions that can predispose patients to adverse reactions are discussed immediately below.

Decreased Respiratory Reserve. Because morphine depresses respiration, it can further compromise respiration in patients with impaired pulmonary function. Accordingly, the drug should be used with caution in patients with asthma, emphysema, kyphoscoliosis, chronic cor pulmonale, and extreme obesity. Caution is also needed in patients taking other drugs that can depress respiration (eg, barbiturates, benzodiazepines, general anesthetics).

Labor and Delivery. Use of morphine during delivery can suppress uterine contractions and cause respiratory depression in the neonate. Following delivery, respiration in the neonate should be monitored closely. Respiratory depression can be reversed with naloxone. The use of opioids in obstetrics is discussed in depth later in the chapter.

Neonatal Opioid Dependence. Regular use of opioids during pregnancy *can* cause physical dependence in the fetus, resulting in signs of withdrawal a day or so after delivery. Signs of withdrawal include excessive crying, sneezing, tremor, fever, diarrhea, and hyperreflexia. The infant can be weaned by giving progressively smaller doses of dilute paregoric.

Head Injury. Morphine and other opioids must be used with caution in patients with head injury. Head injury can cause respiratory depression accompanied by elevation of ICP. Morphine can exacerbate these symptoms. In addition,

since miosis, mental clouding, and vomiting can be valuable diagnostic signs following head injury, and since morphine can cause these same effects, use of opioids can confound diagnosis.

Other Precautions. *Infants and elderly patients* are especially sensitive to morphine-induced respiratory depression. In patients with *inflammatory bowel disease*, morphine may cause toxic megacolon or paralytic ileus. Since morphine and all other opioids are inactivated by liver enzymes, effects may be intensified and prolonged in patients with *liver impairment*. Severe hypotension may occur in patients with *pre-existing hypotension or reduced blood volume*. In patients with *prostatic hypertrophy*, opioids may cause acute urinary retention; repeated catheterization may be required.

Drug Interactions

The major interactions between morphine and other drugs are summarized in Table 28-4. Some interactions are adverse, and some are beneficial.

CNS Depressants. All drugs with CNS-depressant actions (eg, barbiturates, benzodiazepines, alcohol) can intensify sedation and respiratory depression caused by morphine and other opioids. Outpatients should be warned against use of alcohol and all other CNS depressants.

Anticholinergic Drugs. These agents (eg, antihistamines, tricyclic antidepressants, atropine-like drugs) can exacerbate morphine-induced constipation and urinary retention.

Hypotensive Drugs. Antihypertensive drugs and other drugs that lower blood pressure can exacerbate morphine-induced hypotension.

Monoamine Oxidase Inhibitors. The combination of meperidine (a morphine-like drug) with a monoamine oxidase (MAO) inhibitor has produced a syndrome characterized by excitation, delirium, hyperpyrexia, convulsions, and severe respiratory depression. Deaths have occurred. Although this reaction has not been reported with combined use of an MAO inhibitor and morphine, prudence suggests that the combination should nonetheless be avoided.

Agonist-Antagonist Opioids. Agonist-antagonist opioids (eg, pentazocine, buprenorphine) can precipitate a withdrawal syndrome if given to an individual physically dependent on a pure opioid agonist. The basis of this reaction is considered later in the chapter. Patients taking pure opioid agonists should be weaned from these drugs before beginning treatment with an agonist-antagonist.

Opioid Antagonists. Opioid antagonists (eg, naloxone) can counteract most actions of morphine and other pure opioid agonists. Opioid antagonists are employed primarily to treat opioid overdose. The actions and uses of the opioid antagonists are discussed in detail later in the chapter.

Other Interactions. *Antiemetics* of the phenothiazine type (eg, promethazine [Phenergan]) may be combined with opioids to reduce nausea and vomiting. *Amphetamines, clonidine, and dextromethorphan* can enhance opioid-induced analgesia. *Amphetamines* can also offset sedation.

Toxicity

Clinical Manifestations. Opioid overdose produces a classic triad of signs: *coma, respiratory depression, and pinpoint pupils*. Coma is profound, and the patient cannot be aroused. Respiratory rate may be as low as 2 to 4 breaths per minute. Although the pupils are constricted initially, they may

TABLE 28-4 ■ Interactions of Opioids with Other Drugs

Interacting Drugs	Outcome of the Interaction
Adverse Interactions	
CNS depressants	Increased respiratory depression and sedation
Barbiturates	
Benzodiazepines	
Alcohol	
General anesthetics	
Antihistamines	
Phenothiazines	Precipitation of a withdrawal reaction
Agonist-antagonist opioids	
Anticholinergic drugs	Increased constipation and urinary retention
Atropine-like drugs	
Antihistamines	
Phenothiazines	
Tricyclic antidepressants	
Hypotensive agents	Increased hypotension
Monoamine oxidase inhibitors	Hyperpyrexia
Beneficial Interactions	
Amphetamines	Increased analgesia and decreased sedation
Antiemetics	Suppression of nausea and vomiting
Naloxone	Suppression of symptoms of opioid overdose
Dextromethorphan	Increased analgesia; possible reduction in tolerance

dilate as hypoxia sets in (secondary to respiratory depression). Hypoxia may cause blood pressure to fall. Prolonged hypoxia may result in shock. When death occurs, respiratory arrest is almost always the immediate cause.

Treatment. Treatment consists primarily of *ventilatory support* and giving an *opioid antagonist*. Naloxone [Narcan] is the traditional antagonist of choice. The pharmacology of the opioid antagonists is discussed later.

Preparations

Morphine Alone. Morphine sulfate, by itself, is available in 11 formulations:

- *Immediate-release (IR) tablets* (15 and 30 mg)
- *Controlled-release tablets* (15, 30, 60, 100, and 200 mg) sold as MS Contin and Oramorph SR
- *Extended-release (ER) tablets* (15, 30, 60, 100, and 200 mg)
- *Sustained-release capsules* (10, 20, 30, 50, 60, 80, 100, and 200 mg) sold as Kadian and Morphine SR
- *Extended-release capsules* (30, 60, 90, and 120 mg) sold as Avinza and M-Eslon
- *Standard oral solution* (10 and 20 mg/5 mL) sold as MSIR
- *Concentrated oral solution* (100 mg/5 mL) sold as MSIR and Roxcanol
- *Rectal suppositories* (5, 10, 20, and 30 mg) sold as RMS and States
- *Soluble tablets for injection* (10, 15, and 30 mg)
- *Standard solution for injection* (0.5, 1, 2, 4, 5, 8, 10, 15, 25, and 50 mg/mL) sold as Astramorph PF, Duramorph, and Infumorph
- *Extended-release liposomal solution for injection* (10 mg/mL) sold as DepoDur

Morphine/Naltrexone [Embeda]. In 2010, the FDA approved *Embeda*, a fixed-dose combination of morphine and naltrexone, an opioid antagonist (see below). The product is designed to discourage morphine abuse. *Embeda* capsules are filled with tiny pellets that have an outer layer of

tended-release morphine and an inner core of naltrexone. When the capsules are swallowed intact, only the morphine is absorbed. However, if the pellets are crushed, the naltrexone will be absorbed too, thereby blunting the effects of the morphine. As a result, potential abusers cannot get a quick high by crushing the pellets to release all of the morphine at once. However, abusers can still get high by simply taking a large dose. Embeda capsules are more expensive than other extended-release morphine products, and hence should be prescribed only when abuse appears likely.

Alcohol can accelerate release of morphine from Embeda pellets. As a result, the entire dose can be absorbed quickly—rather than over 24 hours—thereby causing a potentially fatal spike in morphine blood levels. Accordingly, patients should be warned against alcohol consumption.

Embeda capsules are available in six morphine/naltrexone strengths: 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg. Dosing is done once or twice daily. Patients can swallow Embeda capsules whole, or they can open the capsules and sprinkle the pellets on applesauce, which must be ingested without chewing.

Dosage and Administration

General Guidelines. Dosage must be individualized. High doses are required for patients with a low tolerance to pain or with extremely painful disorders. Patients with sharp, stabbing pain need higher doses than patients with dull pain. Elderly adults generally require lower doses than younger adults. Neonates require relatively low doses because their blood-brain barrier is not fully developed. For all patients, dosage should be reduced as pain subsides. Outpatients should be warned not to increase dosage without consulting the prescriber.

Before an opioid is administered, respiratory rate, blood pressure, and pulse rate should be determined. The drug should be withheld and the prescriber notified if respiratory rate is at or below 12 breaths per minute, if blood pressure is significantly below the pretreatment value, or if pulse rate is significantly above or below the pretreatment value.

As a rule, *opioids should be administered on a fixed schedule—not PRN.* With a fixed schedule, medication is given before intense pain returns. As a result, the patient is spared needless discomfort. Furthermore, anxiety about recurrence of pain is reduced. If breakthrough pain occurs, supplemental doses of a short-acting preparation should be given.

Morphine and practically all other opioid agonists are classified under Schedule II of the Controlled Substances Act, and must be dispensed accordingly.

Routes and Dosages. *Oral.* Oral dosing is generally reserved for patients with chronic, severe pain, such as that associated with cancer. Because oral morphine undergoes extensive metabolism on its first pass through the liver, oral doses are usually higher than parenteral doses. A typical dosage is 10 to 30 mg repeated every 4 hours as needed. However, oral dosing is highly individualized, and hence some patients may require 75 mg or more. Controlled-release formulations may be administered every 8 to 12 hours. Pa- and the extended-release formulation [Avinza] is given every 24 hours. Patients should be instructed to swallow these products intact, without crushing or chewing. Also, warn patients using Avinza or Embeda capsules not to drink alcohol, which can accelerate release of morphine from these products.

Intramuscular and Subcutaneous. Both routes are painful and unreliable, and hence should generally be avoided. For adults, dosing is initiated at 5 to 10 mg every 4 hours, and then adjusted up or down as needed. The usual dosage for children is 0.1 to 0.2 mg/kg repeated every 4 hours as needed.

Intravenous. Intravenous morphine should be injected slowly (over 4 to 5 minutes). Rapid IV injection can cause severe adverse effects (profound hypotension, cardiac arrest, respiratory arrest) and should be avoided. When IV injections are made, an opioid antagonist (eg, naloxone) and facilities for respiratory support should be available. Injections should be given with the patient lying down to minimize hypotension. The usual dose for adults is 4 to 10 mg (diluted in 4 to 5 mL of sterile water for injection). The usual pediatric dose is 0.05 to 0.1 mg/kg.

Epidural and Intrathecal. When morphine is employed for spinal analgesia, epidural injection is preferred to intrathecal. With either route, onset of analgesia is rapid and the duration prolonged (up to 24 hours). The most troubling side effects are delayed respiratory depression and delayed cardiac depression. Be alert for possible late reactions. The usual adult epidural dose is 5 mg. Intrathecal doses are much smaller—about one-tenth the epidural dose.

The *extended-release liposomal formulation* [DepoDur], used only for postsurgical pain, is intended for *epidural use only*. Inadvertent intrathecal and subarachnoid administration has been associated with profound and prolonged respiratory depression, which can be managed with a naloxone infusion. Dosing is highly individualized, and must account for age, body mass, physical status, history of opioid use, risk factors for respiratory depression, and medications to be coadministered before and during surgery.

Other Strong Opioid Agonists

In an effort to produce a strong analgesic with a low potential for respiratory depression and abuse, pharmaceutical scientists have created many new opioid analgesics. However, none of the newer pure opioid agonists can be considered truly superior to morphine. These drugs are essentially equal to morphine with respect to analgesic action, abuse liability, and the ability to cause respiratory depression. Also, to varying degrees, they all cause sedation, euphoria, constipation, urinary retention, cough suppression, hypotension, and miosis. However, despite their similarities to morphine, the newer drugs do have unique qualities. Hence one agent may be more desirable than another in a particular clinical setting. With all of the newer pure opioid agonists, toxicity can be reversed with an opioid antagonist (eg, naloxone). Important differences between morphine and the newer strong opioid analgesics are discussed below. Table 28-5 summarizes dosages, routes, and time courses for morphine and the newer agents.

Fentanyl

Fentanyl [Sublimaze, Duragesic, Abstral, Actiq, Fentora, Onsolis, Lazanda] is a strong opioid analgesic with a high milligram potency (about 100 times that of morphine). Seven formulations are available, for administration by four different routes: parenteral, transdermal, transmucosal, and intranasal. Depending on the route, fentanyl may be used for surgical analgesia, chronic pain control, and control of breakthrough pain in patients taking other opioids. All preparations are regulated under Schedule II of the Controlled Substances Act.

Fentanyl, regardless of route, has the same adverse effects as other opioids: respiratory depression, sedation, constipation, urinary retention, nausea, and so forth. Of these, respiratory depression is the greatest concern. Signs of toxicity can be reversed with an opioid antagonist (eg, naloxone).

Fentanyl is metabolized by CYP3A4 (the 3A4 isozyme of cytochrome P450), and hence fentanyl levels can be increased by CYP3A4 inhibitors (eg, ritonavir, ketoconazole). Patients taking these inhibitors should be closely monitored for severe respiratory depression and other signs of toxicity.

Parenteral. Parenteral fentanyl [Sublimaze], administered IM or IV, is employed primarily for induction and maintenance of surgical anesthesia. The drug is well suited for these applications owing to its rapid onset and short duration. Most effects are like those of morphine. In addition, fentanyl can cause muscle rigidity, which can interfere with induction of anesthesia. As discussed in Chapter 27 (General Anesthetics), the combination of fentanyl plus droperidol is used to produce a state known as "neurolept analgesia."

TABLE 28-5 • Clinical Pharmacology of Pure Opioid Agonists

Drug and Route*	Equianalgesic Dose (mg) [†]	Time Course of Analgesic Effects		
		Onset (min)	Peak (min)	Duration (hr)
Codeine			60–120	4–6
PO	200	30–45	30–60	4–6
IM	130	10–30	30–60	4–6
SubQ	130			
Fentanyl			—	1–2
IM	0.1	7–8	—	0.5–1
IV	0.1	—	24–72	72
Transdermal [‡]	—	Delayed	20	1–2
Transmucosal [§]	—	10–15	15–20	1–2
Nasal spray	—	10–15		
Hydrocodone			30–60	4–6
PO	30	10–30		
Hydromorphone			90–120	4
PO (IR)	7.5	30	360–480	18–24
PO (ER)	7.5	—	30–60	4–5
IM	1.5	15	15–30	2–3
IV	1.5	10–15	30–90	4
subQ	1.5	15		
Levorphanol			90–120	6–8
PO	4	10–60	60	6–8
IM	2	—	Within 20	6–8
IV	2	—	60–90	6–8
subQ	2	—		
Meperidine			60–90	2–4
PO	300	15	30–50	2–4
IM	75	10–15	5–7	2–4
IV	75	1	30–50	2–4
subQ	75	10–15		
Methadone			90–120	4–6 [¶]
PO	20	30–60	60–120	4–5 [¶]
IM	10	10–20	15–30	3–4 [¶]
IV	10	—		
Morphine			60–120	4–5
PO (IR)	30	—	420	8–12
PO (ER)	30	—	30–60	4–5
IM	10	10–30	20	4–5
IV	10	—	50–90	4–5
subQ	10	10–30		
Epidural	—	15–60	—	Up to 24
Intrathecal	—	15–60	—	Up to 24
Oxycodone			60	3–4
PO (IR)	20	15–30	120–180	Up to 12
PO (CR)	20	—		
Oxymorphone			—	4–6
PO (IR)	10	—	—	Up to 12
PO (ER)	10	—	30–90	3–6
IM	1	10–15	15–30	3–4
IV	1	5–10	—	3–6
subQ	1	10–20	120	3–6
Rectal	10	15–30		
Tapentadol			90–120	4–8
PO	100	45–60		

CR = controlled release, ER = extended release, IR = immediate release.

*IM administration should be avoided whenever possible.

[†]Dose in milligrams that produces a degree of analgesia equivalent to that produced by a 10-mg IM dose of morphine.

[‡]Data are for the transdermal patch, not the transdermal iontophoretic system, which is no longer available in the United States.

[§]Data are for the Actiq lozenge on a stick.

[¶]With repeated doses, methadone's duration of action may increase up to 48 hours.

Transdermal System. The fentanyl transdermal system [Duragesic] consists of a fentanyl-containing patch that is applied to the skin of the upper torso. The drug is slowly released from the patch and absorbed through the skin, reaching effective levels in 24 hours. Levels remain steady for another 48 hours, after which the patch should be replaced. If a new patch is not applied, effects will nonetheless persist for several hours, owing to continued absorption of residual fentanyl remaining in the skin. A different transdermal formulation—*lonsys*—has been withdrawn.

Transdermal fentanyl is indicated only for persistent severe pain in patients who are already opioid tolerant. Use in non-tolerant patients can cause fatal respiratory depression. The patch should not be used in children under 2 years old, or in anyone under 18 who weighs less than 110 pounds. Also, the patch should not be used for postoperative pain, intermittent pain, or pain that responds to a less powerful analgesic.

Like other strong opioids, fentanyl overdose poses a risk of fatal respiratory depression. If respiratory depression develops, it may persist for hours following patch removal, owing to continued absorption of fentanyl from the skin.

Fentanyl patches are available in five strengths, which deliver fentanyl to the systemic circulation at rates of 12.5, 25, 50, 75, and 100 mcg/hr. The smallest effective patch should be used. If a dosage greater than 100 mcg/hr is required, a combination of patches can be applied. Once the patch is in place, it must not be exposed to direct heat (eg, heating pads, hot baths, electric blankets), because doing so can accelerate fentanyl release, as can fever, sunbathing, and strenuous exercise. Because full analgesic effects can take up to 24 hours to develop, PRN therapy with a short-acting opioid may be required until the patch takes effect. As with other long-acting opioids, if breakthrough pain occurs, supplemental dosing with a short-acting opioid is indicated. For the majority of patients, patches can be replaced every 72 hours, although some may require a new patch in 48 hours. Used or damaged patches should be flushed down the toilet. Unused patches should be stored out of reach of children.

Transmucosal. Fentanyl for transmucosal administration is available in four formulations: lozenges on a stick [Actiq], buccal film [Onsolis], buccal tablets [Fentora], and sublingual tablets [Abstral]. All four products are approved only for *breakthrough cancer pain in patients at least 18 years old who are already taking opioids around-the-clock and have developed some degree of tolerance*, defined as needing, for 1 week or longer, at least: 60 mg of oral morphine a day, or 30 mg of oral oxycodone a day, or 25 mg of oral oxymorphone a day, or 8 mg of oral hydromorphone a day, or 25 mcg of fentanyl/hr, or an equianalgesic dose of another opioid. Transmucosal fentanyl must not be used for acute pain, postoperative pain, headache, or athletic injuries. Furthermore, it is essential to appreciate that the dose of fentanyl in these formulations is sufficient to kill nontolerant individuals—especially children. Accordingly, these products must be stored in a secure, child-resistant location. All fentanyl transmucosal formulations are regulated as Schedule II products.

Adverse effects of transmucosal fentanyl are like those of other opioid preparations. The most common are dizziness, anxiety, confusion, nausea, vomiting, constipation, dyspnea, weakness, and headache. The biggest concerns are respiratory depression and shock.

Because of differences in bioavailability, *transmucosal fentanyl products are not interchangeable on a mg-for-mg basis*. For example, a 100-mcg buccal tablet produces about the same fentanyl blood level as does a 200-mcg lozenge. Accordingly, if a patient switches from one transmucosal product to another, dosage of the new product must be titrated to determine a strength that is safe and effective.

Lozenge on a Stick. The fentanyl lozenge on a stick [Actiq]—also known as OTFC (oral transmucosal fentanyl citrate)—consists of a raspberry-flavored lozenge on a plastic handle, and looks much like a lollipop. Six strengths are available: 200, 400, 600, 800, 1200, and 1600 mcg.

To administer the unit, patients place it between the cheek and the lower gum and actively suck it. Periodically, the unit should be moved from one side of the mouth to the other. Consumption of the entire lozenge should take 15 minutes. As the patient sucks, some of the drug is absorbed directly and rapidly through the oral mucosa, and some is swallowed and absorbed slowly from the GI tract. Analgesia begins in 10 to 15 minutes, peaks in 20 minutes, and persists 1 to 2 hours.

Dosing should begin with a 200-mcg unit. If breakthrough pain persists, the patient can take another 200-mcg unit 15 minutes after finishing the first one (ie, 30 minutes after starting the first). Unit size should be gradually increased until an effective dose is determined. If the patient needs more than 4 units/day, it may be time to give a higher dose of his or her long-acting opioid.

To promote safe and effective use of the Actiq system, the manufacturer provides an Actiq Welcome Kit with the initial drug supply. The kit contains educational materials and safe storage containers for unused, partially used, and completely used units.

Soluble Buccal Film. Fentanyl buccal film [Onsolis] is made using a drug-delivery technology known as BioErodible MucoAdhesive. Five film strengths are available: 200, 400, 600, 800, and 1200 mcg. A single dose of the film is about 1 cm square and very thin, with a pink side (that delivers the fentanyl) and a white side (that indicates the strength). Patients should press the pink side against the inside of the cheek for 5 seconds, and then leave it there. If the site is dry, it should be moistened first with saliva or water. Patients can drink after 5 minutes, but should avoid eating until the film has dissolved (in 15 to 30 minutes). Patients should not tear, chew, or swallow the film. Dosing is begun at 200 mcg, and can be titrated up, in 200-mcg increments, to a maximum of 1200 mcg/pain episode. At least 2 hours should elapse between doses. No more than four doses should be used in one day. Owing to risks of misuse, abuse, and overdose, fentanyl buccal film is available only through a restricted distribution program, called the FOCUS Program.

Buccal Tablets. Fentanyl buccal tablets [Fentora] are available in six strengths: 100, 200, 300, 400, 600, and 800 mcg. Patients should place the tablet above a rear molar between the cheek and the gum and let it dissolve in place, usually in 15 to 30 minutes. Remaining fragments should be swallowed with a glass of water. Patients should not split, chew, suck, or swallow the tablets. The initial dose is 100 mcg. If 100 mcg is inadequate, another 100 mcg can be taken in 30 minutes. During each subsequent episode, dosage may be gradually increased, if needed, until an effective dose is established.

Sublingual Tablets. Fentanyl sublingual tablets [Abstral] are available in six strengths: 100, 200, 300, 400, 600, and 800 mcg. Each strength is a different color and shape. Patients should place the tablet on the floor of the mouth directly under the tongue, and allow it to dissolve completely. If the mouth is dry, it should be moistened with water before dosing. Tablets must not be chewed, sucked, or swallowed. Patients should not eat or drink until the tablet is gone. Abstral is available only through pharmacies enrolled in the Abstral REMS Program.

The initial dosage is 100 mcg. If 100 mcg is inadequate, another 100 mcg can be taken in 30 minutes. No more than two doses should be used for any pain episode, and patients should wait at least 2 hours before dosing again. With each subsequent episode, the dose should be titrated until a safe and effective dose is identified.

Intranasal. Fentanyl nasal spray [Lazanda], approved in 2011, is much like transmucosal fentanyl. Like transmucosal fentanyl, Lazanda is indicated only for *breakthrough cancer pain in patients at least 18 years old who are already taking opioids around-the-clock and have developed some degree of tolerance*. The spray must not be used for acute pain, postoperative pain, headache, or athletic injuries. Because of differences in bioavailability, Lazanda is not interchangeable with other fentanyl products on a mg-for-mg basis. Adverse effects are like those of other opioid preparations. The biggest concerns are respiratory depression and shock. As with the transmucosal products, the dose of fentanyl in Lazanda is sufficient to kill nontolerant in-

dividuals, and hence the spray must be stored in a secure, child-resistant location.

Intranasal fentanyl is supplied in 5-ml bottles that have a metered-dose nasal spray pump. Each bottle contains enough solution for 8 sprays. Two strengths are available: 100 or 400 mcg/spray. Dosing starts with 100 mcg. If needed, dosage can be titrated upward at subsequent pain episodes as follows: 200 mcg (100 mcg in each nostril), 400 mcg (400 mcg in 1 nostril), and then 800 mcg (400 mcg in 2 nostrils). Patients should allow at least 2 hours between doses. If more than 5 days elapse since the last dose, the bottle should be discarded and replaced with a new one.

Alfentanil and Sufentanil

Alfentanil [Alfenta] and sufentanil [Sufenta] are intravenous opioids related to fentanyl. Both drugs are used for induction of anesthesia, for maintenance of anesthesia (in combination with other agents), and as sole anesthetic agents. Pharmacologic effects are like those of morphine. Sufentanil has an especially high milligram potency (about 1000 times that of morphine). Alfentanil is about 10 times more potent than morphine. Both drugs have a rapid onset, and both are Schedule II agents.

Remifentanyl

Remifentanyl [Ultiva] is an intravenous opioid with a rapid onset and brief duration. The brief duration results from rapid metabolism by plasma and tissue esterases, and not from hepatic metabolism or renal excretion. Like fentanyl, remifentanyl is about 100 times more potent than morphine. Remifentanyl is approved for analgesia during surgery and during the immediate postoperative period. Administration is by continuous IV infusion. Effects begin in minutes, and terminate 5 to 10 minutes after the infusion is stopped. For surgical analgesia, the infusion rate is 0.05 to 2 mcg/kg/min. For postoperative analgesia, the infusion rate is 0.025 to 0.2 mcg/kg/min. Adverse effects during the infusion include respiratory depression, hypotension, bradycardia, and muscle rigidity sufficient to compromise breathing. Postinfusion effects include nausea (44%), vomiting (22%), and headache (18%). Remifentanyl is regulated as a Schedule II substance.

Meperidine

Meperidine [Demerol] shares the major pharmacologic properties of morphine. With parenteral and oral administration, analgesia is strong. In the past, meperidine was considered a first-line drug for relief of moderate to severe pain. Now, however, use of meperidine is in decline. Why? First, the drug has a short half-life, and hence dosing must be repeated at short intervals. Second, meperidine interacts adversely with a number of drugs. Third, with continuous use, there is a risk of harm owing to accumulation of a toxic metabolite. Accordingly, routine use of the drug should be avoided. However, meperidine may still be appropriate for patients who can't take other opioids, and for patients with drug-induced rigors or postanesthesia shivering.

Meperidine can interact with MAO inhibitors to cause excitation, delirium, hyperpyrexia, and convulsions. Coma and death can follow. The underlying mechanism appears to be excessive activation of serotonin receptors owing to meperidine-induced blockade of serotonin reuptake. Clearly, the combination of meperidine with an MAO inhibitor should be avoided. Other drugs that increase serotonin availability (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors) may also pose a risk.

Repeated dosing results in accumulation of normeperidine, a toxic metabolite that can cause dysphoria, irritability, tremors, and seizures. To avoid toxicity, treatment should not exceed 48 hours, and the dosage should not exceed 600 mg/24 hr.

Meperidine is available in tablets (50 and 100 mg) and a syrup (10 mg/mL) for oral use, and in solution (25, 50, 75, and 100 mg/mL) for injection (IV, IM, or subQ). The usual adult dosage is 50 to 150 mg (IM, subQ, or PO) repeated every 3 to 4 hours as needed—up to a maximum of 600 mg/day. The usual dosage for children is 1 to 1.8 mg/kg (IM, subQ, or PO) repeated every 3 to 4 hours as needed. As noted, prolonged use must be avoided.

Methadone

Methadone [Diskets, Dolophine, Methadose, Metadol] has pharmacologic properties very similar to those of morphine. The drug is effective orally and has a long duration of action. Repeated dosing can result in accumulation. Methadone is used to relieve pain and to treat opioid addiction. In the United States, methadone prescriptions for pain relief rose sevenfold between 1997 and 2004. The use of methadone in drug-abuse treatment programs is discussed in Chapter 40.

Methadone prolongs the QT interval, and hence may pose a risk of potentially fatal dysrhythmias. Torsades de pointes has developed in patients taking 65 to 400 mg/day. To reduce risk, methadone should be used with great caution—if at all—in patients with existing QT prolongation or a family history

of long QT syndrome, and in those taking other QT-prolonging drugs (eg, amiodarone, quinidine, erythromycin, tricyclic antidepressants). In addition, all patients should receive an electrocardiogram (ECG) before treatment, and all patients should receive an ECG before treatment, and all patients should receive an ECG before treatment. If the QT interval exceeds 500 msec, stopping methadone or reducing the dosage should be considered.

There have been increasing reports of deaths and life-threatening side effects (especially dysrhythmias and respiratory depression) among patients taking methadone to relieve pain. The presumed cause of toxicity is high drug levels, owing largely to excessive dosage. To reduce risk, patients should be warned against taking more methadone than was prescribed, and should be cautioned to avoid other CNS depressants, such as benzodiazepines, alcohol, and other opioids. Drugs that inhibit CYP3A4 (the enzyme that metabolizes methadone) can raise methadone levels, and hence should be used with care. Among these inhibitors are clarithromycin, azole antifungal drugs, and HIV protease inhibitors.

Methadone is supplied in IR tablets (5 and 10 mg) and in solution (1, 2, and 10 mg/mL) for oral use, and in solution (10 mg/mL) for IM and subQ injection. In addition, the drug is available in dispersible 40-mg tablets for detoxification and maintenance of opioid addicts. Usual oral analgesic doses for adults range from 2.5 to 20 mg repeated every 3 to 4 hours as needed.

Heroin

Heroin is a strong opioid agonist very similar to morphine in structure and actions. The drug is an effective analgesic and is employed legally in Europe to relieve pain. In the United States, federal legislation prohibits the medical use of this drug. Why? Because heroin has a high abuse liability and is no better than other opioids at relieving pain.

What makes heroin so attractive as a drug of abuse? Pharmacokinetics: Heroin has greater lipid solubility than morphine, and therefore crosses the blood-brain barrier more readily. As a result, when heroin is injected IV, it accumulates in the brain more rapidly and to a higher level than would an equivalent dose of morphine. Once in the brain, heroin (diacetylmorphine) is rapidly converted into active metabolites: monoacetylmorphine and morphine (Fig. 28-2). It is these metabolites, and not heroin itself, that produce the subjective effects that follow heroin injection. In this regard, heroin can be viewed as a vehicle for facilitating transport of morphine into the brain.

Hydromorphone, Oxycodone, and Levorphanol

Basic Pharmacology. All three drugs are strong opioid agonists with pharmacologic actions like those of morphine, and all three are indicated for moderate to severe pain. Dosages and time courses are summarized in Table 28-5. Adverse effects include respiratory depression, sedation, cough suppression, constipation, urinary retention, nausea, and vomiting. Of note, hydromorphone may cause less nausea than morphine. Toxicity can be reversed with an opioid antagonist (eg, naloxone). All three drugs are Schedule II agents.

Preparations, Dosage, and Administration. *Hydromorphone.* Hydromorphone [Dilaudid, Exalgo] is available in six formulations:

- IR tablets (2, 4, and 8 mg) sold as *Dilaudid*
- ER tablets (8, 12, and 16 mg) sold as *Exalgo* and *Jurmista*♦
- Oral liquid (1 mg/mL) sold as *Dilaudid*
- Rectal suppositories (3 mg) sold as *Dilaudid*
- Solutions (1, 2, 4, and 10 mg/mL), sold as *Dilaudid*, for IM and subQ injection
- Powder (250 mg), sold as *Dilaudid*, to be reconstituted to a 10-mg/mL solution for IM and subQ injection

With the IR tablets, the usual adult dosage is 2 mg every 4 to 6 hours. With the ER tablets, dosage is based on how much opioid was being used before switching to the ER tablets. With the oral liquid, the usual adult dosage is 2.5 to 10 mg every 3 to 6 hours. With the rectal suppositories, the usual dosage is 3 mg every 6 to 8 hours. With subQ and IM injection, dosages range from 1 to 4 mg every 4 to 6 hours.

Oxycodone. Oxycodone [Opana] is available in three formulations:

- IR tablets (5 and 10 mg) sold as *Opana*
- ER tablets (5, 7.5, 10, 15, 20, 30, and 40 mg) sold as *Opana ER*
- Solution (1 mg/mL), sold as *Opana*, for IM, IV, or subQ injection

All oxycodone tablets should be taken on an empty stomach, because dosing with food can produce excessive peak levels. Also, alcohol should be avoided, since it can increase blood levels of oral oxycodone. For oral therapy in opioid-naïve patients, the usual initial dosage is 10 to 20 mg every 4 to 6 hours (using IR tablets) or 5 mg every 12 hours (using ER tablets). For IV therapy, the initial dose is 0.5 mg. Usual subQ and IM dosages are 1 to 1.5 mg every 4 to 6 hours as needed.

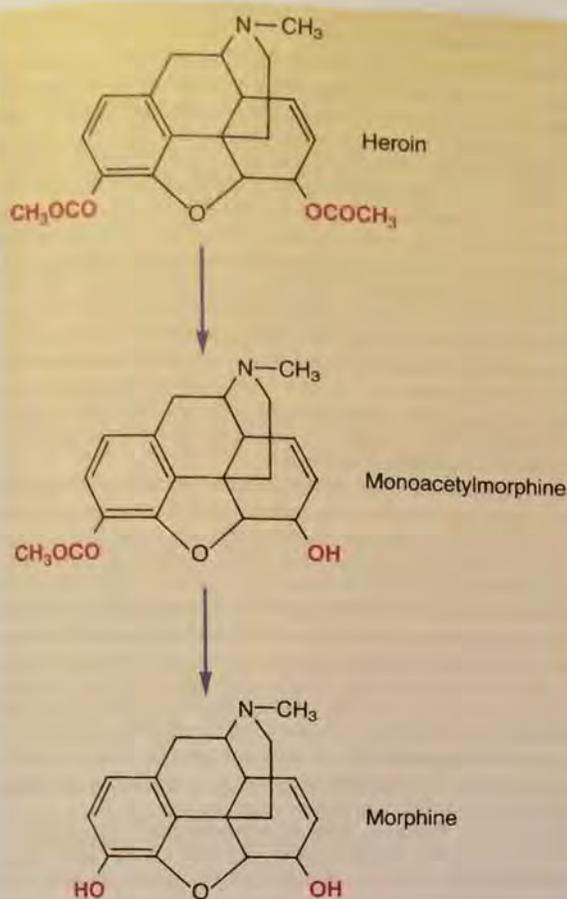


Figure 28-2 • Biotransformation of heroin into morphine. Heroin, as such, is biologically inactive. After crossing the blood-brain barrier, heroin is converted to monoacetylmorphine (MAM) and then into morphine itself. MAM and morphine are responsible for the effects elicited by injection of heroin.

Levorphanol. Levorphanol [Levo-Dromoran] is available in 2-mg oral tablets and in solution (2 mg/mL) for IM, IV, or subQ injection. The usual adult oral dosage is 2 mg, repeated in 6 to 8 hours as needed. For IV therapy, the usual dosage is 1 mg, repeated in 3 to 6 hours as needed, up to a maximum of 4 to 8 mg/24 hr. For IM or subQ therapy, the usual dosage is 1 to 2 mg, repeated in 6 to 8 hours as needed, up to a maximum of 3 to 8 mg/24 hr.

Moderate to Strong Opioid Agonists

The moderate to strong opioid agonists are similar to morphine in most respects. Like morphine, these drugs produce analgesia, sedation, and euphoria. In addition, they can cause respiratory depression, constipation, urinary retention, cough suppression, and miosis. Differences between the moderate to strong opioids and morphine are primarily quantitative: The moderate to strong opioids produce less analgesia and respiratory depression than morphine and have a somewhat lower potential for abuse. As with morphine, toxicity from the moderate to strong agonists can be reversed with naloxone.

Codeine

Codeine is indicated for relief of mild to moderate pain. The drug is usually administered by mouth. Side effects are dose limiting. As a result, although taking codeine can produce significant pain relief, the degree of pain relief that can be

achieved *safely* is quite low—much lower than with morphine. When taken in its usual analgesic dose (30 mg), codeine produces about as much pain relief as 325 mg of aspirin or 325 mg of acetaminophen.

In the liver, about 10% of each dose of codeine undergoes conversion to *morphine*, the active form of codeine. The enzyme responsible is CYP2D6 (the 2D6 isomer of cytochrome P450). Among people who lack an effective gene for CYP2D6, codeine cannot be converted to morphine, and hence codeine cannot produce analgesia. Conversely, among ultrarapid metabolizers, who carry multiple copies of the CYP2D6 gene, codeine is unusually effective. Ultrarapid metabolism occurs in 7% of whites, 3% of blacks, and 1% of Hispanics and Asians.

Very rarely, severe toxicity develops in breast-fed infants whose mothers are taking codeine. The cause is high levels of morphine in breast milk, owing to ultrarapid codeine metabolism. Nursing mothers who are taking codeine should be alert for signs of infant intoxication—excessive sleepiness, breathing difficulties, lethargy, poor feeding—and should seek medical attention if these develop.

For analgesic use, codeine is formulated alone and in combination with nonopioid analgesics (either aspirin or acetaminophen). Since codeine and nonopioid analgesics relieve pain by different mechanisms, the combinations can produce greater pain relief than either agent alone. Codeine alone is classified under Schedule II of the Controlled Substances Act. The combination preparations are classified under Schedule III. Although codeine is classified along with morphine in Schedule II, the abuse liability of codeine appears to be significantly lower.

Codeine is an extremely effective cough suppressant and is widely used for this action. The antitussive dose (10 mg) is lower than analgesic doses. Codeine is formulated in combination with various agents to suppress cough. These mixtures are classified under Schedule V.

Preparations, Dosage, and Administration. Codeine is administered orally and parenterally (IV, IM, and subQ). For oral therapy, the drug is available in tablets (15, 30, and 60 mg) and in solution (15 mg/5 mL). For parenteral therapy, the drug is available in solution (15 and 30 mg/mL).

The usual analgesic dosage for adults is 15 to 60 mg (PO, IV, IM, or subQ) every 3 to 6 hours (up to a maximum of 120 mg/24 hr). The usual analgesic dosage for children 1 year and older is 0.5 mg/kg (PO, IM, or subQ) every 4 to 6 hours (up to a maximum of 60 mg/24 hr).

Oxycodone

Oxycodone [OxyContin, Roxicodone, Combunox, Oxecta, Percodan, Percocet, OxyIR \clubsuit , others] has analgesic actions equivalent to those of codeine. Administration is oral. Oxycodone is available by itself in immediate-release tablets (5, 10, 15, 20, and 30 mg), immediate-release capsules (5 mg), controlled-release tablets (10, 15, 20, 30, 40, 60, and 80 mg), and oral solutions (1 and 20 mg/mL). In addition, the drug is available in combination with aspirin (as Percodan), acetaminophen (as Percocet, Roxicet, others), and ibuprofen (as Combunox). All formulations are classified under Schedule II.

Oxycodone is metabolized by CYP3A4, and hence drugs that induce or inhibit CYP3A4 can alter oxycodone levels. Specifically, drugs that induce CYP3A4 (eg, carbamazepine, phenytoin, rifampin), can lower oxycodone levels, and thereby compromise pain relief. Conversely, drugs that inhibit CYP3A4 (eg, clarithromycin,azole antifungal drugs, HIV protease inhibitors) can raise oxycodone levels, and thereby pose a risk of toxicity.

Controlled-release oxycodone [OxyContin] is a long-acting analgesic designed to relieve moderate to severe pain around-the-clock for an extended time. Dosing is done every 12 hours—not PRN. If breakthrough pain occurs, supplemental dosing with a short-acting analgesic is indicated.

Owing to increasing reports of OxyContin abuse, safety warnings have been strengthened, and, in 2010, the product was reformulated. The new formulation bears the imprint OP; the old formulation bears the imprint OC. Why the reformulation? Because abusers could crush the OxyContin OC tablets and then “snort” the resulting powder, or dissolve the powder in water and inject it IV. Both practices allowed immediate absorption of the entire dose, and thereby produced blood levels that were much higher than those produced when the tablets were ingested whole and absorbed gradually. The result was an intense “high” coupled with a risk of fatal respiratory depression. Compared with the old tablets, OxyContin OP tablets are much harder to crush into a powder. And if exposed to water or alcohol, the tablets just form a gummy blob, rather than a solution that can be drawn into a syringe and injected.

To minimize risk, patients should swallow OxyContin tablets whole, without breaking, crushing, or chewing. Furthermore, the 80-mg formulation must be reserved for patients who are already opioid tolerant. As with all other opioids, concerns about abuse and addiction should not interfere with using OxyContin to manage pain. Rather, the drug must simply be prescribed appropriately and then used as prescribed.

Like OxyContin OP, a new *immediate-release* formulation [Oxecta] is designed to discourage abuse. If Oxecta tablets are crushed and snorted, they will burn the nasal passages. If the tablets are exposed to a solvent (eg, water, alcohol), they will form a gel that can't be drawn into a syringe. However, the formulation does nothing to deter oral abuse.

Hydrocodone

Hydrocodone is the most widely prescribed drug in the United States. In 2008, more than 121 million prescriptions were written—far more than the 87 million for levothyroxine (thyroid hormone) or the 59 million for atorvastatin (a cholesterol-lowering drug). Hydrocodone has analgesic actions equivalent to those of codeine. The drug is taken orally to relieve pain and to suppress cough. The usual dosage is 5 mg. Hydrocodone is available only in combination with other drugs. For analgesic use, hydrocodone is combined with aspirin, acetaminophen, or ibuprofen. For cough suppression, the drug is combined with antihistamines and nasal decongestants. All of these combination products are currently classified under Schedule III. However, owing to widespread abuse of hydrocodone-containing products, the Drug Enforcement Agency (DEA) would like the classification changed to Schedule II. Trade names for combination products containing hydrocodone include *Vicodin*, *Vicoprofen*, and *Lortab*.

Tapentadol

Actions and Uses. Tapentadol [Nucynta], approved in 2008, is indicated for oral therapy of moderate to severe pain—acute or chronic—in patients age 18 years and older. Analgesic effects are equivalent to those of oxycodone. Like other opioids, tapentadol can cause CNS depression and respiratory depression, and has a significant potential for abuse. However the drug differs from other opioids in two important ways. First, in addition to activating mu opioid receptors, tapentadol blocks reuptake of norepinephrine (NE), similar to tramadol, discussed below. Second, tapentadol causes less constipation than traditional opioids. Because tapentadol is relatively new, and hence experience with the drug is limited, it would seem prudent to re-

serve tapentadol for patients who need a strong opioid but cannot tolerate the GI side effects of traditional agents.

Pharmacokinetics. Tapentadol is administered PO, and plasma levels peak about 1.5 hours after dosing. Because of extensive first-pass metabolism, bioavailability is only 32%. The drug is eliminated primarily by renal excretion. Its half-life is approximately 4 hours.

Adverse Effects. The most common adverse effects are nausea, vomiting, headache, dizziness, and drowsiness. Like other opioids, tapentadol can cause respiratory depression, and hence should be avoided in patients with pre-existing respiratory depression and in those with acute or severe asthma. As noted, the drug causes less constipation than other opioids. Nonetheless, tapentadol is contraindicated in patients with paralytic ileus. As discussed below, tramadol, a drug similar to tapentadol, poses a risk of seizures. To date, seizures have not been reported with tapentadol. Nonetheless, caution should be exercised in patients with a history of seizure disorders. Owing to its abuse potential, tapentadol is classified as a Schedule II substance. Patients should be monitored for abuse and addiction. Tapentadol is classified in FDA Pregnancy Risk Category C, indicating that no adequate studies in pregnant patients have been performed.

Drug Interactions. The depressant effects of tapentadol can add with those of other agents (eg, alcohol, opioids, barbiturates, benzodiazepines), and can thereby increase the risk of respiratory depression, sedation, and even coma. Because tapentadol can increase serum levels of NE (by blocking NE uptake), combined use with a monoamine oxidase (MAO) inhibitor might result in hypertensive crisis (see Chapter 32). Accordingly, tapentadol should not be used within 14 days of taking an MAO inhibitor. Package labeling says that a life-threatening serotonin syndrome could result from combining tapentadol with a selective serotonin reuptake inhibitor (SSRI; eg, fluoxetine), a serotonin/norepinephrine reuptake inhibitor (eg, venlafaxine), a tricyclic antidepressant (eg, amitriptyline), or a serotonin agonist (eg, eletriptan). However, in clinical trials, combined use with an SSRI had no ill effects. Tapentadol neither inhibits nor induces P450 enzymes, and hence clinically relevant interactions involving the P450 system seem unlikely.

Preparations, Dosage, and Administration. Tapentadol is available in two formulations: immediate-release (IR) tablets (50, 75, and 100 mg), sold as *Nucynta*, and extended-release (ER) tablets (50, 100, 150, 200, and 250 mg), sold as *Nucynta ER*. The IR tablets are indicated only for moderate to severe acute pain. The ER tablets are indicated only for moderate to severe chronic pain, and then only in patients who require continuous, around-the-clock treatment with an opioid analgesic. Dosages are as follows:

- **IR Tablets.** The recommended dosage is 50, 75, or 100 mg every 4 to 6 hours. When initiating treatment, a second dose can be given 1 hour after the first. The maximum dosage on day one is 700 mg. The maximum dosage on all subsequent days is 600 mg. In patients with moderate hepatic impairment, the dosage should be no more than 50 mg every 8 hours. In patients with severe hepatic or renal impairment, tapentadol should not be used.
- **ER Tablets.** The initial dosage is 50 mg twice a day, and the maximum dosage is 250 mg twice a day. For patients with moderate hepatic impairment, the initial dosage is 50 mg once a day, and the maximum dosage is 100 mg once a day. As with the IR tablets, the ER tablets should not be used in patients with severe hepatic or renal impairment.

Propoxyphene

In 2010, the FDA recommended that all propoxyphene-containing products, such as *Darvon* and *Darvocet*, be removed from the market. The stated reason was concern about cardiotoxicity: Results of a 2010 study showed that propoxyphene, at therapeutic doses, could promote potentially fatal dysrhythmias. However, long before these data were available, many authorities felt the drug should be banned. Why? Because the benefits of propoxyphene are limited (pain relief is no better than with aspirin or acetaminophen), whereas the risk of lethal overdose is substantial (the drug has been associated with at least 10,000 deaths since 1957, the year it was introduced). Prior to its removal, propoxyphene was among the top 25 most commonly prescribed drugs in the United States. Safer alternatives to propoxyphene include aspirin, acetaminophen, tramadol, acetaminophen plus codeine, and acetaminophen plus hydrocodone.

Agonist-Antagonist Opioids

Four agonist-antagonist opioids are available: pentazocine, nalbuphine, butorphanol, and buprenorphine. With the exception of buprenorphine, these drugs act as antagonists at mu receptors and agonists at kappa receptors (see Table 28-2). Con-

pared with pure opioid agonists, the agonist-antagonists have a low potential for abuse, produce less respiratory depression, and generally have less powerful analgesic effects. If given to a patient who is physically dependent on a pure opioid agonist, these drugs can precipitate withdrawal. The clinical pharmacology of the agonist-antagonists is summarized in Table 28-6.

Pentazocine

Actions and Uses. Pentazocine [Talwin] was the first agonist-antagonist opioid available and can be considered the prototype for the group. The drug is indicated for mild to moderate pain. Pentazocine is much less effective than morphine against severe pain.

Pentazocine acts as an *agonist* at kappa receptors and as an *antagonist* at mu receptors. By activating kappa receptors, the drug produces analgesia, sedation, and respiratory depression. However, unlike the respiratory depression caused by morphine, *respiratory depression caused by pentazocine is limited*: Beyond a certain dose, no further depression occurs. Because it lacks agonist actions at mu receptors, pentazocine produces little or no euphoria. In fact, at supratherapeutic doses, pentazocine produces unpleasant reactions (anxiety, strange thoughts, nightmares, hallucinations). These psychotomimetic effects may result from activation of kappa receptors. Because of its subjective effects, pentazocine has a low potential for abuse and is classified under Schedule IV.

Adverse effects are generally like those of morphine. However, in contrast to the pure opioid agonists, pentazocine increases cardiac work. Accordingly, a pure agonist (eg, morphine) is preferred to pentazocine for relieving pain in patients with myocardial infarction.

If administered to a patient who is physically dependent on a pure opioid agonist, pentazocine can precipitate withdrawal. Recall that mu receptors mediate physical dependence on pure opioid agonists and that pentazocine acts as an

antagonist at these receptors. By blocking access of the pure agonist to mu receptors, pentazocine will prevent receptor activation, thereby triggering withdrawal. Accordingly, *pentazocine and other drugs that block mu receptors should never be administered to a person who is physically dependent on a pure opioid agonist.* If a pentazocine-like agent is to be used, the pure opioid agonist must be withdrawn first.

Physical dependence can occur with pentazocine, but symptoms of withdrawal are generally mild (eg, cramps, fever, anxiety, restlessness). Treatment is rarely required. As with pure opioid agonists, toxicity from pentazocine can be reversed with naloxone.

Preparations, Dosage, and Administration. Pentazocine is available alone for parenteral therapy and in combination with acetaminophen or naloxone for oral therapy.

Parenteral. For parenteral therapy, pentazocine is available in solution (30 mg/mL) sold as *Talwin*. Administration may be subQ, IM, or IV. The usual dosage is 30 mg every 3 to 4 hours, but no more than 360 mg/day.

Oral. For oral therapy, pentazocine is available in two formulations: *pentazocine/acetaminophen* (25 mg/650 mg), formerly available as *Talacen*, and *pentazocine/naloxone* (50 mg/0.5 mg), sold generically. For pentazocine/acetaminophen, the usual dosage is 1 tablet every 4 hours, for a daily maximum of 6 tablets (300 mg pentazocine). For pentazocine/naloxone, the usual dosage is 1 tablet every 3 to 4 hours, but may be increased to 2 tablets every 3 to 4 hours if needed, for a daily maximum of 12 tablets (600 mg pentazocine).

Nalbuphine

Nalbuphine [Nubain] has pharmacologic actions similar to those of pentazocine. The drug is an agonist at kappa receptors and an antagonist at mu receptors. At low doses, nalbuphine has analgesic actions equal to those of morphine. However, as dosage increases, a ceiling to analgesia is reached. As a result, the maximal pain relief that can be produced with nalbuphine is much lower than with morphine. As with pain relief, there is also a ceiling to respiratory depression. Like pentazocine, nalbuphine can cause psychotomimetic reactions. With prolonged treatment, physical dependence can develop. Symptoms of abstinence are less intense than with morphine but more intense than with pentazocine. When used during labor and delivery, nalbuphine has caused serious adverse effects, including bradycardia in the fetus and apnea, cyanosis, and hypotonia in the neonate. Accordingly, use during

TABLE 28-6 ■ Clinical Pharmacology of Opioid Agonist-Antagonists

Drug and Route*	Equianalgesic Dose (mg) [†]	Time Course of Analgesic Effects		
		Onset (min)	Peak (min)	Duration (hr)
Buprenorphine				
IM	0.3	15	60	Up to 6
IV	0.3	Under 15	Under 60	Up to 6
Butorphanol				
IM	2-3	10	30-60	3-4
IV	2-3	2-3	30-60	3-4
Intranasal	2-3	Within 15	60-120	4-5
Nalbuphine				
IM	10	Within 15	60	3-6
IV	10	2-3	30	3-6
SubQ	10	Within 15	60	3-6
Pentazocine				
PO	—	15-30	60-90	3 [‡]
IM	30	15-20	30-60	4-6 [‡]
IV	30	2-3	15-30	4-6 [‡]
SubQ	30	15-20	30-60	4-6 [‡]

*IM administration should be avoided whenever possible.

[†]Dose in milligrams that produces a degree of analgesia equivalent to that produced by a 10-mg IM dose of morphine.

[‡]Duration may increase greatly in patients with liver disease.

labor and delivery should be avoided. Nalbuphine has a low abuse potential and is not regulated under the Controlled Substances Act. As with the pure opioid agonists, toxicity can be reversed with naloxone. Like pentazocine, nalbuphine will precipitate a withdrawal reaction if administered to an individual physically dependent on a pure opioid agonist. Nalbuphine is supplied in solution (10 and 20 mg/mL) for IV, IM, and subQ injection. The usual adult dosage is 10 mg repeated every 3 to 6 hours as needed.

Butorphanol

Butorphanol [Stadol] has actions similar to those of pentazocine. The drug is an agonist at kappa receptors and an antagonist at mu receptors. Analgesic effects are less than those of morphine. As with pentazocine, there is a "ceiling" to respiratory depression. The drug can cause psychotomimetic reactions, but these are rare. Butorphanol increases cardiac work and should not be given to patients with myocardial infarction. Physical dependence can occur, but symptoms of withdrawal are relatively mild. The drug may induce a withdrawal reaction in patients physically dependent on a pure opioid agonist. Butorphanol has a low potential for abuse and is regulated as a Schedule IV substance. Toxicity can be reversed with naloxone.

Butorphanol is administered parenterally (IM and IV) and by nasal spray (primarily to treat migraine). The usual adult IV dosage is 1 mg every 3 to 4 hours as needed. The usual IM dosage is 2 mg every 3 to 4 hours as needed. The usual intranasal dosage is 1 mg (1 spray from the metered-dose spray device) repeated in 60 to 90 minutes if needed. The two-dose sequence may then be repeated every 3 to 4 hours as needed.

Buprenorphine

Basic Pharmacology. Buprenorphine [Buprenex, Butrans, Subutex, Suboxone] differs significantly from other opioid agonist-antagonists. The drug is a partial agonist at mu receptors and an antagonist at kappa receptors. Analgesic effects are like those of morphine, but significant tolerance has not been observed. Although buprenorphine can depress respiration, severe respiratory depression has not been reported. Like pentazocine, buprenorphine can precipitate a withdrawal reaction in persons physically dependent on a pure opioid agonist. Physical dependence on buprenorphine develops, but symptoms of abstinence are delayed: Peak responses may not occur until 2 weeks after the final dose was taken. Although pretreatment with naloxone can prevent toxicity from buprenorphine, naloxone cannot readily reverse toxicity that has already developed. (Buprenorphine binds very tightly to its receptors, and hence cannot be readily displaced by naloxone.) Buprenorphine is classified as a Schedule III substance. In addition to its use for analgesia, buprenorphine is used to treat opioid addiction (see Chapter 40).

Buprenorphine prolongs the QT interval, posing a risk of potentially fatal dysrhythmias. Accordingly, the drug should not be used by patients with long QT syndrome or a family history of long QT syndrome, or by patients using QT-prolonging drugs (eg, quinidine, amiodarone).

The risk of adverse effects may be increased by coexisting conditions, including psychosis, alcoholism, adrenocortical insufficiency, and severe liver or renal impairment. In addition, buprenorphine can cause spasm of the sphincter of Oddi (where the bile duct and pancreatic duct enter the duodenum), and can thereby pose a risk to patients with pancreatitis or biliary disease.

Preparations. Buprenorphine is available in four formulations: transdermal patch, solution for injection, sublingual tablets, and a sublingual film. The patch and solution are approved for pain management. The sublingual products are approved only for opioid addiction—but are used off-label for pain management.

Transdermal Patch. The buprenorphine patch, sold as *Butrans*, is indicated for moderate to severe chronic pain in patients who need continuous analgesia for an extended time. The patch is applied once every 7 days. Three strengths are available, delivering 5, 10, or 20 mcg/hr. The lowest strength is used for opioid-naïve patients, or for those using an opioid in low dosage (eg, oral morphine, 30 mg/day). Dosage may be titrated to the next higher strength after a minimum of 72 hours. Breakthrough pain can be managed with acetaminophen, a nonsteroidal anti-inflammatory drug, or a short-acting opioid.

Patches are applied to eight sites: upper outer arm, upper front of chest, upper side of chest, and upper back—on the right and left sides of the body. The site should be rotated when a new patch is applied, and no site should be reused within 21 days. The site should be hairless, or nearly so. If needed, hair can be removed by clipping, not by shaving. The site may be cleaned, but only with water, not with soaps, alcohol, or abrasives. No lotion or oil should be applied. Patches should not be cut or exposed to heat, including heating pads, heated waterbeds, hot baths, saunas, heat lamps, or extended sunshine. If a patch falls off during the 7-day dosing interval, a new patch should be applied, but at a different site. If patch use is stopped, opioids should not be given for 24 hours.

Solution for Injection. Buprenorphine solution (0.3 mg/mL), sold as *Buprenex*, is indicated only for parenteral management of pain. Dosing is by

IM or slow IV injection. The usual dosage for patients ages 13 years and older is 0.3 mg repeated every 6 hours as needed.

Sublingual Tablets and Sublingual Film. Buprenorphine is available in three sublingual formulations. One formulation, tablets marketed as *Subutex*, contains buprenorphine alone (2 or 8 mg). The other two formulations, tablets and films marketed as *Suboxone*, contain a mixture of buprenorphine/naloxone (2 mg/0.5 mg or 8 mg/2 mg). All three sublingual formulations are approved only for managing opioid addiction. However, they are also used off-label for analgesia. For opioid addiction, dosing is done once a day. For pain management, dosing is done 3 or 4 times a day. Use of these products for opioid addiction is discussed further in Chapter 40.

CLINICAL USE OF OPIOIDS

Dosing Guidelines

Pain Assessment

Assessment is an essential component of pain management. Pain status should be evaluated prior to opioid administration and about 1 hour after. Unfortunately, because pain is a subjective experience, affected by multiple factors (eg, cultural influences, patient expectations, associated disease), there is no reliable objective method for determining just how much discomfort the patient is feeling. That is, we cannot measure pain with instruments equivalent to those employed to monitor blood pressure, bone loss, and other physiologic parameters. As a result, assessment must ultimately be based on the patient's description of his or her experience. Accordingly, you should ask the patient where the pain is located, what type of pain is present (eg, dull, sharp, stabbing), how the pain changes with time, what makes the pain better, what makes it worse, and how much does it impair your ability to function. In addition, you should assess for psychologic factors that can reduce pain threshold (anxiety, depression, fear, anger).

When attempting to assess pain, keep in mind that, on occasion, what the patient says may not accurately reflect his or her experience. For example, a few patients who are pain free may claim to feel pain so as to receive medication for its euphoriant effects. Conversely, some patients may claim to feel fine even though they have considerable discomfort. Reasons for under-reporting pain include fear of addiction, fear of needles, and a need to be stoic and bear the pain. Patients suspected of under-reporting pain must be listened to with care if their true pain status is to be evaluated.

Pain assessment is discussed at length in Chapter 29 (Pain Management in Patients with Cancer).

Dosage Determination

Dosage of opioid analgesics must be adjusted to accommodate individual variation. "Standard" doses cannot be relied upon as appropriate for all patients. For example, if a "standard" 10-mg dose of morphine were employed for all adults, only 70% would receive adequate relief; the other 30% would be undertreated. Not all patients have the same tolerance for pain, and hence some need larger doses than others for the same disorder. Some conditions hurt more than others. For example, patients recovering from open chest surgery are likely to experience greater pain and need larger doses than patients recovering from an appendectomy. Elderly patients metabolize opioids slowly, and therefore require lower doses than younger adults. Because the blood-brain barrier of newborns is poorly developed, these patients are especially sensitive to opioids; therefore, they generally require smaller doses (on a milligram-per-kilogram basis) than do older infants and young children.

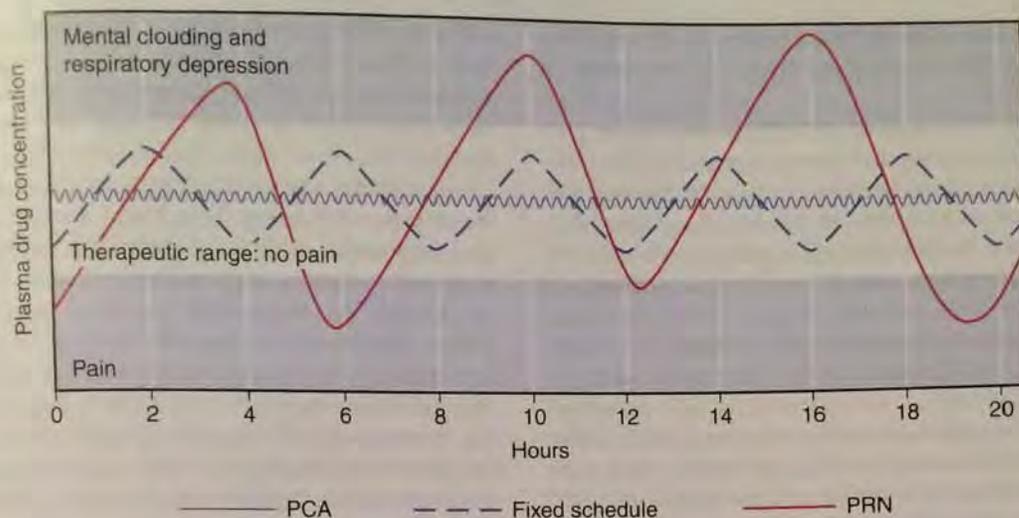


Figure 28-3 ■ Fluctuation in opioid blood levels seen with three dosing procedures.

Note that with PRN dosing, opioid levels can fluctuate widely, going from subtherapeutic to excessive and back again. In contrast, when opioids are administered with a PCA device or on a fixed schedule, levels stay within the therapeutic range, allowing continuous pain relief with minimal adverse effects.

Dosing Schedule

As a rule, *opioids should be administered on a fixed schedule* (eg, every 4 hours) rather than PRN. With a fixed schedule, each dose is given before pain returns, thereby sparing the patient needless discomfort. In contrast, when PRN dosing is employed, there can be a long delay between onset of pain and production of relief: Each time pain returns, the patient must call the nurse, wait for the nurse to respond, wait for the nurse to evaluate the pain, wait for the nurse to sign out medication, wait for the nurse to prepare and administer the injection, and then wait for the drug to undergo absorption and finally produce analgesia. This delay causes unnecessary discomfort and creates anxiety about pain recurrence. Use of a fixed dosing schedule reduces these problems. As discussed below, allowing the patient to self-administer opioids with a patient-controlled analgesia (PCA) device can provide even greater protection against pain recurrence than can be achieved by having you administer opioids on a fixed schedule. The differences between PRN dosing, fixed-schedule dosing, and use of a PCA device are shown graphically in Figure 28-3.

Avoiding a Withdrawal Reaction

When opioids are administered in high doses for 20 days or more, clinically significant physical dependence may develop. Under these conditions, abrupt withdrawal will precipitate an abstinence syndrome. To minimize symptoms of abstinence, opioids should be withdrawn slowly, tapering the dosage over 3 days. If the degree of dependence is especially high, as can occur in opioid addicts, dosage should be tapered over 7 to 10 days.

Physical Dependence, Abuse, and Addiction as Clinical Concerns

Most people in our society, including many health professionals, harbor strong fears about the ability of “narcotics” to cause “addiction.” In a clinical setting, such excessive concern is both unwarranted and counterproductive. Because of

inappropriate fears, physicians frequently prescribe less pain medication than patients need, and nurses frequently administer less than was prescribed. The result, according to one estimate, is that only 25% of patients receive doses of opioids that are sufficient to relieve suffering. One pain specialist described this unacceptable situation as follows: “The excessive and unrealistic concern about the dangers of addiction in the hospitalized medical patient is a significant and potent force for the undertreatment with narcotics [opioids].”

When treating a patient for pain, you may have to decide how much opioid to give and when to give it. If you are excessively concerned about the ability of opioids to cause physical dependence and addiction, you will be unable to make a rational choice. Furthermore, in your role as patient advocate, it is your responsibility to intervene and request an increase in dosage if the prescribed dosage has proved inadequate. If you fear that dosage escalation may cause “addiction,” you are less likely to make the request.

The object of the following discussion is to dispel excessive concerns about dependence, abuse, and addiction in the medical patient so these concerns do not result in undermedication and needless suffering.

Definitions

Before we can discuss the clinical implications of physical dependence, abuse, and addiction, we need to define these terms.

Physical Dependence. As noted, physical dependence is a state in which an abstinence syndrome will occur if the dependence-producing drug is abruptly withdrawn. *Physical dependence is NOT the same as addiction.*

Abuse. Abuse can be broadly defined as *drug use that is inconsistent with medical or social norms*. By this definition, abuse is determined primarily by the reason for drug use and by the setting in which that use occurs—and not by the pharmacologic properties of the drug itself. For example, whereas it is *not* considered abuse to administer 20 mg of morphine in a hospital to relieve pain, it *is* considered abuse

to administer the same dose of the same drug on the street to produce euphoria. The concept of abuse is discussed at length in Chapter 37.

Addiction. Addiction can be defined as a *behavior pattern characterized by continued use of a psychoactive substance despite physical, psychologic, or social harm*. Note that nowhere in this definition is addiction equated with physical dependence. In fact, physical dependence is not even part of the definition. The concept of addiction is discussed further in Chapter 37.

Although physical dependence is not required for addiction to occur, physical dependence *can* contribute to addictive behavior. If an individual has already established a pattern of compulsive drug use, physical dependence can reinforce that pattern. For the individual with a marginal resolve to discontinue opioid use, the desire to avoid symptoms of withdrawal may be sufficient to promote continued drug use. However, in the presence of a strong desire to become drug free, physical dependence, by itself, is insufficient to motivate continued addictive behavior.

Minimizing Fears About Physical Dependence

For two important reasons, there is little to fear regarding physical dependence on opioids in the hospitalized patient:

- Development of significant physical dependence is extremely rare when opioids are used short term to relieve pain. For most patients, the doses employed and the duration of treatment are insufficient to cause significant dependence.
- Even when physical dependence *does* occur, patients rarely develop addictive behavior and continue opioid administration after their pain has subsided. The vast majority of patients who become physically dependent in a clinical setting simply go through gradual withdrawal and never take opioids again. This observation emphasizes the point that physical dependence per se is insufficient to cause addiction.

From the preceding, we can see there is little to fear regarding physical dependence during the therapeutic use of opioids. We can conclude, therefore, that there is no justification for withholding opioids from patients in pain on the basis of concerns about physical dependence.

Minimizing Fears About Addiction

The principal reason for abandoning fears about opioid addiction in patients is simple: *Development of addiction to opioids as a result of clinical exposure to these drugs is extremely rare*. Results of the Boston Collaborative Drug Study showed that, of 12,000 hospitalized patients taking opioids, only 4 became drug abusers. Furthermore, as discussed below, if abuse or addiction *does* occur, it is probable that these behaviors reflect tendencies that existed before the patient entered the hospital, and hence are not the result of inappropriate medical use of opioids during the hospital stay.

For the purpose of this discussion, the population can be divided into two groups: individuals who are prone to drug abuse and individuals who are not. One source estimates that about 8% of the population is prone to drug abuse, whereas the other 92% is not. Individuals who are prone to drug abuse have a tendency to abuse drugs inside the hospital and out. Nonabusers, on the other hand, will not abuse drugs in a

clinical setting or anywhere else. Withholding analgesics from abuse-prone individuals is not going to reverse their tendency to abuse drugs. Conversely, administering opioids to non-abuse-prone persons will not convert them into "drug fiends."

If a patient who did not formerly abuse opioids does abuse these drugs following therapeutic exposure, you should not feel responsible for having created an addict. That is, if a patient tries to continue opioid use after leaving the hospital, it is probable that the patient was abuse prone before you met him or her. Therefore, the pattern of abuse that emerged during clinical exposure to opioids was the result of factors that existed before the patient ever entered the hospital—and not the consequence of therapy. The only action that might have prevented opioid abuse by such a patient would have been to withhold opioids entirely—an action that would not have been acceptable.

Balancing the Need to Provide Pain Relief with the Desire to Minimize Abuse

Although concerns about opioid abuse in the clinical setting are small, they cannot be dismissed entirely. You are still obliged to administer opioids with discretion in an effort to minimize abuse. Step 1 is to identify patients at risk for abuse. How? By using a screening tool, such as *NIDA-Modified ASSIST*, available online at www.drugabuse.gov/nidamed/screening/nmassist.pdf. When nonabusers say they need more pain relief, believe them and provide it. In contrast, when a likely abuser requests more analgesic, some healthy skepticism is in order. When there is doubt as to whether a patient is abuse prone or not, logic dictates giving the patient the benefit of the doubt and providing the medication. If the patient is an abuser, little harm will result from giving unneeded medication. However, if the patient is a nonabuser, failure to provide medication would intensify suffering for no justifiable reason.

In order to minimize physical dependence and abuse, opioid analgesics should be administered in the lowest effective dosages for the shortest time needed. Be aware, however, that larger doses are needed for patients who have more intense pain and for those who have developed tolerance. As pain diminishes, opioid dosage should be reduced. As soon as possible, the patient should be switched to a nonopioid analgesic, such as aspirin or acetaminophen.

In summary, when working with opioids, as with any other drugs, you must balance the risks of therapy against the benefits. The risk of addiction from therapeutic use of opioids is real but very small. Consequently, concerns about addiction should play a real but secondary role in making decisions about giving these drugs. Dosages should be sufficient to relieve pain. Suffering because of insufficient dosage is unacceptable. However, it is also unacceptable to promote possible abuse through failure to exercise good judgment.

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) is a method of drug delivery that permits the patient to self-administer parenteral (transdermal, IV, subQ, epidural) opioids on an "as-needed" basis. PCA has been employed primarily for relief of pain in postoperative patients. Other candidates include patients experiencing pain caused by cancer, trauma, myocardial infarction, vaso-occlusive sickle cell crisis, and labor. As discussed

below, PCA offers several advantages over opioids administered by the nurse.

PCA Devices. PCA was made possible by the development of reliable PCA devices. At this time, only one kind of PCA device is available: an electronically controlled infusion pump that can be activated by the patient to deliver a preset bolus dose of an opioid, which is delivered through an indwelling catheter. In addition to providing bolus doses on demand, some PCA pumps can deliver a basal infusion of opioid.

An essential feature of all PCA pumps is a timing control. This control limits the total dose that can be administered each hour, thereby minimizing the risk of overdose. In addition, the timing control regulates the minimum interval (eg, 10 minutes) between doses. This interval, referred to as the "lock-out" or "delay" interval, prevents the patient from administering a second dose before the first has had time to produce its full effect.

Drug Selection and Dosage Regulation. The opioid used most extensively for PCA is morphine. Other pure opioid agonists (eg, methadone, hydromorphone, fentanyl) have also been employed, as have agonist-antagonist opioids (eg, nalbuphine, buprenorphine).

Prior to starting PCA, the postoperative patient should be given an opioid loading dose (eg, 2 to 10 mg of morphine). Once effective opioid levels have been established with the loading dose, PCA can be initiated, provided the patient has recovered sufficiently from anesthesia. For PCA with morphine, initial bolus doses of 1 mg are typical. The size of the bolus should be increased if analgesia is inadequate, and decreased if excessive sedation occurs. The size of the bolus dose is usually increased during sleeping hours, thereby promoting rest by prolonging the interval between doses.

Comparison of PCA with Traditional IM Therapy. The objective of therapy with analgesics is to provide comfort while minimizing sedation and other side effects, especially respiratory depression. This objective is best achieved by maintaining plasma levels of opioids that have minimal fluctuations. In this manner, side effects from excessively high levels can be avoided, as can the return of severe pain when levels dip too low.

In the traditional management of postoperative pain, patients are given an IM injection of an opioid every 3 to 4 hours. With this dosing schedule, plasma drug levels can vary widely. Shortly after the injection, plasma levels may rise very high, causing excessive sedation and possibly respiratory depression. Late in the dosing interval, pain may return as plasma levels drop to their lowest point.

In contrast to traditional therapy, PCA is ideally suited to maintain steady levels of opioids. Why? Because PCA relies on small doses given frequently (eg, 1 mg of morphine every 10 minutes) rather than on large doses given infrequently (eg, 20 mg of morphine every 3 hours). Maintenance of steady drug levels can be facilitated further if the PCA device is capable of delivering a basal infusion. Because plasma drug levels remain relatively steady, PCA can provide continuous pain control while avoiding the adverse effects associated with excessive drug levels.

An additional advantage of PCA is rapid relief. Because the patient can self-administer a parenteral dose of opioid as soon as pain begins to return, there is minimal delay between detection of pain and restoration of an adequate drug level.

With traditional therapy, the patient must wait for the nurse to respond to a request for more drug; this delay allows pain to grow more intense.

Studies indicate that PCA is associated with accelerated recovery. When compared with patients receiving traditional IM analgesia, postoperative patients receiving PCA show improved early mobilization, greater cooperation during physical therapy, and a shorter hospital stay.

Patient Education. Patient education is important for successful PCA. Surgical patients should be educated preoperatively. Education should include an explanation of what PCA is, along with instruction on how to activate the PCA device.

Patients should be told not to fear overdose; the PCA device will not permit self-administration of excessive doses. Patients should be informed that there is a time lag (about 10 minutes) between activation of the device and production of maximal analgesia. To reduce discomfort associated with physical therapy, changing of dressings, ambulation, and other potentially painful activities, patients should be taught to activate the pump prophylactically (eg, 10 minutes prior to the anticipated activity). Patients should be informed that, at night, the PCA device will be adjusted to deliver larger doses than during waking hours. This will prolong the interval between doses and thereby facilitate sleep.

Using Opioids for Specific Kinds of Pain

Postoperative Pain. Opioid analgesics offer several benefits to the postoperative patient. The most obvious is increased comfort through reduction of pain. In addition, by reducing painful sensation, opioids can facilitate early movement and intentional cough. In patients who have undergone thoracic surgery, opioids permit chest movement that would otherwise be too uncomfortable for adequate ventilation. By promoting ventilation, opioids can reduce the risk of hypoxia and pneumonia.

Opioids are not without drawbacks for the postoperative patient. These agents can cause constipation and urinary retention. Suppression of reflex cough can result in respiratory tract complications. In addition, analgesia may delay diagnosis of postoperative complications—because pain will not be present to signal them.

Obstetric Analgesia. When administered to relieve pain during delivery, opioids may depress fetal respiration and uterine contractions. Since these effects are less likely with meperidine than with other strong opioids, *meperidine* is often the preferred opioid for obstetric use. Dosage should be high enough to reduce maternal discomfort to a tolerable level, but not so high as to cause pronounced respiratory depression in the neonate. Because opioids cross the blood-brain barrier of the infant more readily than that of the mother, doses that have little effect on maternal respiration may nonetheless cause profound respiratory depression in the infant. For *meperidine*, the usual dosage is 50 to 100 mg every 2 to 3 hours. Administration should be parenteral (IV or IM). Timing of administration is important: If the drug is given too early, it can inhibit or delay the progress of uterine contractions; if given too late, it can cause excessive neonatal sedation and respiratory depression. Following delivery, respiration in the neonate should be monitored closely. Naloxone can reverse respiratory depression and should be on hand.

Myocardial Infarction. Morphine is the opioid of choice for decreasing pain of myocardial infarction. With careful control of dosage, morphine can reduce discomfort without causing excessive respiratory depression and adverse cardiovascular effects. In addition, by lowering blood pressure, morphine can decrease cardiac work. If excessive hypotension or respiratory depression occurs, it can be reversed with naloxone. Because pentazocine and butorphanol increase cardiac work and oxygen demand, these agonist-antagonist opioids should generally be avoided.

Head Injury. Opioids must be employed with caution in patients with head injury. Head injury can cause respiratory depression accompanied by elevation of ICP; opioids can exacerbate these symptoms. In addition, since miosis, mental clouding, and vomiting can be valuable diagnostic signs following head injury, and since opioids can cause these same effects, use of opioids can complicate diagnosis.

Cancer-Related Pain. Treating chronic pain of cancer differs substantially from treating acute pain of other disorders. When treating cancer pain, the objective is to maximize comfort. Psychologic and physical dependence are minimal concerns. Patients should be given as much medication as needed to relieve pain. In the words of one pain specialist, "No patient should wish for death because of the physician's reluctance to use adequate amounts of opioids." With proper therapy, cancer pain can be effectively managed in about 90% of patients. Cancer pain is discussed fully in Chapter 29.

Chronic Noncancer Pain. In patients with chronic pain of nonmalignant origin, opioids can reduce discomfort, improve mood, and enhance function. Accordingly, pain experts now recommend that opioids not be withheld from these people. Nonetheless, because of concerns about addiction, tolerance, adverse effects, diversion to street use, and regulatory action, physicians and nurse practitioners are often reluctant to prescribe these drugs. To some degree, all of these concerns are legitimate. However, patients still have a right to effective treatment. Hence there is a need to balance patients' rights with prescribers' concerns. To help achieve that balance, the American Academy of Pain Medicine and the American Pain Society issued guidelines for using opioids in patients with chronic noncancer pain. Provisions include

- Using opioids only after nonopioid analgesics have failed
- Discussing the benefits and risks of long-term opioids with the patient
- When possible, using only one prescriber and one pharmacy
- Ensuring comprehensive follow-up to assess efficacy and side effects of treatment, and to monitor for signs of opioid abuse
- Stopping opioids if they don't work
- Fully documenting the entire process

REMS to Reduce Opioid-Related Morbidity, Mortality, and Abuse

In 2011, the FDA introduced a new Risk Evaluation and Mitigation Strategy (REMS) for prescription opioids. The objective is to reduce injuries and death from prescription opioids and to reduce abuse. Why is this REMS needed? Because, since 1990, efforts to improve pain management have led to a 10-fold increase in opioid prescriptions, accompanied by a substantial

increase in abuse, serious injuries, and deaths. In 2007, accidental overdose with prescription opioids resulted in 11,499 fatalities, more than from heroin and cocaine combined.

What does the REMS consist of? The central component is education for prescribers (eg, physicians, nurse practitioners, physicians assistant) and patients. Training for prescribers will focus on patient selection, balancing the risks and benefits of opioids, monitoring treatment, and recognizing opioid misuse, abuse, and addiction. In addition, prescribers will be taught how to counsel patients on the safe use of opioids, and will be given written instructions for their patients. When patients have a prescription filled, the pharmacy will provide a Medication Guide. Who will develop these training materials? The companies that market opioids will develop and pay for all training, but the content will be reviewed by the FDA.

Do the new REMS have limitations? Yes. First, prescriber participation is *voluntary*, not mandatory. Hence, prescribers who chose not to accept training may do so. Second, the REMS applies only to *long-acting* (LA) and *extended-release* (ER) opioids. Immediate-release (IR) products are exempt. Why are IR products excluded? Because they are safer than the LA and ER products. Yes, IR products can cause death. However, the risk is much greater with the LA and ER products. Why? Because the dose of opioid in the LA and ER products is much greater than in the IR products. In the future, the IR opioids may be included in the REMS. Products currently covered by the REMS include the following:

- Buprenorphine, transdermal [Butrans]
- Fentanyl, transdermal [Duragesic]
- Hydromorphone, ER [Exalgo]
- Methadone [Dolophine]
- Morphine, SR [Avinza, Embeda, Kadian, MS Contin, Oramorph]
- Morphine/naltrexone, ER [Embeda]
- Oxycodone, CR [OxyContin]
- Oxymorphone, ER [Opana ER]

OPIOID ANTAGONISTS

Opioid antagonists are drugs that block the effects of opioid agonists. Principal uses are treatment of opioid overdose, relief of opioid-induced constipation, reversal of postoperative opioid effects (eg, respiratory depression, ileus), and management of opioid addiction. Four pure antagonists are available: naloxone [Narcan], methylnaltrexone [Relistor], alvimopan [Entereg], and naltrexone [ReVia, Vivitrol]. A fifth agent—nalmefene [Revex]—has been voluntarily withdrawn.

Naloxone

Mechanism of Action

Naloxone [Narcan] is a structural analog of morphine that acts as a competitive antagonist at opioid receptors, thereby blocking opioid actions. Naloxone can reverse most effects of the opioid agonists, including respiratory depression, coma, and analgesia.

Pharmacologic Effects

When administered in the absence of opioids, naloxone has no significant effects. If administered prior to giving an opioid, naloxone will block opioid actions. If administered to a

patient who is already receiving opioids, naloxone will reverse analgesia, sedation, euphoria, and respiratory depression. If administered to an individual who is physically dependent on opioids, naloxone will precipitate an immediate withdrawal reaction.

Pharmacokinetics

Naloxone may be administered IV, IM, or subQ. Following IV injection, effects begin almost immediately and persist about 1 hour. Following IM or subQ injection, effects begin within 2 to 5 minutes and persist several hours. Elimination is by hepatic metabolism. The half-life is approximately 2 hours. Naloxone cannot be used orally because of rapid first-pass inactivation.

Therapeutic Uses

Reversal of Opioid Overdose. Naloxone is the drug of choice for treating overdose with a pure opioid agonist. The drug reverses respiratory depression, coma, and other signs of opioid toxicity. Naloxone can also reverse toxicity from agonist-antagonist opioids (eg, pentazocine, nalbuphine). However, the doses required may be higher than those needed to reverse poisoning by pure agonists.

Dosage must be carefully titrated when treating toxicity in opioid addicts. Why? Because the degree of physical dependence in these individuals is usually high, and hence an excessive dose of naloxone can transport the patient from a state of poisoning to one of acute withdrawal. Accordingly, treatment should be initiated with a series of small doses rather than one large dose. Because the half-life of naloxone is shorter than that of most opioids, repeated dosing is required until the crisis has passed.

In some cases of accidental poisoning, there may be uncertainty as to whether unconsciousness is due to opioid overdose or to overdose with a general CNS depressant (eg, barbiturate, alcohol, benzodiazepine). When uncertainty exists, naloxone is nonetheless indicated. If the cause of poisoning is a barbiturate or another general CNS depressant, naloxone will be of no benefit—but neither will it cause any harm. If a cumulative dose of 10 mg fails to elicit a response, it is unlikely that opioids are involved, and hence other intoxicants should be suspected.

Reversal of Postoperative Opioid Effects. Following surgery, naloxone may be employed to reverse excessive respiratory and CNS depression caused by opioids given preoperatively or intraoperatively. Dosage should be titrated with care; the objective is to achieve adequate ventilation and alertness without reversing opioid actions to the point of unmasking pain.

Reversal of Neonatal Respiratory Depression. When opioids are given for analgesia during labor and delivery, respiratory depression may occur in the neonate. If respiratory depression is substantial, naloxone should be administered to restore ventilation.

Preparations, Dosage, and Administration

Preparations and Routes. Naloxone [Narcan] is available in solution (0.4 mg/mL) for IV, IM, and subQ injection.

Opioid Overdose. The initial dose is 0.4 mg for adults and 10 mcg/kg for children. The preferred route is IV. However, if IV administration is not possible, then IM or subQ injection may be employed. Dosing is repeated at 2- to 3-minute intervals until a satisfactory response has been achieved. Additional doses may be needed at 1- to 2-hour intervals for up to 72 hours, depending on the duration of the offending opioid.

Postoperative Opioid Effects. Initial therapy for adults consists of 0.1 to 0.2 mg IV repeated every 2 to 3 minutes until an adequate response has been achieved. Additional doses may be required at 1- to 2-hour intervals.

Neonatal Respiratory Depression. The initial dose is 10 mcg/kg (IV, IM, or subQ). This dose is repeated every 2 to 3 minutes until respiration is satisfactory.

Other Opioid Antagonists

Methylnaltrexone

Actions and Therapeutic Use. Methylnaltrexone [Relistor], approved in 2008, is a selective mu opioid antagonist indicated for opioid-induced constipation in patients with end-stage illness (eg, cancer, HIV/AIDS, heart failure, emphysema) who are taking opioids continuously to relieve pain, and who have not responded to standard laxative therapy. Benefits derive from blocking mu opioid receptors in the GI tract. In clinical trials, the drug worked in about half of those treated: Within 4 hours of receiving subQ methylnaltrexone, defecation occurred in 48% of patients, compared with only 15% of those receiving placebo. In about 30% of methylnaltrexone recipients, defecation occurred rapidly—within 30 minutes. Because it contains a methyl group, methylnaltrexone cannot readily cross membranes, including those of the blood-brain barrier, and hence does not block opioid receptors in the CNS. Accordingly, the drug does not decrease analgesia and cannot precipitate opioid withdrawal.

Pharmacokinetics. Methylnaltrexone is rapidly absorbed following subQ injection, reaching peak plasma levels within 30 minutes. Because membrane passage is restricted, distribution of the drug is limited. Methylnaltrexone undergoes minimal metabolism and is excreted in the urine (50%) and feces (50%), primarily as unchanged drug. The terminal half-life is 8 hours.

Adverse Effects, Precautions, and Drug Interactions. Methylnaltrexone is generally well tolerated. The most common adverse effects are *abdominal pain* (28.5%), *flatulence* (13.3%), *nausea* (11.5%), *dizziness* (4.3%), and *diarrhea* (5.5%). In the event of severe or persistent diarrhea, the drug should be discontinued. In patients with known or suspected mechanical GI obstruction, methylnaltrexone should be avoided. No significant drug interactions have been reported.

Preparations, Dosage, and Administration. Methylnaltrexone [Relistor] is available in solution (12 mg/0.6 mL) for subQ injection into the upper arm, abdomen, or thigh. Because defecation can occur rapidly, a bathroom should be immediately available. Dosing is usually done once every 48 hours, and should not exceed once every 24 hours. Dosage is based on weight as follows: 8 mg for patients from 38 kg to under 62 kg (84 lb to under 136 lb); 12 mg for patients 62 to 114 kg (136 to 251 lb); and 0.15 mg/kg for patients under 38 kg or over 114 kg. In patients with severe renal impairment, defined as creatinine clearance below 30 mL/min, dosage should be reduced by 50%. Methylnaltrexone should be stored at room temperature and protected from light.

Alvimopan

Like methylnaltrexone, alvimopan [Entereg] is a selective, peripherally acting mu opioid antagonist developed to counteract the adverse effects of opioids on bowel function. At therapeutic doses, alvimopan does not reduce opioid-mediated analgesia, in part because of limited ability to cross the blood-brain barrier. In contrast to methylnaltrexone, which is approved for long-term therapy of constipation in patients taking opioids for chronic pain, alvimopan is approved only for short-term therapy of opioid-induced ileus following partial small or large bowel resection with primary anastomosis. The goal is to accelerate time to recovery of upper and lower bowel function, which can be impaired by opioids used for analgesia during and after surgery.

When used short term in postoperative patients, alvimopan is very well tolerated. However, when used long term in patients taking opioids for chronic

pain, the drug has been associated with an increased incidence of myocardial infarction, although a causal relationship has not been established. Because myocardial infarction may be a risk with prolonged dosing, the drug is approved only for short-term (7-day) use, and only for hospitalized patients. Furthermore, hospitals that dispense the drug must enroll in the Entereg Access Support and Education program, designed to minimize risk of myocardial infarction.

Alvimopan is available in 12-mg capsules for oral dosing. The regimen consists of 12 mg given 0.5 to 5 hours before surgery, followed by 12 mg twice daily (beginning the day after surgery) for a total of 15 doses or less.

Naltrexone

Naltrexone [ReVia, Vivitrol], given PO or IM, is a pure opioid antagonist used for opioid and alcohol abuse. In opioid abuse, the goal is to prevent euphoria if the abuser should take an opioid. Since naltrexone can precipitate a withdrawal reaction in persons who are physically dependent on opioids, candidates for treatment must be rendered opioid free before naltrexone is started. Although naltrexone can block opioid-induced euphoria, the drug does not prevent craving for opioids. As a result, many addicts fail to comply with treatment. Therapy with naltrexone has been considerably less successful than with methadone, a drug that eliminates craving for opioids while blocking euphoria. Use of naltrexone for alcohol dependence and opioid addiction is discussed further in Chapters 38 and 40, respectively.

When dosage is excessive, naltrexone can cause hepatocellular injury. Accordingly, the drug is contraindicated for patients with acute hepatitis or liver failure. Warn patients about the possibility of liver injury, and advise them to discontinue the drug if signs of hepatitis develop.

Intramuscular administration can cause injection-site reactions, which are sometimes severe. Moderate reactions include pain, tenderness, induration, swelling, erythema, bruising, and pruritus. Severe reactions—cellulitis, hematoma, abscess, necrosis—can cause significant scarring, and may require surgical intervention.

Naltrexone is available in two formulations: (1) 50-mg tablets, marketed as *ReVia*, for oral dosing; and (2) an extended-release suspension (380 mg/vial), marketed as *Vivitrol*, for IM dosing. For oral therapy, a typical dosing schedule consists of 100 mg on Monday and Wednesday and 150 mg on Friday. Alternatively, the drug can be administered daily in 50-mg doses. For IM dosing, the usual regimen is 380 mg once a month.

NONOPIOID CENTRALLY ACTING ANALGESICS

Four centrally acting analgesics—tramadol [Ultram], clonidine [Duraclon], ziconotide [Prialt], and dexmedetomidine [Precedex]—relieve pain by mechanisms largely or completely unrelated to opioid receptors. These drugs cause little or no respiratory depression, physical dependence, or abuse, and are not regulated under the Controlled Substances Act.

Tramadol

Tramadol [Ultram, Ultram ER, Ryzolt, Rybix ODT] is a moderately strong analgesic with a low potential for dependence, abuse, or respiratory depression. The drug relieves pain through a combination of opioid and nonopioid mechanisms.

Mechanism of Action. Tramadol is an analog of codeine that relieves pain in part through weak agonist activity at mu opioid receptors. However, it seems to work primarily by blocking uptake of norepinephrine and serotonin, thereby activating monoaminergic spinal inhibition of pain. Naloxone, an opioid antagonist, only partially blocks tramadol's effects.

Therapeutic Use. Tramadol is approved for moderate to moderately severe pain. The drug is less effective than morphine and no more effective than codeine combined with aspirin or acetaminophen. Analgesia begins 1 hour after oral dosing, is maximal at 2 hours, and continues for 6 hours.

Pharmacokinetics. Tramadol is administered by mouth and reaches peak plasma levels in 2 hours. Elimination is by hepatic metabolism and renal excretion. The half-life is 5 to 6 hours.

Adverse Effects. Tramadol has been used by millions of patients, and serious adverse effects have been rare. Respiratory depression is minimal at recommended doses. The most common side effects are *sedation, dizziness, headache, dry mouth, and constipation*. Seizures have been reported in over 280 patients, and hence the drug should be avoided in patients with epilepsy and other neurologic disorders. Severe allergic reactions occur rarely. Although generally very safe, tramadol can be fatal in overdose, especially when combined with another CNS depressant.

Drug Interactions. Tramadol can intensify responses to CNS depressants (eg, alcohol, benzodiazepines), and therefore should not be combined with these drugs.

By inhibiting uptake of norepinephrine, tramadol can precipitate a hypertensive crisis if combined with an MAO inhibitor. Accordingly, the combination is absolutely contraindicated.

By inhibiting uptake of serotonin, tramadol can cause serotonin syndrome in patients taking drugs that enhance serotonergic transmission. Among these are selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, MAO inhibitors, and triptans. If these drugs must be combined with tramadol, the patient should be monitored carefully, especially during initial therapy and times of dosage escalation.

Abuse Liability. Abuse liability is very low, and hence tramadol is not regulated under the Controlled Substances Act. Nonetheless, there have been reports of abuse, dependence, withdrawal, and intentional overdose, presumably for subjective effects. Consequently, tramadol should not be given to patients with a history of drug abuse, and the recommended dosage should not be exceeded.

Warning: Suicide. Tramadol can be a vehicle for suicide. When taken alone, and especially when combined with another CNS depressant, tramadol can cause severe respiratory and CNS depression. Deaths have occurred, primarily in patients with a history of emotional disturbance, suicidal ideation or behavior, or misuse of alcohol and/or other CNS depressants. To reduce risk, tramadol should not be prescribed for patients who are suicidal or addiction prone, and should be used with caution in patients who are depressed, taking sedatives or antidepressants, or prone to excessive alcohol use.

Preparations, Dosage, and Administration. Tramadol is available alone and in combination with acetaminophen. Tramadol *alone* is available in two formulations: (1) 50-mg immediate-release (IR) tablets, sold as Ultram; (2) 50-mg orally disintegrating tablets (ODTs), sold as Rybix ODT, and (3) extended-release tablets (100, 200, and 300 mg), sold as Ultram ER and Ryzolt. Dosages are as follows:

- **IR tablets [Ultram] and ODTs [Rybix ODT]**—The recommended adult dosage is 50 to 100 mg every 4 to 6 hours as needed, up to a maximum of 400 mg/day. In patients with significant renal or hepatic impairment, the dosing interval should be increased to 12 hours, and the total daily dose should not exceed 200 mg (with renal impairment) or 100 mg (with hepatic impairment). Inform patients that the ODTs should be placed on the tongue until dissolved (about 1 minute), and then swallowed, with or without water.
- **ER tablets [Ultram ER, Ryzolt]**—For patients who are not currently taking IR tramadol, the dosage is 100 mg once a day initially, and then titrated every 5 days in 100-mg increments to a maximum of 300 mg once a day. For patients currently taking IR tramadol, the initial once-daily dosage should equal the total daily dosage of IR tramadol (rounded down to the nearest 100 mg). Dosage can then be titrated up or down as needed. Extended-release tramadol should not be used by patients with severe hepatic or renal impairment.

Tramadol combined with acetaminophen [Ultracet] is indicated for short-term therapy of acute pain. Each tablet contains 37.5 mg tramadol and 325 mg acetaminophen. The recommended dosage is 2 tablets every 4 to 6 hours (but should not exceed 8 tablets/day). Treatment should not exceed 5 days.

Clonidine

Clonidine [Duraclon] has two approved applications: treatment of hypertension and relief of severe pain. To relieve pain, clonidine is administered by continuous epidural infusion. To treat hypertension, the drug is given by mouth or as a transdermal patch. Because the antihypertensive pharmacology of clonidine differs dramatically from its analgesic pharmacology, antihypertensive pharmacology is discussed separately (in Chapters 19 and 47). To avoid errors, you should know that the trade name employed for clonidine as *Duraclon*; when used for pain relief, clonidine is marketed as *Casagren*. Clonidine has no abuse potential and is not regulated under the Controlled Substances Act.

Mechanism of Pain Relief. As discussed in Chapter 19, clonidine is an alpha₂-adrenergic agonist. The drug appears to relieve pain by binding with presynaptic and postsynaptic alpha₂ receptors in the spinal cord. The result is blockade of nerve traffic in pathways that transmit pain signals from the periphery to the brain. Pain relief is not blocked by opioid antagonists.

Analgesic Use. Clonidine, in combination with an opioid analgesic, is approved for treating severe cancer pain that cannot be relieved by an opioid alone. Administration is by continuous infusion through an implanted epidural catheter. The drug is more effective against neuropathic pain (electrical, burning, or shooting in nature) than diffuse (unlocalized)

visceral pain. Pain relief occurs only in regions innervated by sensory nerves that come from the part of the spinal cord where clonidine is present in high concentration.

Pharmacokinetics. Clonidine is highly lipid soluble, and hence readily moves from the spinal cord to the blood. About half of each dose undergoes hepatic metabolism. The rest is excreted unchanged in the urine. Because urinary excretion is substantial, dosage should be reduced in patients with significant renal impairment.

Adverse Effects. Hypotension. The greatest concern is severe hypotension secondary to extensive vasodilation. The cause of vasodilation is activation of α_2 receptors in the CNS. Hypotension is most likely during the first 4 days of treatment—and is most intense following infusion into the upper thoracic region of the spinal cord. Because of the risk of hypotension, vital signs should be monitored closely, especially during the first few days. Hypotension can be managed by infusing IV fluids. If necessary, IV ephedrine can be used to promote vasoconstriction.

Bradycardia. Clonidine can slow heart rate. The underlying mechanism is activation of α_2 receptors in the CNS. Severe bradycardia can be managed with atropine.

Rebound Hypertension. As discussed in Chapter 19, abrupt discontinuation of clonidine can cause rebound hypertension. Accordingly, when the drug is withdrawn, dosage should be tapered over 2 to 4 days. Rebound hypertension can be managed with IV clonidine or phentolamine.

Catheter-Related Infection. Infection is common with implanted epidural catheters. If the patient develops a fever of unknown origin, infection should be suspected.

Other Adverse Effects. As with oral clonidine, epidural clonidine can cause dry mouth, dizziness, sedation, anxiety, and depression.

Contraindications. Because of the risk of severe hypotension and bradycardia, epidural clonidine is contraindicated for patients who are hemodynamically unstable, and for obstetric, postpartum, or surgical patients. Additional contraindications are infection at the site of infusion, administration above the C4 dermatome, and use by patients receiving anticoagulants.

Preparations, Dosage, and Administration. Clonidine for analgesia [Duraclon] is available in 10-mL vials containing 100 or 500 mcg/mL. The drug is administered through an implanted epidural catheter using a continuous infusion device. The initial infusion rate is 30 mcg/hr.

Ziconotide

Ziconotide [Prialt], approved in 2004, is a centrally acting analgesic with a novel structure and mechanism. Administration is intrathecal (IT). The drug is indicated only for severe, chronic pain in patients for whom IT therapy is warranted, and who are intolerant of or refractory to other treatments, including systemic and IT morphine. In clinical trials, analgesic responses were modest (at least in opioid-resistant patients), and adverse effects (eg, hallucinations, confusion, muscle injury) were common. Accordingly, ziconotide cannot be considered a first-choice drug.

Mechanism of Action. Ziconotide is a small synthetic peptide equivalent to a peptide found naturally in *Conus magus*, a marine snail. The drug is a selective antagonist at N-type voltage-sensitive calcium channels on neurons. Benefits derive from blocking calcium channels on primary nociceptive afferent neurons in the dorsal horn of the spinal cord, an action that prevents transmission of pain signals from the periphery to the brain. To maximize analgesia and minimize effects on peripheral nerves, ziconotide must be administered by IT infusion. The drug does not interact with opioid receptors, and does not cause tolerance, physical dependence, or respiratory depression. Abrupt discontinuation does not cause a withdrawal syndrome.

Clinical Trials. Ziconotide was evaluated in three randomized, placebo-controlled trials involving patients with severe, intractable pain. In all three trials, pain relief was modest. In one trial, for example, patients had severe pain that was unresponsive to IT morphine, IT clonidine, and/or IT bupivacaine. At baseline, mean pain scores were 81, as measured with a Visual Analog Scale of Pain Intensity (where 100 mm equals the worst pain possible and 0 mm equals no pain). Patients were randomized to receive IT ziconotide or IT placebo. The result? At the end of 3 weeks, the mean improvement in pain scores was only 12% in the ziconotide group, compared with 5% in the placebo group. Only 16% of ziconotide recipients improved by 30% or more, and nearly 50% did not respond at all. Keep in mind, however, that none of these patients responded to IT morphine either. Hence, before concluding that ziconotide is not very effective, it would be nice to see if the drug works well in patients who do respond to morphine.

Pharmacokinetics. Following IT infusion, ziconotide distributes throughout the cerebrospinal fluid (CSF) and spinal cord, and then undergoes

transport to the systemic circulation, followed by uptake into most tissues of the body, where it undergoes cleavage by peptidases at multiple sites on the molecule. The resulting fragments have not been identified, nor has their biological activity been assessed. Little or no proteolytic cleavage takes place in the CSF or blood. The drug's half-life in CSF is 4.6 hours.

Adverse Effects. Adverse CNS effects—mainly cognitive impairment and psychiatric symptoms—are common. In clinical trials, patients reported the following cognitive effects: *confusion* (33%), *memory impairment* (22%), *speech impairment* (14%), *aphasia* (12%), and *abnormal thinking* (8%). As a rule, these resolved within 2 weeks after stopping treatment. The most common psychiatric effect—*hallucinations*—developed in 12% of patients. Ziconotide can also cause *paranoid reactions* and *depression*. Patients with a history of psychiatric disorders should probably avoid this drug.

Ziconotide can cause *muscle injury*. In clinical trials, 40% of patients had abnormally high serum levels of creatine kinase (CK), a marker for muscle breakdown. However, serious muscle pain, soreness, or weakness was uncommon. Because of the risk of muscle injury, serum CK should be monitored. In patients with high CK levels combined with symptoms of muscle injury, the prescriber should consider reducing ziconotide dosage or discontinuing treatment.

Drug Interactions. Formal studies on drug interactions have not been conducted. However, given that ziconotide is a peptide that is not metabolized by CYP450 enzymes, the drug is unlikely to affect the disposition of most other drugs, which are metabolized by CYP450 enzymes. Combined use with CNS depressants may increase the risk of adverse CNS events, such as dizziness and confusion. Combined use with systemic opioids appears safe, but combined use with intrathecal opioids is not recommended.

Preparations, Dosage, and Administration. Ziconotide [Prialt] is available in single-use vials (25 and 100 mcg/mL) for IT infusion using a programmable microinfusion device, either external or implanted. The initial infusion rate is 0.1 mcg/hr (2.4 mcg/day). The rate may be gradually increased in steps of 0.1 mcg/hr every 2 to 3 days, up to a maximum of 0.8 mcg/hr (19.2 mcg/day) at the end of 3 weeks. Dosage adjustments are based on pain relief and tolerability of side effects.

Dexmedetomidine

Actions and Therapeutic Use. Dexmedetomidine [Precedex], like clonidine, is a selective α_2 -adrenergic agonist. The drug acts in the CNS to cause sedation and analgesia. The drug has two approved indications: (1) short-term sedation in critically ill patients who are initially intubated and undergoing mechanical ventilation, and (2) sedation for nonintubated patients prior to and/or during surgical and other procedures. However, in addition to these approved uses, dexmedetomidine has a variety of off-label uses, including sedation during awake craniotomy, prevention and treatment of postanesthetic shivering, and enhancement of sedation and analgesia in patients undergoing general anesthesia. In contrast to clonidine, which is administered by epidural infusion, dexmedetomidine is administered by IV infusion.

Pharmacokinetics. With IV infusion, dexmedetomidine undergoes wide distribution to tissues. In the blood, the drug is 94% protein bound. Dexmedetomidine undergoes rapid and complete hepatic metabolism, followed by excretion in the urine. The elimination half-life is 2 hours.

Adverse Effects. The most common adverse effects are *hypotension* and *bradycardia*. The mechanism is activation of α_2 -adrenergic receptors in the CNS and periphery, which results in decreased release of norepinephrine from sympathetic neurons innervating the heart and blood vessels. If these cardiovascular effects are too intense, they can be managed in several ways, including (1) decreasing or stopping the infusion, (2) infusing fluid, and (3) elevating the lower extremities. Giving a muscarinic antagonist (eg, atropine) can increase heart rate.

Additional adverse effects include *nausea*, *dry mouth*, and *transient hypertension*. Importantly, dexmedetomidine does not cause respiratory depression.

Drug Interactions. Dexmedetomidine can enhance the actions of anesthetics, sedatives, hypnotics, and opioids. Excessive CNS depression can be managed by reducing the dosage of dexmedetomidine or the other agents.

Preparations, Dosage, and Administration. Dexmedetomidine [Precedex] is supplied in solution (100 mcg/mL), which must be diluted to 4 mcg/mL prior to use. Administration is by IV infusion. For *intensive care sedation*, treatment consists of a loading dose (1 mcg/kg infused over 10 minutes) followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr for no more than 24 hours. For *procedural sedation*, treatment typically consists of a loading dose (1 mcg/kg infused over 10 minutes) followed by a maintenance infusion of 0.2 to 1 mcg/kg/hr.

KEY POINTS

- Analgesics are drugs that relieve pain without causing loss of consciousness.
- Opioids are the most effective analgesics available.
- There are three major classes of opioid receptors, designated mu, kappa, and delta.
- Morphine and other pure opioid agonists relieve pain by mimicking the actions of endogenous opioid peptides—primarily at mu receptors, and partly at kappa receptors.
- Opioid-induced sedation and euphoria can complement pain relief.
- Because opioids produce euphoria and other desirable subjective effects, they have a high liability for abuse.
- Respiratory depression is the most serious adverse effect of the opioids.
- Other important adverse effects are constipation, urinary retention, orthostatic hypotension, emesis, birth defects, and elevation of ICP.
- Because of first-pass metabolism, oral doses of morphine must be larger than parenteral doses to produce equivalent analgesic effects.
- Because the blood-brain barrier is poorly developed in infants, these patients need smaller doses of opioids (adjusted for body weight) than do older children and adults.
- With prolonged opioid use, tolerance develops to analgesia, euphoria, sedation, and respiratory depression, but not to constipation and miosis.
- Cross-tolerance exists among the various opioid agonists, but not between opioid agonists and general CNS depressants.
- With prolonged opioid use, physical dependence develops. An abstinence syndrome will occur if the opioid is abruptly withdrawn.
- In contrast to the withdrawal syndrome associated with general CNS depressants, the withdrawal syndrome associated with opioids, although unpleasant, is not dangerous.
- To minimize symptoms of abstinence, opioids should be withdrawn gradually.
- Precautions to opioid use include pregnancy, labor and delivery, head injury, and decreased respiratory reserve.
- Patients taking opioids should avoid alcohol and other CNS depressants—because these drugs can intensify opioid-induced sedation and respiratory depression.
- Patients taking opioids should avoid anticholinergic drugs (eg, antihistamines, tricyclic antidepressants, atropine-like drugs)—because these drugs can exacerbate opioid-induced constipation and urinary retention.
- Opioid overdose produces a classic triad of signs: coma, respiratory depression, and pinpoint pupils.
- All strong opioid agonists are essentially equal to morphine with regard to analgesia, abuse liability, and respiratory depression.
- Use of meperidine [Demerol] should not exceed 48 hours—so as to avoid accumulation of normeperidine, a toxic metabolite.
- Like morphine, codeine and other moderate to strong opioid agonists produce analgesia, sedation, euphoria, respiratory depression, constipation, urinary retention, cough suppression, and miosis. These drugs differ from morphine in that they produce less analgesia and respiratory depression and have a lower potential for abuse.
- The combination of codeine with a nonopioid analgesic (eg, aspirin, acetaminophen) produces greater pain relief than can be achieved with either agent alone.
- Most agonist-antagonist opioids act as agonists at kappa receptors and antagonists at mu receptors.
- Pentazocine and other agonist-antagonist opioids produce less analgesia than morphine and have a lower potential for abuse.
- With agonist-antagonist opioids, there is a ceiling to respiratory depression.
- If given to a patient who is physically dependent on pure opioid agonists, an agonist-antagonist will precipitate withdrawal.
- Pure opioid antagonists act as antagonists at mu receptors and kappa receptors.
- Naloxone and other pure opioid antagonists can reverse respiratory depression, coma, analgesia, and most other effects of pure opioid agonists. The only exception is methylnaltrexone, which doesn't cross the blood-brain barrier.
- Pure opioid antagonists are used primarily to treat opioid overdose. One agent—methylnaltrexone—is used for opioid-induced constipation, and another—alvimopan—for opioid-induced ileus.
- If administered in excessive dosage to an individual who is physically dependent on opioid agonists, naloxone will precipitate an immediate withdrawal reaction.
- Opioid dosage must be individualized. Patients with a low tolerance to pain or with extremely painful conditions need high doses. Patients with sharp, stabbing pain need higher doses than patients with dull pain. Elderly adults generally require lower doses than younger adults. Neonates require relatively low doses.
- As a rule, opioids should be administered on a fixed schedule (with supplemental doses for breakthrough pain) rather than PRN.
- Most PCA devices are electronically controlled pumps that can be activated by the patient to deliver a preset dose of opioid through an indwelling catheter. Some PCA devices also deliver a basal opioid infusion.
- PCA devices provide steady plasma drug levels, thereby maintaining continuous pain control while avoiding unnecessary sedation and respiratory depression.
- Use of parenteral opioids during delivery can suppress uterine contractions and cause respiratory depression in the neonate.
- Addiction is a behavior pattern characterized by continued use of a psychoactive substance despite physical, psychological, or social harm. Physical dependence and addiction are not the same.
- Abuse is defined as drug use that is inconsistent with medical or social norms.
- Because of excessive and inappropriate fears about addiction and abuse, physicians frequently prescribe less

pain medication than patients need, and nurses frequently administer less medication than was prescribed.

- Please! Dispel your concerns about abuse and addiction and give your patients the medication they need to relieve suffering. That's what opioids are for, after all.

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Summary of Major Nursing Implications*

PURE OPIOID AGONISTS

Alfentanil
Codeine
Fentanyl
Hydrocodone
Hydromorphone
Levorphanol
Meperidine
Methadone
Morphine
Oxycodone
Oxymorphone
Remifentanil
Sufentanil
Tapentadol

Preadministration Assessment

Therapeutic Goal

Relief or prevention of moderate to severe pain while causing minimal respiratory depression, constipation, urinary retention, and other adverse effects.

Baseline Data

Pain Assessment. Assess pain before administration and 1 hour later. Determine the location, time of onset, and quality of pain (eg, sharp, stabbing, dull). Also, assess for psychologic factors that can lower pain threshold (anxiety, depression, fear, anger). Because pain is subjective and determined by multiple factors (eg, cultural influences, patient expectations, associated disease), there is no reliable objective method for determining how much discomfort the patient is experiencing. Ultimately, you must rely on your ability to interpret what patients have to say about their pain. When listening to patients, be aware that a few may claim discomfort when their pain is under control, and others may claim to feel fine when they actually hurt.

Vital Signs. Prior to administration, determine respiratory rate, blood pressure, and pulse rate.

Identifying High-Risk Patients

All opioids are *contraindicated* for premature infants (both during and after delivery). *Morphine* is *contraindicated* following biliary tract surgery. *Meperidine* is *contraindicated* for patients taking MAO inhibitors.

Use opioids with *caution* in patients with head injury, profound CNS depression, coma, respiratory depression, pulmonary disease (eg, emphysema, asthma), cardiovascular disease, hypotension, reduced blood volume, prostatic hy-

per trophy, urethral stricture, and liver impairment. *Caution* is also required when treating infants, elderly or debilitated patients, and patients receiving MAO inhibitors, CNS depressants, anticholinergic drugs, and hypotensive agents. In addition, use opioids with *caution* in patients deemed at high risk of opioid abuse.

Implementation: Administration

Routes

Oral, IM, IV, subQ, rectal, epidural, intrathecal, transdermal (fentanyl), and transmucosal (fentanyl). Routes for specific opioids are summarized in Tables 28-5 and 28-6.

Dosage

General Guidelines. Adjust dosage to meet individual needs. Higher doses are required for patients with low pain tolerance or with especially painful conditions. Patients with sharp, stabbing pain need higher doses than patients with dull, constant pain. Elderly patients generally require lower doses than younger adults. Neonates require relatively low doses because the blood-brain barrier is poorly developed. For all patients, dosage should be reduced as pain subsides.

Oral doses are larger than parenteral doses. Check to ensure that the dose is appropriate for the intended route.

Tolerance may develop with prolonged treatment, necessitating dosage escalation.

Warn outpatients not to increase dosage without consulting the prescriber.

Dosage in Patients with Cancer. Treatment of cancer pain is done long term. The objective is to maximize comfort. Physical dependence is a minor concern. Cancer patients should receive opioids on a fixed schedule around-the-clock—not PRN. If breakthrough pain occurs, fixed dosing should be supplemented PRN with a short-acting opioid. Because of tolerance to opioids or intensification of pain, dosage escalation may be required. Hence, patients should be re-evaluated on a regular basis to determine if pain control is adequate.

Discontinuing Opioids. Although significant dependence in hospitalized patients is rare, it can occur. To minimize symptoms of abstinence, withdraw opioids slowly, tapering the dosage over 3 days. **Warn outpatients against abrupt discontinuation of treatment.**

Administration

Prior to administration, determine respiratory rate, blood pressure, and pulse rate. Withhold medication and notify the prescriber if respiratory rate is at or below 12 breaths per minute, if blood pressure is significantly below the pretreat-

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

ment value, or if pulse rate is significantly above or below the pretreatment value.

As a rule, opioids should be administered on a fixed schedule, with supplemental doses as needed.

Perform IV injections slowly (over 4 to 5 minutes). Rapid injection may produce severe adverse effects (profound hypotension, respiratory arrest, cardiac arrest) and should be avoided. When making an IV injection, have an opioid antagonist (eg, naloxone) and facilities for respiratory support available.

Perform injections (especially IV) with the patient lying down to minimize hypotension.

Warn patients using fentanyl patches to avoid exposing the patch to direct heat (eg, heating pad, hot tub) because doing so can accelerate fentanyl release.

Warn patients not to crush or chew controlled-release oxycodone [OxyContin] tablets.

Warn patients using morphine/naltrexone [Embeda] not to crush or chew the capsules or to drink alcohol, because these actions can accelerate absorption of morphine from the product.

Instruct patients using tramadol ODTs [Rybix ODT] to place the tablet on the tongue until it dissolves (about 1 minute), and then swallow with or without water.

Opioid agonists are regulated under the Controlled Substances Act and must be dispensed accordingly. All pure agonists are Schedule II substances, except hydrocodone (Schedule III).

Concern for Opioid Abuse as a Factor in Dosage and Administration

Although opioids have a high potential for abuse, abuse is rare in the clinical setting. Consequently, when balancing the risk of abuse against the need to relieve pain, do not give excessive weight to concerns about abuse. The patient must not be allowed to suffer because of your unwarranted fears about abuse and dependence.

Although abuse is rare in the clinical setting, it can occur. To keep abuse to a minimum: (1) screen patients for abuse risk, (2) exercise clinical judgment when interpreting requests for opioid doses that seem excessive, (3) use opioids in the lowest effective doses for the shortest time required, (4) reserve opioid analgesics for patients with moderate to severe pain, and (5) switch to a nonopioid analgesic when the intensity of pain no longer justifies an opioid.

Responses to analgesics can be reinforced by nondrug measures, such as positioning the patient comfortably, showing concern and interest, and reassuring the patient that the medication will provide relief. Rest, mood elevation, and diversion can raise pain threshold and should be promoted. Conversely, anxiety, depression, fatigue, fear, and anger can lower pain threshold and should be minimized.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Evaluate for pain control 1 hour after opioid administration. If analgesia is insufficient, consult the prescriber about an increase in dosage. Patients taking opioids chronically for

suppression of cancer pain should be re-evaluated on a regular basis to determine if dosage is adequate.

Minimizing Adverse Effects

Respiratory Depression. Monitor respiration in all patients. If respiratory rate is 12 breaths per minute or less, withhold medication and notify the prescriber. **Warn outpatients about respiratory depression and instruct them to notify the prescriber if respiratory distress occurs.**

Certain patients, including the very young, the elderly, and those with respiratory disease (eg, asthma, emphysema), are especially sensitive to respiratory depression and must be monitored closely.

Delayed respiratory depression may develop following spinal administration of morphine. Be alert to this possibility.

When employed during labor and delivery, opioids may cause respiratory depression in the neonate. Monitor the infant closely. Have naloxone available to reverse opioid toxicity.

Sedation. Inform patients that opioids may cause drowsiness. **Warn them against doing hazardous activities (eg, driving) if sedation is significant.** Sedation can be minimized by (1) using smaller doses given more frequently, (2) using opioids with short half-lives, and (3) giving small doses of a CNS stimulant (methylphenidate, dextroamphetamine) in the morning and early afternoon. Modafinil, a nonamphetamine stimulant, may also be tried.

Orthostatic Hypotension. Monitor blood pressure and pulse rate. **Inform patients about symptoms of hypotension (dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when assuming an erect posture. Warn patients against walking if hypotension is significant.** If indicated, assist hospitalized patients with ambulation.

Constipation. The risk of constipation can be reduced by maintaining physical activity, increasing intake of fiber and fluids, and prophylactic treatment with a stimulant laxative (eg, senna, bisacodyl) plus a stool softener (eg, docusate), and perhaps polyethylene glycol (an osmotic laxative). A strong osmotic laxative (eg, lactulose, sodium phosphate) may be used for rescue therapy. If these measures fail, methylnaltrexone (an opioid antagonist) may help.

Urinary Retention. To evaluate urinary retention, monitor intake and output, and palpate the lower abdomen for bladder distention every 4 to 6 hours. If there is a change in intake/output ratio, if bladder distention is detected, or if the patient reports difficulty voiding, notify the prescriber. Catheterization may be required. Difficulty with voiding is especially likely in men with prostatic hypertrophy.

Because opioids may suppress awareness of bladder stimuli, encourage patients to void every 4 hours.

Biliary Colic. By constricting the common bile duct, morphine can increase pressure within the biliary tract, thereby causing severe pain. Biliary colic may be less pronounced with meperidine.

Emesis. Initial doses of opioids may cause nausea and vomiting. These reactions can be minimized by pretreatment with an antiemetic (eg, promethazine) and by having the patient remain still. Tolerance to emesis develops quickly.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Cough Suppression. Cough suppression may result in accumulation of secretions in the airway. **Instruct patients to cough at regular intervals.** Auscultate the lungs for rales.

Miosis. Miosis can impair vision in dim light. Keep hospital room lighting bright during waking hours.

Neurotoxicity. Neurotoxicity—delirium, agitation, myoclonus, hyperalgesia—can develop with prolonged high-dose therapy. Symptoms can be reduced with hydration, dose reduction, and opioid rotation.

Birth Defects. When taken just before conception or during early pregnancy, opioids increase the risk spina bifida, gastroschisis, and congenital heart defects (eg, atrioventricular septal defects, hypoplastic left heart syndrome, conoventricular septal defects). Use of opioids prior to and during pregnancy should be discouraged.

Opioid Dependence in the Neonate. The infant whose mother abused opioids during pregnancy may be born drug dependent. Observe the infant for signs of withdrawal (eg, excessive crying, sneezing, tremor, hyperreflexia, fever, diarrhea), which usually develop within a few days after birth. The infant can be weaned from drug dependence by administering dilute paregoric in progressively smaller doses.

Dysrhythmias. Methadone prolongs the QT interval, and hence can pose a risk of fatal dysrhythmias. Use methadone with great caution in patients with existing QT prolongation or a family history of long QT syndrome, and in those taking other QT-prolonging drugs (eg, amiodarone, quinidine, erythromycin, tricyclic antidepressants). All patients should receive an ECG before treatment, 30 days later, and annually thereafter. If the QT interval exceeds 500 msec, stopping methadone or reducing the dosage should be considered.

Minimizing Adverse Interactions

CNS Depressants. Opioids can intensify responses to other CNS depressants (eg, barbiturates, benzodiazepines, alcohol, antihistamines), thereby presenting a risk of profound sedation and respiratory depression. **Warn patients against use of alcohol and other depressants.**

Anticholinergic Drugs. These agents (eg, atropine-like drugs, tricyclic antidepressants, phenothiazines, antihistamines) can exacerbate opioid-induced constipation and urinary retention.

Hypotensive Drugs. Antihypertensive agents and other drugs that lower blood pressure can exacerbate opioid-induced orthostatic hypotension.

Opioid Antagonists. Opioid antagonists (eg, naloxone) can precipitate an abstinence syndrome if administered in excessive dosage to a patient who is physically dependent on opioids. To avoid this problem, carefully titrate the dosage of the antagonist.

Agonist-Antagonist Opioids. These drugs (eg, pentazocine, nalbuphine) can precipitate an abstinence syndrome if administered to a patient who is physically dependent on a pure opioid agonist. Before administering an agonist-antagonist, make certain the patient has been withdrawn from opioid agonists.

MAO Inhibitors. Combining *meperidine* or *tapentadol*

with an MAO inhibitor can cause delirium, hyperthermia, rigidity, convulsion, coma, and death. Obviously, these combinations must be avoided.

CYP3A4 Inhibitors. Inhibitors of CYP3A4 (eg, ritonavir, ketoconazole) can increase levels of *fentanyl*, thereby posing a risk of fatal respiratory depression. Monitor patients using this combination with care.

AGONIST-ANTAGONIST OPIOIDS

Buprenorphine

Butorphanol

Nalbuphine

Pentazocine

Except for the differences presented below, the nursing implications for these drugs are much like those for the pure opioid agonists.

Therapeutic Goal

Relief of moderate to severe pain.

Routes

Oral, IV, IM, and subQ. Routes for individual agents are summarized in Table 28-6.

Differences from Pure Opioid Agonists

Maximal pain relief with the agonist-antagonists is generally lower than with pure opioid agonists.

Most agonist-antagonists have a ceiling to respiratory depression, thereby minimizing concerns about insufficient oxygenation.

Agonist-antagonists cause little euphoria. Hence, abuse liability is low.

Agonist-antagonists increase cardiac work and should not be given to patients with acute myocardial infarction.

Because of their antagonist properties, agonist-antagonists can precipitate an abstinence syndrome in patients physically dependent on opioid agonists. Accordingly, patients must be withdrawn from pure opioid agonists before receiving an agonist-antagonist.

NALOXONE

Therapeutic Goal

Reversal of postoperative opioid effects, opioid-induced neonatal respiratory depression, and overdose with pure opioid agonists.

Routes

Intravenous, IM, and subQ. For initial treatment, administer IV. Once opioid-induced CNS depression and respiratory depression have been reversed, IM or subQ administration may be employed.

Dosage

Titrate dosage carefully. In opioid addicts, excessive doses can precipitate withdrawal. In postoperative patients, excessive doses can unmask pain by reversing opioid-mediated analgesia.

*Patient education information is highlighted as blue text.

Pain Management in Patients with Cancer

Pathophysiology of Pain Management Strategy

Assessment and Ongoing Evaluation

Comprehensive Initial Assessment

Ongoing Evaluation

Barriers to Assessment

Drug Therapy

Nonopioid Analgesics

Opioid Analgesics

Adjuvant Analgesics

Nondrug Therapy

Invasive Procedures

Physical and Psychosocial Interventions

Pain Management in Special Populations

The Elderly

Young Children

Opioid Abusers

Patient Education

The Joint Commission Pain Management Standards

Our topic for this chapter—management of cancer pain—is of note both for its good news and its bad news. The good news is that cancer pain can be relieved with simple interventions in 90% of patients. The bad news is that, despite the availability of effective treatments, pain goes unrelieved far too often. Multiple factors contribute to undertreatment (Table 29–1). Important among these are inadequate prescriber training in pain management; unfounded fears of addiction (shared by prescribers, patients, and families); and a healthcare system that focuses more on treating disease than relieving suffering.

Pain has a profound impact on both the patient and family. Pain undermines quality of life for the patient and puts a heavy burden on the family. Unrelieved pain compromises the patient's ability to work, enjoy leisure activities, and fulfill his or her role in the family and in society at large. Furthermore, pain can impede recovery, hasten death from cancer, and possibly even create a risk of suicide.

Every patient has the right to expect that pain management will be an integral part of treatment throughout the course of his or her disease. The goal is to minimize pain and thereby maintain a reasonable quality of life, including the ability to function at work and at play, and within the family and society. In addition, if the cancer is incurable, treatment should permit the patient a relatively painless death when that time comes.

TABLE 29–1 ■ Barriers to Cancer Pain Management

Barriers Related to Healthcare Professionals

- Inadequate knowledge of pain management
- Poor assessment of pain
- Concerns stemming from regulations on controlled substances
- Fear of patient addiction
- Concern about side effects of analgesics
- Concern about tolerance to analgesics

Barriers Related to Patients

- Reluctance to report pain
- Fear of distracting physicians from treating the cancer
- Fear that pain means the cancer is worse
- Concern about not being a “good” patient
- Reluctance to take pain medication
- Fear of addiction or being thought of as an addict
- Worries about unmanageable side effects
- Concern about becoming tolerant to pain medications
- Inability to pay for treatment

Barriers Related to the Healthcare System

- Low priority given to cancer pain management
- Inadequate reimbursement: The most appropriate treatment may not be reimbursed
- Restrictive regulation of controlled substances
- Treatment is unavailable or access is limited

Adapted from Jacox A, Carr DB, Payne R, et al: Management of Cancer Pain (Clinical Practice Guideline No. 9; AHCPR Publication No. 94-0592). Rockville, MD: Agency for Health Care Policy and Research, 1994.

PATHOPHYSIOLOGY OF PAIN

What Is Pain?

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Note that, by this definition, pain is not simply a sensory experience resulting from activation of pain receptors. Rather, it also includes the patient's emotional and cognitive responses to both the sensation of pain and the underlying cause (eg, tissue damage caused by cancer). Most importantly, we must appreciate that pain is inherently *personal and subjective*. Hence, when assessing pain, the most reliable method is to have the patient describe his or her experience.

Neurophysiologic Basis of Painful Sensations

The following discussion is a simplified version of how we perceive pain. Nonetheless, it should be adequate as a basis for understanding the interventions used for pain relief.

Sensation of pain is the net result of activity in two opposing neuronal pathways. The first pathway carries pain impulses from their site of origin to the brain, and thereby generates pain sensation. The second pathway, which originates in the brain, suppresses impulse conduction along the first pathway, and thereby diminishes pain sensation.

Pain impulses are initiated by activation of pain receptors, which are simply free nerve endings. These receptors can be activated by three types of stimuli: mechanical (eg, pressure), thermal, and chemical (eg, bradykinin, serotonin, histamine). In addition, *prostaglandins* and *substance P* can enhance the sensitivity of pain receptors to activation, although these compounds do not activate pain receptors directly.

Conduction of pain impulses from the periphery to the brain occurs by way of a multineuron pathway. The first neuron carries impulses from the periphery to a synapse in the spinal cord, where it releases either *glutamate* or *substance P* as a transmitter. The next neuron carries the impulse up the cord to a synapse in the thalamus. And the next neuron carries impulses from the thalamus to the cerebral cortex.

The brain is able to suppress pain conduction using endogenous opioid compounds, especially *enkephalins* and *beta-endorphin*. These compounds are released at synapses in the brain and spinal cord. Release within the spinal cord is controlled by a descending neuronal pathway that originates in the brain. The opioids that we give as drugs (eg, morphine) produce analgesia by activating the same receptors that are activated by this endogenous pain-suppressing system.

Nociceptive Pain Versus Neuropathic Pain

In patients with cancer, pain has two major forms, referred to as *nociceptive* and *neuropathic*. Nociceptive pain results from injury to *tissues*, whereas neuropathic pain results from injury to *peripheral nerves*. These two forms of pain respond differently to analgesic drugs. Accordingly, it is important to differentiate between them. Among cancer patients, nociceptive pain is more common than neuropathic pain.

Nociceptive pain has two forms, known as *somatic* and *visceral*. Somatic pain results from injury to somatic tissues (eg, bones, joints, muscles), whereas visceral pain results from injury to visceral organs (eg, small intestine). Patients generally describe somatic pain as localized and sharp. In contrast, they describe visceral pain as vaguely localized with a diffuse, aching quality. Both forms of nociceptive pain respond well to *opioid analgesics* (eg, morphine). In addition, they may respond to *nonopioids* (eg, ibuprofen).

Neuropathic pain produces different sensations than does nociceptive pain and responds to a different group of drugs. Patients describe neuropathic pain with such words as "burning," "shooting," "jabbing," "tearing," "numb," "dead," and "cold." Unlike nociceptive pain, neuropathic pain responds poorly to opioid analgesics. However, it does respond to drugs known collectively as *adjuvant analgesics*. Among these are certain antidepressants (eg, imipramine), anticonvulsants (eg, carbamazepine, gabapentin), and local anesthetics/antidysrhythmics (eg, lidocaine).

Pain in Cancer Patients

Among patients with cancer, pain can be caused by the cancer itself and by therapeutic interventions. Cancer can cause pain through direct invasion of surrounding tissues (eg, nerves, muscles, visceral organs) and through metastatic invasion at

distant sites. Metastases to bone are very common, causing pain in up to 50% of patients. Cancer can cause neuropathic pain through infiltration of nerves, and visceral pain through infiltration, obstruction, and compression of visceral structures.

The incidence and intensity of cancer-induced pain is a function of cancer type and the stage of disease progression. Among patients with advanced disease, about 75% experience significant pain. Of these, 40% to 50% report moderate to severe pain, and 25% to 30% report very severe pain.

Therapeutic interventions—especially chemotherapy, radiation, and surgery—cause significant pain in at least 25% of patients, and probably more. Chemotherapy can cause painful mucositis, diffuse neuropathies, and aseptic necrosis of joints. Radiation can cause osteonecrosis, chronic visceral pain, and peripheral neuropathy (secondary to causing fibrosis of nerves). Surgery can cause a variety of pain syndromes, including phantom limb syndrome and postmastectomy syndrome.

MANAGEMENT STRATEGY

Management of cancer pain is an ongoing process that involves repeating cycles of assessment, intervention, and reassessment. The goal is to create and implement a flexible treatment plan that can meet the changing needs of the individual patient. The flow chart in Figure 29-1 summarizes the steps involved. Management begins with a comprehensive assessment. Once the nature of the pain has been determined, a treatment modality is selected. Analgesic drugs are preferred, and hence are usually tried first. If drugs are ineffective, other modalities can be implemented. Among these are radiation, surgery, and nerve blocks. After each intervention, pain is reassessed. Once relief has been achieved, the effective intervention is continued, accompanied by frequent reassessments. If severe pain returns or new pain develops, a new comprehensive assessment should be performed—followed by appropriate interventions and reassessment. Throughout this process, the healthcare team should make every effort to ensure active involvement of the patient and his or her family. Without their involvement, maximal benefits cannot be achieved. The importance of patient and family involvement is reflected in the clinical approach to pain management recommended by the Agency for Healthcare Research and Quality (AHRQ):

- A Ask** about pain regularly.
Assess pain systematically.
- B Believe** the patient and family in their reports of pain and what relieves it.
- C Choose** pain control options appropriate for the patient, family, and setting.
- D Deliver** interventions in a timely, logical, and coordinated fashion.
- E Empower** patients and their families.
Enable patients to control their treatment to the greatest extent possible.

ASSESSMENT AND ONGOING EVALUATION

Assessment is the foundation of treatment. In the absence of thorough assessment, effective pain management is impossible. Assessment begins with a comprehensive evaluation and then

ment of new pain. Each time an analgesic drug is administered, pain should be evaluated after sufficient time has elapsed for the drug to take effect. Because most patients are treated at home, patients and caregivers should be taught to conduct and document pain evaluations. The prescriber will use the documented record to make adjustments to the pain management plan.

Prescribers, patients, and caregivers should be alert for new pain. In the majority of cases, new pain results from a new cause (eg, metastasis, infection, fracture). Accordingly, whenever new pain occurs, a rigorous diagnostic work-up is indicated.

Barriers to Assessment

As stressed above, pain assessment relies heavily on a report from the patient. Unfortunately, the report is not always accurate: Some patients report more pain than they have, some report less, and some are unable to report at all. With other pa-

tients, cultural and language differences impede assessment. In all cases, reliance on behavioral cues and facial expression is a poor substitute for an accurate report by the patient.

Many patients under-report pain, frequently because of misconceptions. Some fear addiction to opioids, and hence want to minimize opioid use. Some believe they are expected to be stoic and "tough it out." Some deny their pain because they fear pain signifies disease progression. When under-reporting of pain is suspected, the patient should be interviewed in an effort to discover the reason. If a misconception is responsible for under-reporting, educating the patient can help fix the problem.

Some patients fear they may be denied sufficient pain medication, and hence, to ensure adequate dosing, report more pain than they actually have. When exaggeration is suspected, the patient should be reassured that adequate pain relief will be provided, and should be taught that inaccurate reporting serves only to make appropriate treatment more difficult.

Language barriers and cultural barriers can impede pain assessment. For patients who do not speak English, a translator should be provided. Obtaining a pain rating scale in the patient's own language would obviously help. A *pain affect* *FACES* scale can be useful, since facial expressions reflecting discomfort are the same in all cultures. Cultural beliefs may cause some patients to hide overt expression of pain and report less pain than is present. The interviewer should be alert to this possibility.

When assessing pain, we must keep in mind that behavior and facial expression may be poor indicators of pain status. For example, in patients approaching the end of life, behavioral cues of pain (eg, vocalizing, grimacing) are often absent. Other patients may simply have good coping skills, and hence may smile and move around in apparent comfort, even though they are in considerable pain. Because appearances can be deceiving, we must not rely on them to assess pain.

Assessment in young children and other nonverbal patients is a special challenge. By definition, nonverbal patients are unable to self-report pain. Accordingly, we must use less reliable methods of assessment, including observing the patient for cues. Assessment in children is discussed further under *Pain Management in Special Populations*.

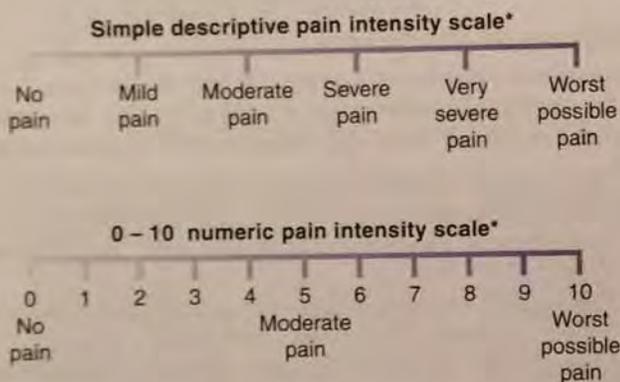


Figure 29-2 • Linear pain intensity scales.

*If used as a graphic rating scale, a 10-cm baseline is recommended. (From Acute Pain Management Guideline Panel: Acute Pain Management: Operative or Medical Procedures and Trauma [Clinical Practice Guideline No. 1; AHCPR Publication No. 92-0032]. Rockville, MD: Agency for Health Care Policy and Research, 1992.)

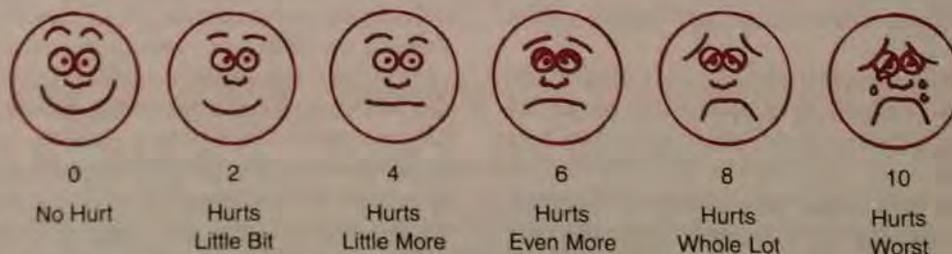


Figure 29-3 • Wong-Baker FACES pain rating scale.

Explain to the patient that the first face represents a person who feels happy because he or she has no pain, and that the other faces represent people who feel sad because they have pain, ranging from a little to a lot. Explain that face 10 represents a person who hurts as much as you can imagine, but that you don't have to be crying to feel this bad. Ask the patient to choose the face that best reflects how he or she is feeling. The numbers below the faces correspond to the values in the numeric pain scale shown in Figure 29-2. (From Hockenberry MJ, Wilson D: *Wong's Essentials of Pediatric Nursing*, 8th ed. St. Louis: Elsevier, 2009.)

DRUG THERAPY

Analgesic drugs are the most powerful weapons we have for overcoming cancer pain. With proper use, these agents can relieve pain in 90% of patients. Because analgesics are so effective, drug therapy is the principal modality for pain treatment. Three types of analgesics are employed:

- Nonopioid analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs] and acetaminophen)
- Opioid analgesics (eg, oxycodone, fentanyl, morphine)
- Adjuvant analgesics (eg, amitriptyline, carbamazepine, dextroamphetamine)

These classes differ in their abilities to relieve pain. With the nonopioid and adjuvant analgesics, there is a ceiling to how much relief we can achieve. In contrast, there is no ceiling to relief with the opioids.

Selection among the analgesics is based on pain intensity and pain type. To help guide drug selection, the World Health Organization (WHO) devised a drug selection ladder (Fig. 29-4). The first step of the ladder—for mild to moderate pain—consists of nonopioid analgesics: NSAIDs and acetaminophen. The second step—for more severe pain—adds opioid analgesics of moderate strength (eg, oxycodone, hydrocodone). The top step—for severe pain—substitutes powerful opioids (eg, morphine, fentanyl) for the weaker ones. Adjuvant analgesics, which are especially effective against neuropathic pain, can be used on any step of the ladder. Specific drugs to avoid are listed in Table 29-2.

Traditionally, patients have been given opioid analgesics only after a trial with nonopioids has failed. Guidelines from the National Comprehensive Cancer Network (NCCN) recommend a different approach, in which initial drug selection is based on pain intensity. Specifically, if the patient reports pain in the 4 to 10 range (as measured on a numeric rating scale), then treatment should start directly with an opioid; an initial trial with a nonopioid is considered unnecessary. If the patient reports pain in the 1 to 3 range, then treatment usually begins with a nonopioid, although starting with an opioid remains an alternative.

It is common practice to combine an opioid with a nonopioid. Why? Because the combination can be more effective than either drug alone. When pain is only moderate, opioids and nonopioids can be given in a fixed-dose combination formulation, thereby simplifying dosing. However, when pain is severe, these drugs must be given separately. Why? Because, with a fixed-dose combination, side effects of the nonopioid would become intolerable as the dosage grew large, and hence would limit how much opioid could be given.

Drug therapy of cancer pain should adhere to the following principles:

- Perform a comprehensive pretreatment assessment to identify pain intensity and the underlying cause.
- Individualize the treatment plan.
- Use the WHO analgesic ladder and NCCN guidelines to guide drug selection.
- Use oral therapy whenever possible.
- Avoid IM injections whenever possible.
- For persistent pain, administer analgesics on a fixed schedule around-the-clock (ATC), and provide additional rescue doses of a short-acting agent if breakthrough pain occurs.
- Evaluate the patient frequently for pain relief and drug side effects.

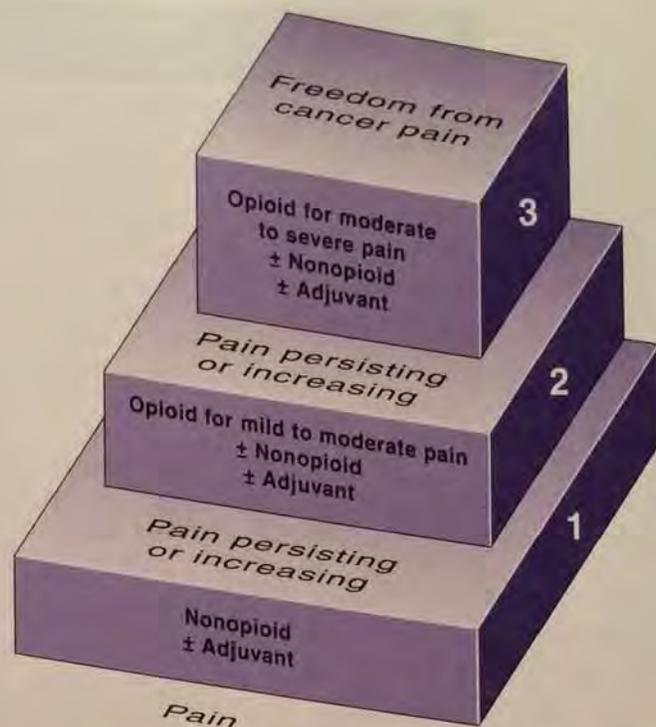


Figure 29-4 ■ The WHO analgesic ladder for cancer pain management.

Note that steps represent pain intensity. Accordingly, if a patient has intense pain at the outset, then treatment can be initiated with an opioid (step 2), rather than trying a nonopioid first (step 1). (Adapted from Cancer Pain Relief, 2nd ed. Geneva: World Health Organization, 1996.)

Nonopioid Analgesics

The nonopioid analgesics—NSAIDs and acetaminophen—constitute the first rung of the WHO analgesic ladder. These agents are the initial drugs of choice for patients with mild pain. There is a ceiling to how much pain relief nonopioid drugs can provide. Hence, there is no benefit to exceeding recommended dosages (Table 29-3). Acetaminophen is about equal to the NSAIDs in analgesic efficacy but lacks anti-inflammatory actions. Because of this difference and others, acetaminophen is considered separately below. The NSAIDs and acetaminophen are discussed at length in Chapter 71. Accordingly, discussion here is brief.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs (eg, aspirin, ibuprofen) can produce a variety of effects. Primary beneficial effects are pain relief, suppression of inflammation, and reduction of fever. Primary adverse effects are gastric ulceration, acute renal failure, and bleeding. In addition, all NSAIDs except aspirin increase the risk of thrombotic events (eg, myocardial infarction, stroke). In contrast to opioids, NSAIDs do not cause tolerance, physical dependence, or psychologic dependence.

NSAIDs are effective analgesics that can relieve mild to moderate pain. All of the NSAIDs have essentially equal analgesic efficacy, although individual patients may respond better to one NSAID than to another. NSAIDs relieve pain by a mechanism different from that of the opioids. As a result,

TABLE 29-2 ■ Drugs That Are Not Recommended for Treating Cancer Pain

Drug Class	Drug	Why the Drug Is Not Recommended
Opioids		
Pure agonists	Meperidine	A toxic metabolite accumulates with prolonged use
	Codeine	Maximal pain relief is limited owing to dose-limiting side effects
Agonist-antagonists	Buprenorphine	Ceiling to analgesic effects; can precipitate withdrawal in opioid-dependent patients; cause psychotomimetic reactions
	Butorphanol	
	Nalbuphine	
	Pentazocine	
Opioid Antagonists		Can precipitate withdrawal in opioid-dependent patients; limit use to reversing life-threatening respiratory depression caused by opioid overdose
Naloxone		
Nalmefene		
Benzodiazepines		Sedation from benzodiazepines limits opioid dosage; no demonstrated analgesic action
Diazepam		
Lorazepam others		
Barbiturates		Sedation from barbiturates limits opioid dosage; no demonstrated analgesic action
Amobarbital		
Secobarbital others		
Miscellaneous		No analgesic efficacy, either alone or in combination with an opioid
Cocaine		
Marijuana		
		Side effects (dysphoria, drowsiness, hypotension, bradycardia) preclude routine use as an analgesic
Brompton's cocktail*		
		Analgesic efficacy is no better than that of a single opioid

*Brompton's cocktail consists of heroin (in variable amounts), 10 mg of cocaine, 2.5 mL of 98% ethanol, 5 mL of syrup, and chloroform water.

combined use of an NSAID with an opioid can produce greater pain relief than either agent alone.

NSAIDs produce their effects—both good and bad—by inhibiting cyclooxygenase (COX), an enzyme that has two forms, known as COX-1 and COX-2. Most NSAIDs inhibit both COX-1 and COX-2, although a few are selective for COX-2. The selective COX-2 inhibitors (eg, celecoxib [Celebrex]) cause less GI damage than the nonselective inhibitors. Unfortunately, the selective inhibitors pose a greater risk of thrombotic events, and hence long-term use of these drugs is not recommended.

For patients undergoing chemotherapy, inhibition of platelet aggregation by NSAIDs is a serious concern. Many anticancer drugs suppress bone marrow function, and thereby decrease platelet production. The resultant thrombocytopenia puts patients at risk of bruising and bleeding. Obviously, this risk will be increased by drugs that inhibit platelet function. Among the conventional NSAIDs, only one subclass—the nonacetylated salicylates (eg, magnesium salicylate)—does not inhibit platelet aggregation, and hence is safe for patients with thrombocytopenia. All other conventional NSAIDs should be avoided. *Aspirin* is especially dangerous because it causes *irreversible* inhibition of platelet aggregation. Hence, its effects persist for the life of the platelet (about 8 days). Because COX-2 inhibitors do not affect platelets, these drugs are safe for patients with thrombocytopenia.

Acetaminophen

Acetaminophen [Tylenol, others] is similar to the NSAIDs in some respects and different in others. Like the NSAIDs, acetaminophen is an effective analgesic, and hence can relieve mild to moderate pain. Benefits derive from inhibiting COX in the central nervous system (CNS), but not in the periphery. Combining acetaminophen with an opioid can produce greater analgesia than either drug alone (because acetaminophen and opioids relieve pain by different mechanisms).

Acetaminophen differs from the NSAIDs in several important ways. Because it does not inhibit COX in the periphery, acetaminophen lacks anti-inflammatory actions, does not inhibit platelet aggregation, and does not promote gastric ulceration, renal failure, or thrombotic events. Because acetaminophen does not affect platelets, the drug is safe for patients with thrombocytopenia.

Acetaminophen has important interactions with two other drugs: alcohol and warfarin (an anticoagulant). Combining acetaminophen with alcohol, even in moderate amounts, can result in potentially fatal liver damage. Accordingly, patients taking acetaminophen should minimize alcohol consumption. Acetaminophen also can increase the risk of bleeding in patients taking warfarin. The mechanism appears to be inhibition of warfarin metabolism, which causes warfarin to accumulate to dangerous levels.

TABLE 29-3 • Dosages for Nonopioid Analgesics: Acetaminophen and Selected NSAIDs

Drug	Usual Adult Dosage*	
	Body Weight 50 kg or More	Body Weight Less Than 50 kg
Acetaminophen	650 mg q 4 h <i>or</i> 975 mg q 6 h <i>or</i> 1300 mg q 8 h	10–15 mg/kg q 4 h <i>or</i> 15–20 mg/kg q 4 h (rectal)
NSAIDs: Salicylates		
Aspirin	650 mg q 4 h <i>or</i> 975 mg q 6 h	10–15 mg/kg q 4 h <i>or</i> 15–20 mg/kg q 4 h (rectal)
Magnesium salicylate [Magan]†	650 mg q 4 h	—
Sodium salicylate	325–650 mg q 3–4 h	—
NSAIDs: Propionic Acid Derivatives		
Fenoprofen	300–600 mg q 6 h	—
Ibuprofen [Motrin, Advil, others]	400–800 mg q 6 h	10 mg/kg q 6–8 h
Ketoprofen	25–60 mg q 6–8 h	—
Naproxen [Naprosyn]	250–275 mg q 6–8 h	5 mg/kg q 8 h
Naproxen sodium [Anaprox, Aleve, Napreelan, others]	275 mg q 6–8 h	—
NSAIDs: Miscellaneous		
Diflunisal	500 mg q 12 h	—
Etodolac	200–400 mg q 6–8 h	—
Meclofenamate sodium	50–100 mg q 6 h	—
Mefenamic acid [Ponstel, Ponstan♦]	250 mg q 6 h	—
NSAIDs: Selective COX-2 Inhibitors		
Celecoxib [Celebrex]	200 mg q 12 h	—

*All dosages are oral except where indicated.

†Magnesium salicylate and sodium salicylate are nonacetylated, and hence, unlike aspirin, are safe for patients with thrombocytopenia.

Opioid Analgesics

Opioids are the most effective analgesics available, and hence are the primary drugs for treating moderate to severe cancer pain. With proper dosing, opioids can safely relieve pain in about 90% of cancer patients. Unfortunately, many patients are denied adequate doses, owing largely to unfounded fears of addiction. In the past, opioids were known as *narcotics*, a term that is now obsolete.

Opioids produce a variety of pharmacologic effects. In addition to analgesia, they can cause sedation, euphoria, constipation, respiratory depression, urinary retention, and miosis. With continuous use, tolerance develops to most of these effects, with the notable exception of constipation. Continuous use also results in physical dependence, which must not be equated with addiction.

The opioids are discussed at length in Chapter 28. Discussion here focuses on their use in patients with cancer.

Mechanism of Action and Classification

Opioid analgesics relieve pain by mimicking the actions of endogenous opioid peptides (enkephalins, dynorphins, endorphins), primarily at mu receptors and partly at kappa receptors.

Based on their actions at mu and kappa receptors, the opioids fall into two major groups: (1) *pure (full) agonists* (eg, morphine) and (2) *agonist-antagonists* (eg, butorphanol). The pure agonists can be subdivided into (1) agents for mild to

moderate pain and (2) agents for moderate to severe pain. The pure agonists act as agonists at mu receptors *and* at kappa receptors. In contrast, the agonist-antagonists act as agonists only at kappa receptors; at mu receptors, these drugs act as *antagonists*. Because their agonist actions are limited to kappa receptors, the agonist-antagonists have a ceiling to their analgesic effects. Furthermore, because of their antagonist actions, the agonist-antagonists can block access of the pure agonists to mu receptors, and can thereby prevent the pure agonists from relieving pain. Accordingly, agonist-antagonists are not recommended for managing cancer pain.

Tolerance and Physical Dependence

Over time, opioids cause tolerance and physical dependence. These phenomena, which are generally inseparable, reflect neuronal adaptations to prolonged opioid exposure. Some degree of tolerance and physical dependence develops after 1 to 2 weeks of opioid use.

Tolerance. Tolerance can be defined as a state in which a specific dose (eg, 10 mg of morphine) produces a smaller effect than it could when treatment began. Put another way, tolerance is a state in which dosage must be increased to maintain the desired response. In patients with cancer, however, a need for larger doses isn't always a sign of tolerance. In fact, it's usually a sign that pain is getting worse (owing to disease progression).

Tolerance develops to some opioid effects but not to others. Tolerance develops to analgesia, euphoria, respiratory depression, and sedation. In contrast, little or no tolerance develops to constipation.

There is cross-tolerance among opioids. Accordingly, significant tolerance to one opioid confers a similar degree of tolerance to all others.

Physical Dependence. Physical dependence is a state in which an abstinence syndrome will occur if a drug is abruptly withdrawn. With opioids, the abstinence syndrome can be very unpleasant—but not dangerous. The intensity and duration of the abstinence syndrome are determined in part by the duration of drug use and in part by the half-life of the drug taken. Because drugs with a short half-life leave the body rapidly, the abstinence syndrome is brief but intense. Conversely, for drugs with long half-lives, the syndrome is prolonged but relatively mild. The abstinence syndrome can be minimized by withdrawing opioids slowly (ie, by giving progressively smaller doses over several days). Please note that *physical dependence is not the same as addiction!*

Addiction

Opioid addiction is an important issue in pain management—not because addiction occurs (it rarely does), but because *inappropriate fears of addiction* are a major cause for undertreatment.

The American Society of Addiction Medicine defines addiction as *a disease process characterized by continued use of a psychoactive substance despite physical, psychologic, or social harm*. According to this definition, addiction is primarily a *behavior pattern*—and is *not* equated with physical dependence. Although it is true that physical dependence can contribute to addictive behavior, other factors—especially *psychologic dependence*—are the primary underlying cause. All cancer patients who take opioids chronically develop substantial physical dependence, but only a few (less than 1%) develop addictive behavior. Most patients, if their cancer were cured, would simply go through gradual withdrawal, and never think about or use opioids again. Clearly, these patients cannot be considered addicted, despite their physical dependence.

Because of misconceptions about opioid addiction, prescribers often order lower doses than patients need, nurses administer lower doses than were ordered, patients report less pain than they actually have, and family members discourage opioid use. The end result? The majority of cancer patients receive lower doses of opioids than they need. How can we improve this unacceptable situation? We must educate physicians, nurses, patients, and family members. Specifically, we must teach them about the nature of addiction and inform them that development of addiction in the therapeutic setting is very rare. Hopefully, this information will dispel unfounded fears of addiction, and will thereby help ensure delivery of opioids in doses that are sufficient to relieve suffering. After all, that is what opioids are for.

Drug Selection

Preferred Opioids. For all cancer patients, *pure opioid agonists* are preferred to the agonist-antagonists. If pain is not too intense, a moderately strong opioid (eg, oxycodone) is appropriate. If pain is moderate to severe, a strong opioid (eg, morphine) should be used. Since morphine is inexpensive,

TABLE 29-4 • Equianalgesic Doses of Pure Opioid Agonists and Tramadol

Drug	Equianalgesic Dose ^a		Duration (hours) ^b
	Parenteral	Oral	
Agents for Mild to Moderate Pain			
Codeine ^{c,d}	—	200 mg	3-4
Hydrocodone ^e	NA	30-45 mg	3-5
Oxycodone ^f	NA	15-20 mg	3-5
Tramadol ^{f,g}	NA	50-100 mg	3-7
Agents for Moderate to Severe Pain			
Morphine ^{c,h}	10 mg	30 mg	3-4
Fentanyl ^{i,j}	100 mcg	NA	1-3
Hydromorphone ^c	1.5 mg	7.5 mg	2-3
Levorphanol ^k	2 mg	4 mg	3-6
Methadone ^{k,l}	—	—	—
Oxymorphone ^f	1 mg	10 mg	3-6

NA = not available.

^aEquianalgesic dose = dose that will produce the same degree of analgesia as 10 mg of parenteral morphine.

^bShorter time generally applies to parenteral opioids. Longer time generally applies to immediate-release oral opioids. Sustained-release oral opioids have a prolonged duration.

^cCodeine, morphine, and hydromorphone should be used with caution in patients with impaired renal function owing to potential accumulation of renally-cleared metabolites. Monitor for neurologic adverse effects.

^dCodeine is not generally recommended for chronic therapy because the doses required to produce significant analgesia also produce significant side effects.

^eEquivalence data not substantiated. Usually combined with aspirin or acetaminophen.

^fAvailable in a sustained-release formulation administered every 12 hours.

^gTramadol is a weak opioid agonist with some antidepressant activity. Reserve for mild to moderate pain. The recommended dosage is 100 mg 4 times a day. At the maximum dosage of 400 mg/day, tramadol is less effective than morphine and other strong pure opioid agonists.

^hAvailable in sustained-release formulations administered every 12 or 24 hours.

ⁱThe equianalgesic dose listed applies to IV fentanyl compared with other IV opioids.

^jAvailable in a long-acting transdermal system (applied every 48 to 72 hours) for around-the-clock pain relief, and in short-acting transmucosal and intranasal formulations for breakthrough pain.

^kHas a long half-life, so observe for adverse effects after 2 to 5 days. May need to be dosed every 4 hours initially, and then every 6 to 8 hours after steady state is achieved (in 1 to 2 weeks).

^lFor patients converting from morphine to methadone, choosing the proper methadone dosage is complex, and should be done with the advice of a pain specialist familiar with methadone prescribing. Modified from NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain, Version 1.2011. Atlanta: National Comprehensive Cancer Network, Inc., 2011.

available in multiple dosage forms, and clinically well understood, this opioid is used more than any other. Preferred opioids are listed in Table 29-4.

Opioid Rotation. Opioid rotation—switching from one opioid to another—is now an accepted practice. Because opi-

oids have different side effect profiles, switching among them can help minimize adverse effects while maintaining good analgesia. To make the switch, the current opioid is stopped abruptly and immediately replaced with an equianalgesic dose of an alternative opioid.

Opioids to Use with Special Caution. *Methadone* [Dolophine, Methadose] and *levorphanol* [Levo-Dromoran] must be used with caution. Both drugs have prolonged half-lives, which makes dosage titration difficult. If dosing is not done skillfully, these drugs can accumulate to dangerous levels, causing excessive sedation and respiratory depression.

Codeine deserves special comment. Although codeine is capable of producing significant analgesia, side effects limit the dose that can be given. As a result, the degree of pain relief that can be achieved safely is quite low.

Opioids to Avoid. *Meperidine* [Demerol], a pure opioid agonist, may be used for a few days, but no longer. When the drug is taken chronically, a toxic metabolite—normeperidine—can accumulate, thereby posing a risk of adverse CNS effects (dysphoria, agitation, seizures).

The *agonist-antagonists*—buprenorphine, butorphanol, nalbuphine, and pentazocine—should be avoided. Why? First, they are less effective than pure opioid agonists, and hence, there is little reason to choose them. Second, if given to a patient who is physically dependent on a pure opioid agonist, these drugs can prevent the pure agonist from working, and can thereby block analgesia and precipitate withdrawal. Third, the agonist-antagonists can cause adverse psychologic reactions (nightmares, hallucinations, dysphoria).

Dosage

Dosage must be individualized. The objective is to find a dosage that can relieve pain without causing intolerable side effects. For patients with moderate pain and low opioid tolerance, very low doses (eg, 2 mg of parenteral morphine every 4 hours) can be sufficient. In contrast, when pain is severe or tolerance is high, much larger doses (eg, 600 mg of parenteral morphine every few hours) may be required. The upper limit to dosage is determined only by the intensity of side effects. Accordingly, as pain and/or tolerance increase, dosage should be increased until pain is relieved—unless intolerable side effects (eg, excessive respiratory depression) occur first.

The dosing schedule is determined by the temporal pattern of the pain. If pain is intermittent and infrequent, PRN dosing can suffice. However, since most patients have persistent pain, PRN dosing is inappropriate. Instead, dosing should be done on a fixed schedule ATC. Why? Because a fixed schedule can prevent opioid levels from becoming subtherapeutic, and can thereby prevent pain recurrence. As a result, the patient is spared needless suffering, both from the pain itself and from anxiety about its return.

What dose should be used when switching from one opioid to another, or from one route of administration to another? To help make this decision, an *equianalgesia table* such as Table 29-4 should be consulted. Equianalgesia tables indicate equivalent analgesic doses for different opioids, and for the same opioid administered by different routes. Let's assume, for example, that our patient has been getting 10 mg of IV morphine every 4 hours, and we want to switch to oral hydromorphone. By consulting Table 29-4, we can see that 7.5 mg of oral hydromorphone is about

equivalent to 10 mg of parenteral morphine, with both drugs being given every 4 hours. Hence, we might begin oral hydromorphone at 7.5 mg. However, there is a caveat: Because cross-tolerance among opioids is incomplete, the listed equianalgesic dose may actually produce a *stronger* effect than advertised. Accordingly, when switching drugs, it is safer to use a dose that is somewhat *lower* than the equianalgesic dose, and then titrate up.

Routes of Administration

Because most patients with cancer pain must take analgesics continuously, the route should be as convenient, affordable, and noninvasive as possible. Oral administration meets these criteria best, and hence is preferred for most patients. If oral medication cannot be used, the preferred alternative routes are rectal and transdermal: Both are relatively convenient, affordable, and noninvasive. If these routes are ineffective or inappropriate, then parenteral administration (IV or subQ) is indicated (IM injections should be avoided). For patients who cannot be managed with IV or subQ therapy, more invasive routes—intraspinal or intraventricular—can be tried.

Oral. Oral administration is the preferred route for chronic therapy. Why? Because oral dosing is cheap, convenient, and noninvasive. Accordingly, in the absence of contraindications (eg, vomiting, inability to swallow), oral therapy should be considered for all patients. Opioids are available in several formulations (eg, tablets, capsules, solution) for oral use. To reduce the number of daily doses, a long-acting formulation (eg, controlled-release morphine) can be used. Because oral opioids undergo substantial first-pass metabolism, oral doses must be larger than parenteral doses to achieve equivalent analgesic effects.

Rectal. Rectal administration is a preferred alternative for patients who cannot take drugs by mouth. Two opioids—morphine and hydromorphone—are available in rectal formulations (suppositories). When switching from oral to rectal administration, dosing is begun with the same dose that was used orally, and then adjusted as needed. Rectal administration is inappropriate for patients with diarrhea or lesions of the rectum or anus. Also, children frequently object to this route.

Transdermal. Transdermal administration is a preferred alternative to oral therapy. Only one pure opioid agonist—fentanyl [Duragesic]—is available for chronic transdermal use. Fentanyl patches provide steady analgesia for 72 hours, and hence are appropriate for patients with pain that is continuous and does not fluctuate much in intensity. Absorption from the patch is very slow. As a result, when the first patch is applied, effective analgesia may take 12 to 24 hours to develop. During this time, PRN therapy with a short-acting opioid may be required. Fentanyl patches are available in five strengths, allowing dosage to be matched with pain intensity. As with other long-acting opioids, rescue doses with a short-acting opioid are needed when breakthrough pain occurs.

Intravenous and Subcutaneous. Intravenous and subQ administration are acceptable alternatives when less invasive routes (oral, transdermal, rectal) cannot be used. The IV and subQ routes have two advantages: (1) onset of analgesia is quick and (2) these routes permit rapid escalation of dosage. Obvious disadvantages are inconvenience and increased cost. In addition, frequent subQ dosing is uncomfortable.

Conditions that might justify IV or subQ administration include

- Persistent nausea and vomiting (which preclude oral dosing)
- Inability to swallow (which precludes oral dosing)
- Delirium or stupor (which precludes oral dosing)
- Pain that requires a large number of pills (which makes oral dosing inconvenient)
- Unstable pain that requires rapid dosage escalation (which precludes oral, rectal, and transdermal administration)

Dosages for IV and subQ administration are the same.

Intramuscular. Intramuscular administration should be avoided. IM injections are painful, and hence unacceptable for repeated dosing. In addition, absorption from IM sites is inconsistent, hence pain relief is unpredictable.

Intraspinal. Intraspinal administration is reserved for patients with intractable pain that cannot be controlled with less invasive routes (eg, IV, subQ). In this technique, opioids are delivered to the epidural or subarachnoid space via a percutaneous catheter connected to an infusion pump or injection port. By using this route, we can achieve high opioid concentrations at receptors on pain pathways in the spinal cord. It is important to note, however, that effects will not be limited to the spinal cord: Intraspinal opioids undergo absorption into the blood in amounts sufficient to cause systemic effects. In fact, blood levels may be equivalent to those achieved with conventional routes (eg, subQ). Intraspinal administration is especially useful for patients with severe pain in the lower body: Pain is relieved in up to 90% of appropriate candidates. Patients who are tolerant to opioids delivered by other routes will also be tolerant to opioids given intraspinally, and hence dosage should be adjusted accordingly. Patients should have access to rescue medication in case breakthrough pain occurs, owing either to delivery system malfunction or inadequate dosing. Side effects with intraspinal administration are the same as with other routes. In addition, there is a risk of *delayed* respiratory depression as well as infection associated with the catheter.

Intraventricular. Like intraspinal administration, intraventricular administration is reserved for patients whose pain cannot be controlled with less invasive routes. In this procedure, morphine is delivered to the cerebral ventricles via a catheter connected to an external infusion pump (for continuous administration) or a subcutaneous reservoir (for intermittent administration). Because morphine is delivered directly to the brain, bypassing the blood-brain barrier, analgesia can be achieved with extremely low doses (eg, 5 mg daily). Pain is relieved in 90% of patients. Intraventricular administration is especially helpful for patients with intractable pain caused by head and neck malignancies or tumors that affect the brachial plexus.

Patient-Controlled Analgesia. Patient-controlled analgesia (PCA) is a method of drug delivery that permits patients to control the amount of opioid they receive. PCA is accomplished using a PCA device to deliver opioids through an indwelling IV or subQ catheter. The PCA device is an electronically controlled infusion pump that (1) delivers a continuous basal infusion of opioid and (2) can be activated manually by the patient to deliver additional bolus doses for breakthrough pain. To prevent an overdose, the device (1) limits the total dose of opioid that can be delivered per hour

and (2) sets a minimum interval (eg, 10 minutes) between bolus doses, thereby preventing the patient from giving a second dose before the first one can take full effect. PCA devices are safe for use in the hospital and at home, but should not be used by patients who are sedated or confused. PCA administration is discussed at length in Chapter 28.

Managing Breakthrough Pain

Many patients whose pain is well controlled most of the day experience transient episodes of moderate to severe pain, known as breakthrough pain. Breakthrough pain develops quickly, reaches peak intensity in minutes, and may persist from minutes to hours (the median duration is 30 minutes). At least 50% of cancer patients experience these episodes, typically 1 to 4 times a day. Breakthrough pain may occur spontaneously, or it may be precipitated by coughing or other movements. In contrast to end-of-dose pain, which occurs because analgesic levels are lowest at that time, breakthrough pain can occur at any time during the dosing interval.

All patients receiving ATC opioids for persistent pain should have access to a rescue medication to manage breakthrough pain. Because breakthrough pain is both severe and self-limited, the best medication is a strong opioid with a rapid onset and short duration. The rapid onset permits speedy relief, and the short duration facilitates dosage titration. For ease of administration, oral, transmucosal, and intranasal formulations are preferred; examples include immediate-release oral morphine, transmucosal fentanyl [Abstral, Actiq, Fentora, Onsolis] and fentanyl nasal spray [Lazanda]. The dosage, as recommended by the American Pain Society, should be equivalent to one-sixth of the total daily opioid dose, repeated in 2 hours if needed.

Managing Side Effects

Side effects of the opioids include respiratory depression, constipation, sedation, orthostatic hypotension, nausea, and vomiting. All can be effectively managed. In many patients, side effects can be reduced simply by decreasing the dosage (typically by 25%). If dosage reduction causes pain to return, adding a nonopioid analgesic may take care of the problem. Over time, tolerance develops to sedation, respiratory depression, nausea, and vomiting—but not to constipation.

Respiratory Depression. Respiratory depression is the most serious side effect of the opioids; death can result. Fortunately, when dosage and monitoring are appropriate, significant respiratory depression is rare. Pain counteracts the depressant actions of opioids. Hence, as pain decreases, respiratory depression may deepen.

Respiratory depression is greatest at the outset of treatment and then decreases as tolerance develops. As a result, small initial doses of opioids (eg, 5 mg of IV morphine every hour) can pose a greater risk than much larger doses (eg, 1000 mg of IV morphine every hour) later on.

Significant respiratory depression is most likely when dosage is being titrated up. The best way to assess the risk of impending respiratory depression is to monitor opioid-induced sedation. Why? Because an increase in sedation generally precedes an increase in respiratory depression. Hence, if excessive sedation is observed, further dosing should be delayed.

Respiratory depression is increased by other drugs with CNS-depressant actions (eg, alcohol, barbiturates, benzodiazepines). Accordingly, these agents should be avoided.

Severe respiratory depression can be reversed with *naloxone* [Narcan], a pure opioid antagonist. However, caution is required: Excessive dosing will reverse analgesia, thereby putting the patient in great pain. Accordingly, naloxone dosage must be titrated carefully.

When death is near, should opioids be withheld out of fear that respiratory depression may bring death sooner? For several reasons, the answer is "No." First, significant respiratory depression is rare in the tolerant patient. Hence, concerns about hastening death are largely unfounded. Second, unrelieved pain can itself hasten death. Third, when death is imminent, it is more important to provide comfort than prolong life. Accordingly, adequate opioids should be provided, even if doing so means life ends a bit sooner.

Constipation. Constipation occurs in most patients. Opioids promote constipation by decreasing propulsive intestinal contractions, increasing nonpropulsive contractions, increasing the tone of the anal sphincter, and reducing fluid secretion into the intestinal lumen. No tolerance to these effects develops. To reduce constipation, all patients should increase dietary fiber and fluid. However, most patients also need pharmacologic help. Options include stool softeners (eg, docusate), stimulant laxatives (eg, senna), osmotic laxatives (eg, sodium phosphate), and methylaltrexone [Relistor], which blocks opioid receptors in the intestine. For prophylaxis of constipation, current guidelines recommend daily therapy with a combination product, such as Senokot-S, which contains both senna and docusate. Strong osmotic laxatives are reserved for severe constipation. Methylaltrexone [Relistor] is indicated only for constipation in patients with end-stage disease. Drugs with anticholinergic properties (eg, tricyclic antidepressants, antihistamines) can exacerbate opioid-induced constipation (by further depressing bowel function), and hence should be avoided.

Sedation. Sedation is common early in therapy, but tolerance develops quickly. If sedation persists, it can be reduced by giving smaller doses of the opioid more frequently, while keeping the total daily dose the same. This dosing schedule decreases peak opioid levels, and thereby reduces excessive CNS depression. If necessary, sedation can be opposed with a CNS stimulant (eg, caffeine, methylphenidate, dextroamphetamine, modafinil).

Nausea and Vomiting. Initial doses of opioids may cause nausea and vomiting. Fortunately, tolerance develops rapidly. Nausea and vomiting can be minimized by pretreatment with an antiemetic (eg, prochlorperazine, metoclopramide). A serotonin antagonist (eg, granisetron, ondansetron) may also be tried, but these drugs may increase constipation.

Other Side Effects. Opioids promote histamine release, and can thereby cause *itching*, which can be relieved with an antihistamine (eg, diphenhydramine).

Opioids increase the tone in the urinary bladder sphincter, and can thereby cause *urinary retention*. Prostatic hypertrophy and use of anticholinergic drugs will exacerbate the problem. Patients should be monitored for urinary retention and encouraged to void every 4 hours.

Opioids can cause *orthostatic hypotension*. Patients should be informed about symptoms of hypotension (lightheadedness, dizziness) and instructed to sit or lie down if they occur. Orthostatic hypotension can be minimized by moving slowly when changing from a supine or seated position to an upright posture.

Opioid-induced *neurotoxicity* is a recently recognized syndrome. Symptoms include delirium, agitation, myoclonus, and hyperalgesia. Primary risk factors are renal impairment, pre-existing cognitive impairment, and prolonged, high-dose opioid use. Management consists of hydration, dose reduction, and opioid rotation.

Adjuvant Analgesics

Adjuvant analgesics are used to *complement* the effects of opioids. Accordingly, these drugs are employed in *combination* with opioids—not as substitutes. Adjuvant analgesics can (1) enhance analgesia from opioids, (2) help manage concurrent symptoms that exacerbate pain, and (3) treat side effects caused by opioids. Several of the adjuvants are especially useful for *neuropathic pain*. The adjuvant analgesics differ from opioids in that pain relief is limited and less predictable, and often develops slowly.

Adjuvant agents may be employed at any step on the analgesic ladder. The adjuvants are interesting in that, although they can relieve pain, all of them were developed to treat other conditions (eg, depression, seizures, dysrhythmias). Accordingly, it is important to reassure patients that the adjuvant is being used to alleviate pain, and not for its original purpose. Dosages for the adjuvant analgesics are summarized in Table 29–5.

Antidepressants

Tricyclic Antidepressants. *Amitriptyline* [Elavil] and other tricyclic antidepressants (TCAs) can reduce pain of *neuropathic* origin. TCAs have analgesic effects of their own and they enhance the effects of opioids, and may thereby allow a reduction in opioid dosage. As a side benefit, TCAs can elevate mood. Important adverse effects are orthostatic hypotension, sedation, anticholinergic effects (dry mouth, urinary retention, constipation), and weight gain (secondary to improved appetite). Dosing at bedtime takes advantage of sedative effects, and minimizes hypotension during the day. Effects begin in 1 to 2 weeks and reach their maximum in 4 to 6 weeks. The TCAs are discussed at length in Chapter 32.

Other Antidepressants. In addition to the tricyclic agents, certain other antidepressants (eg, bupropion, duloxetine, venlafaxine) can help with neuropathic pain.

Antiseizure Drugs

Certain antiseizure drugs can help relieve *neuropathic pain*. Lancing pain (sharp, darting pain) is especially responsive, although other forms of neuropathic pain (cramping pain, aching pain, burning pain) also respond. Analgesia is thought to result from suppressing spontaneous neuronal firing. Of the available anticonvulsants, *carbamazepine* [Tegretol] has been used most widely. Because carbamazepine is myelosuppressive, it must be used with caution in patients receiving anticancer drugs that suppress bone marrow function. As discussed in Chapter 24, caution is also needed in patients of Asian descent, owing to an increased risk of severe dermatologic reactions. Another drug—*gabapentin* [Neurontin]—is also very effective, and causes fewer side effects than carbamazepine. Dosage should be low initially (100 mg once a day) and then gradually increased; dosages as high as 1200 mg 3 times a day have been employed. The anticonvulsants are discussed at length in Chapter 24.

TABLE 29-5 • Adjuvant Drugs for Cancer Pain

Drug	Usual Adult Dosage	Beneficial Actions
Tricyclic Antidepressants		
Amitriptyline [Elavil]	25–150 mg/day PO	Reduce neuropathic pain
Desipramine [Norpramin]	10–150 mg/day PO	
Doxepin [Sinequan]	25–150 mg/day PO	
Imipramine [Tofranil]	20–100 mg/day PO	
Nortriptyline [Aventyl, Pamelor]	10–150 mg/day PO	
Other Antidepressants		
Bupropion [Wellbutrin]	100–450 mg/day PO	Reduce neuropathic pain
Duloxetine [Cymbalta]	30–60 mg/day PO	
Venlafaxine [Effexor]	37.5–225 mg/day PO	
Antiseizure Drugs		
Carbamazepine [Tegretol]	200–1600 mg/day PO	Reduce neuropathic pain
Gabapentin [Neurontin]	300–3600 mg/day PO	
Lamotrigine [Lamictal]	25–400 mg/day PO	
Phenytoin [Dilantin]	300–500 mg/day PO	
Pregabalin [Lyrica]	100–600 mg/day PO	
Local Anesthetics/Antidysrhythmics		
Lidocaine	5 mg/kg/day IV or subQ	Reduce neuropathic pain
Mexiletine [Mexitil]	450–600 mg/day PO	
CNS Stimulants		
Dextroamphetamine [Dexedrine]	5–10 mg/day PO	Enhance analgesia and reduce sedation from opioids
Methylphenidate [Ritalin]	10–15 mg/day PO	
Antihistamine		
Hydroxyzine [Vistaril]	300–450 mg/day IM	Enhances analgesia and reduces anxiety, insomnia, and nausea
Glucocorticoids		
Dexamethasone [Decadron, others]	16–96 mg/day PO or IV	Reduce pain associated with brain metastases and epidural spinal cord compression
Prednisone	40–100 mg/day PO	
Bisphosphonates		
Etidronate [Didronel]	7.5 mg/kg IV for 3 days	Reduce hypercalcemia and possibly bone pain
Pamidronate [Aredia]	60–90 mg IV once	

Local Anesthetics/Antidysrhythmics

Lidocaine (a local anesthetic and antidysrhythmic) and *mexiletine* (an antidysrhythmic related to lidocaine) are considered second-line agents for *neuropathic pain*. Intravenous infusion of lidocaine produces analgesia in 10 to 15 minutes. The drug may be most appropriate for rapidly escalating neuropathic pain. Both lidocaine and mexiletine are discussed in Chapter 49 (Antidysrhythmic Drugs). Lidocaine is also discussed in Chapter 26 (Local Anesthetics).

CNS Stimulants

The CNS stimulants, such as *dextroamphetamine* [Dexedrine] and *methylphenidate* [Ritalin], have two beneficial effects: They can enhance opioid-induced analgesia and they can counteract opioid-induced sedation. In addition, they can be used for rapid elevation of mood. Principal adverse effects are weight loss (from appetite suppression) and insomnia (from CNS stimulation). To minimize interference with sleep, dosing late in the day should be avoided. The CNS stimulants are discussed in Chapter 36.

Antihistamines

Hydroxyzine [Vistaril], an antihistamine, promotes drowsiness and reduces anxiety. Although widely believed to enhance analgesia, proof is lacking. Drawbacks include worsening of constipation, urinary retention, and cognitive impairment. The antihistamines are discussed in Chapter 70.

Glucocorticoids

Although glucocorticoids lack direct analgesic actions, they can help manage painful cancer-related conditions. Because glucocorticoids can reduce cerebral and spinal edema, they are essential for the emergency management of elevated intracranial pressure and epidural spinal cord compression. Similarly, glucocorticoids are part of the standard therapy for tumor-induced spinal cord compression. In addition to these benefits, glucocorticoids can improve appetite and impart a general sense of well-being; both actions help in managing anorexia (loss of appetite) and cachexia (weakness and emaciation) associated with terminal illness.

Glucocorticoids are very safe when used short term (even in high doses) and very dangerous when used long term (even in low doses). In particular, long-term therapy can cause adrenal insufficiency, osteoporosis, glucose intolerance (hyperglycemia), increased vulnerability to infection, thinning of the skin, and, possibly, peptic ulcer disease (PUD). Therapy with NSAIDs augments the risk of PUD. The risk of osteoporosis can be reduced by giving calcium supplements and vitamin D along with calcitonin or a bisphosphonate (eg, etidronate). The glucocorticoids are discussed in Chapter 72.

Bisphosphonates

Bisphosphonates, such as *etidronate* [Didronel] and *pamidronate* [Aredia], can reduce cancer-related *bone pain* in some patients. Bone pain is common when cancers metastasize to bone. The cause of pain may be tumor-induced bone resorption, which can also cause hypercalcemia, osteoporosis, and related fractures. Bisphosphonates inhibit bone resorption and are approved for treating hypercalcemia of malignancy—but not bone pain. However, when these drugs are given to treat hypercalcemia, many patients report a reduction in bone pain, although others do not. Hence, although these drugs appear promising, their use for management of bone pain is still considered investigational. The bisphosphonates are discussed in Chapter 75.

NONDRUG THERAPY

Invasive Procedures

Invasive therapies are the last resort for relieving intractable pain. Hence, for most patients, all other options should be exhausted first.

Neurolytic Nerve Block

The goal of this procedure is to destroy neurons that transmit pain from a limited area, thereby providing permanent pain relief. Nerve destruction is accomplished through local injection of a neurolytic (neurotoxic) substance, typically alcohol or phenol. To ensure that the correct nerves are destroyed, reversible nerve block is done first, using a local anesthetic. If the local anesthetic relieves the pain, a neurolytic agent is then applied to the same site. Neurolytic nerve block can eliminate pain in up to 80% of patients. However, even if pain relief is only partial, the procedure can still permit some reduction in opioid dosage, and can thereby decrease side effects, such as sedation and constipation. When nerve block is successful and opioids are discontinued, opioid dosage should be tapered gradually to avoid withdrawal. Nerve block is not without risk. Potential complications include hypotension, paresis (slight paralysis), paralysis, and disruption of bowel and bladder function (eg, diarrhea, incontinence). The incidence of complications ranges from 0.5% to 2%.

Neurosurgery

Neurosurgeons can relieve cancer pain in several ways. They can destroy neurons that transmit pain signals; they can implant opioid infusion systems; and, in a procedure known as neuroaugmentation, they can implant electrodes to stimulate neurons that release endogenous opioid peptides (eg, endorphins). Nerve damage incurred during these surgeries can

result in neurologic deficits and new pain. Less than 10% of cancer patients undergo neurosurgery for pain relief.

Tumor Surgery

When curative excision of a tumor is not feasible, it may still be appropriate to surgically debulk the tumor with the goal of relieving pain. Unfortunately, palliative debulking only provides temporary relief: Growth of residual cancer cells eventually causes pain to return. Radiation therapy following the surgery may extend pain relief.

Radiation Therapy

Radiation therapy relieves pain by causing tumor regression. Palliative treatment can be directed at primary tumors and at metastases anywhere in the body.

Radiation can be delivered in three forms: *brachytherapy* (implanted radioactive pellets), *teletherapy* (external beam radiation), and *intravenous radiopharmaceuticals*. With brachytherapy, cell kill is limited to the immediate area of the implanted pellets; hence, the technique is suited only for localized tumors. With teletherapy, cell kill can be localized or widespread, depending on the size of the beam employed; hence, the technique can be used for both local tumors and metastases. Intravenous radiopharmaceuticals travel throughout the body, and hence are best suited for widespread metastases.

With radiation therapy, as with chemotherapy, damage to normal tissue is dose limiting. Therefore, the challenge is to deliver a dose of radiation that is large enough to kill cancer cells, but not so large that it causes intolerable damage to healthy tissue.

Some side effects of radiation occur early and some are late. Early effects develop during or immediately after radiation exposure. Late reactions develop months or years later. The most common early effects are skin inflammation and lesions of the GI mucosa. Fortunately, in the regimens employed for palliation, these acute effects are generally mild. The most common late reaction is fibrosis, which occurs mainly in tissues that have a limited ability to regenerate (eg, brain, peripheral neurons, lung). Late reactions are of limited concern, however, because most patients die from their cancer before late reactions can develop.

Physical and Psychosocial Interventions

Physical and psychosocial interventions can help reduce pain, but the degree of relief is limited. Accordingly, these interventions should be used only in conjunction with drug therapy—not as substitutes.

Physical Interventions

Physical interventions (eg, heat, massage, vibration) can help relieve aches and pains associated with cancer.

Heat. Application of heat can benefit the patient in at least two ways: (1) heat promotes vasodilation, and can thereby increase delivery of oxygen and nutrients to damaged tissue; and (2) heat increases elasticity in muscle, and can thereby reduce stiffness. Heat may be applied in several ways, including use of hot compresses, hot water bottles, and electric heating pads. Heat may be harmful to tissues exposed to radiation, and hence these should be avoided. There is some concern

that heat may actually stimulate tumor growth and metastatic spread, although convincing data are lacking.

Cold. Application of cold can reduce inflammation and muscle spasm. Cold can be applied using ice packs, chemical gel packs, and towels soaked in ice water. Application should last no longer than 15 minutes. Cold should not be applied to areas damaged by radiation. In addition, because cold promotes vasoconstriction, it should be avoided in patients with peripheral vascular disease, Raynaud's phenomenon, and all other disorders that can be exacerbated by vasoconstriction.

Massage. Massage is primarily a comfort measure that provides relief through distraction and relaxation. In addition, massage may help ease discomfort at specific sites by increasing local circulation.

Exercise. Exercise can reduce subacute and chronic pain by increasing muscle strength and joint mobility. Additional benefits include improved cardiovascular conditioning and restoration of coordination and balance. Range-of-motion exercises can preserve strength and joint function. When patients cannot perform these exercises on their own, family members should be taught to assist. Although weight-bearing exercise is desirable, it should be avoided in patients who are at risk of fractures because of tumor invasion or osteoporosis.

Acupuncture and Transcutaneous Electrical Nerve Stimulation. In theory, these techniques reduce pain by stimulating peripheral nerves, which in turn activate central pain-modulating pathways. However, the efficacy of both techniques in cancer patients is uncertain. Acupuncture is performed by inserting solid needles through the skin into the underlying muscle. Transcutaneous electrical nerve stimulation (TENS) is performed using low-voltage cutaneous electrodes. Because the efficacy of these techniques is questionable, pain status must be closely monitored.

Psychosocial Interventions

Psychosocial interventions can help patients cope by (1) increasing the sense of control over pain, (2) reversing negative thoughts and feelings, and (3) offering social support. Interventions that require learning and practice should be introduced early, so that they can be perfected while the patient still has sufficient energy and strength to learn them.

Relaxation and Imagery. The aim of these techniques is to reduce pain by inducing both mental relaxation (alleviation of anxiety) and physical relaxation (release of tension in skeletal muscles). These techniques are easy to learn and require little or no special equipment. Examples include (1) meditation, (2) slow rhythmic breathing, (3) imagining a peaceful scene (eg, gentle waves breaking on a secluded, sunny beach), and (4) active listening to recorded music (eg, tapping a finger in time to an enjoyable tune).

Cognitive Distraction. The goal of cognitive distraction is to divert attention away from pain and associated negative emotions. Distractions may be internal or external. Examples of internal distractions include praying, counting or singing in one's head, and repeating positive thoughts, such as "I can cope." External distractions include watching TV, listening to music, and conversing with friends.

Peer Support Groups. Support groups composed of other cancer patients can help members cope with pain and all other sequelae of their disease. These groups can provide emotional support, cancer-related information, and a sense of

social belonging. Talking with other cancer survivors can be especially helpful for the newly diagnosed. Some support groups welcome patients who have any form of cancer; others are dedicated to just one form of the disease (eg, breast cancer). Resources for locating a support group in your community include (1) the National Coalition for Cancer Survivorship, at 1-877-622-7937; (2) the National Cancer Information Service, at 1-800-4-CANCER; and (3) your local chapter of the American Cancer Society, whose number should be in your phone book.

PAIN MANAGEMENT IN SPECIAL POPULATIONS

The Elderly

In elderly patients, two issues are of special concern: (1) undertreatment of pain and (2) increased risk of adverse effects. Paradoxically, a third issue—heightened drug sensitivity—contributes to both problems.

Heightened Drug Sensitivity. The elderly are more sensitive to drugs than are younger adults, owing largely to a decline in organ function. In particular, rates of hepatic metabolism and renal excretion decline with age. As a result, drugs tend to accumulate in the body, causing responses to be more intense and prolonged.

Undertreatment of Pain. Undertreatment is common in the elderly. In addition to the usual reasons (fears about tolerance, addiction, adverse effects, and regulatory actions), the elderly are denied adequate medication for two more reasons: difficulties with assessment and erroneous ideas about old age.

Assessment is made difficult by cognitive impairment (eg, delirium, dementia) and by impairment of vision and hearing. As a result, self-reporting of pain may be inaccurate or even impossible. Because of these obstacles, special effort must be made to help ensure that assessment is accurate. However, because accuracy cannot be guaranteed, frequent reassessment is recommended.

Misconceptions about the elderly contribute to undertreatment. Specifically, providers may believe (incorrectly) that dosage should be low because (1) the elderly are relatively insensitive to pain; (2) if pain occurs, the elderly can tolerate it well; and (3) the elderly are highly sensitive to opioid side effects. The first two concepts have no basis in fact, and therefore must not be allowed to influence treatment. Although there is some truth to the third concept, concern about side effects is no excuse for inadequate dosing.

Increased Risk of Side Effects and Adverse Interactions. For several reasons, elderly patients may experience more side effects than younger adults. As noted, drug elimination in the elderly is impaired, posing a risk that drug levels may rise dangerously high. However, with careful dosing, drug levels can be kept within a range that is both safe and effective. Drugs with prolonged half-lives (eg, methadone) pose an increased risk of excessive accumulation, and should be avoided.

The risk of gastric ulceration and renal toxicity from NSAIDs is increased in older patients. Gastric erosion can be reduced by concurrent therapy with misoprostol. There is no specific way to prevent renal toxicity. Hence, the best we can do is monitor closely for evolving kidney damage.

Older patients are at increased risk of adverse drug-drug interactions. Why? Because, in addition to the disorder that's causing pain, the elderly are likely to have other disorders, and hence require more drugs than younger adults. The risk of serious injury from drug interactions can be reduced by careful drug selection and by monitoring for potential reactions.

Young Children

Management of cancer pain in children is much like management in adults. The principal difference is that assessment in children is more difficult. In addition, children frequently experience more pain from chemotherapy and other interventions than from the cancer itself.

Assessment

Assessment must be tailored to the child's developmental level and personality. Selecting an appropriate assessment method is especially important for children with developmental delays, learning disabilities, and emotional disturbances. Assessment can be greatly facilitated by open communication about pain between the child, family, and healthcare team.

Assessment methods include self-reporting, behavioral observation, and measurement of physiologic parameters (eg, heart rate, blood pressure, respiratory rate, sweating). As stressed earlier, self-reporting is preferred and should be employed whenever appropriate. Behavioral observation is a distant second choice. Because many factors other than pain can alter physiologic parameters, measuring these is the least reliable way to assess pain.

Verbal Children. For children who can verbalize and are over the age of 4 years, self-reporting is the most reliable way to assess pain. Since children rarely claim to have pain that isn't there, there is little risk of error from over-reporting. However, there is a significant risk of error from under-reporting. Children may report less pain than they have for several reasons. These include (1) fear that revealing their pain will lead to additional injections and other painful procedures, (2) lack of awareness that we can help their pain go away, (3) a desire to protect their parents from the knowledge that their cancer is getting worse, and (4) a desire to please. Because the self-report may conceal pain, it can be helpful to supplement the self-report with behavioral observation (see below).

Preverbal and Nonverbal Children. Since preverbal and nonverbal children cannot self-report pain, a less reliable method must be used for assessment. The principal alternative is *behavioral observation*. Behavioral cues suggesting pain include vocalization (crying, whining, groaning), facial expression (grimacing, frowning, reduced affect), muscle tension, inability to be consoled, protection of body areas, and reduced activity. The biggest drawback to behavioral observation is the risk of a false-negative conclusion. That is, a child may be in pain although his or her behavior may lead the observer to conclude otherwise. For example, sleeping, watching TV, or laughing may suggest that a child is comfortable. However, these behaviors can actually represent an attempt to control pain. Similarly, although sitting quietly might indicate comfort, it could also mean that moving and talking are painful. When behavioral observation leaves doubt about whether the child is in pain, a trial with an analgesic can help confirm the assessment.

Treatment

Therapy of cancer pain in children is essentially the same as in adults. As in adults, drugs are the cornerstone of treatment; nondrug therapies are used only as supplements. Drug selection is guided by the WHO analgesic ladder. Because of the risk of Reye's syndrome, children with influenza or chickenpox should not receive NSAIDs. Acetaminophen is a safe alternative. As in adults, oral dosing is preferred. More invasive routes should be reserved for patients who cannot take drugs by mouth. Children generally object to rectal administration, and may refuse treatment by this route. Administration with a PCA device is an option for children over the age of 7 years.

Neonates and infants are highly sensitive to drugs, and hence must be treated with special caution. Drug sensitivity occurs for two reasons: (1) the blood-brain barrier is incompletely formed, giving drugs ready access to the CNS; and (2) the kidneys and liver are poorly developed, causing drug elimination to be slow. Because of heightened drug sensitivity, neonates and infants are at increased risk of respiratory depression from opioids. Accordingly, when opioids are given to nonventilated infants, the initial dosage should be very low (about one-third the dosage employed for older children). Furthermore, use of opioids should be accompanied by intensive monitoring of respiration.

Opioid Abusers

When treating cancer pain in opioid abusers, we have two primary obligations: we must try to (1) relieve the pain and (2) avoid giving opioids simply because the patient wants to get high. Both obligations are difficult to meet. Because of the challenge, treatment should be directed by a clinician trained in substance abuse as well as pain management.

Concerns about abuse can result in undertreatment of pain. This must be avoided. Remember, abusers feel pain like everyone else, and therefore need opioids like everyone else. Clinicians must take special care not to withhold opioids because they have confused relief-seeking behavior with drug-seeking behavior. In the end, we have little choice but to base treatment on the patient's self-report of pain. Hence, if the patient tells us that pain is persisting, adequate doses of opioids should be provided.

Because of opioid tolerance, initial doses in abusers must be higher than in nonabusers. To estimate how high the initial dosage should be, we must try to estimate the existing degree of tolerance by interviewing the patient about the extent of opioid use.

As with other adults, drug selection can be guided by the WHO analgesic ladder and the NCCN guidelines. If pain is sufficient to justify opioids, then opioids should be used; nonopioids (NSAIDs and acetaminophen) should not be substituted for opioids out of concern for addiction. If the patient is on methadone maintenance, methadone can be used for the pain. However, because regulations limit the dosage of methadone that drug-abuse clinics can dispense, the increased dosage required to manage pain will have to come from another source. One group of opioids—the agonist-antagonists—will precipitate withdrawal in opioid abusers, and hence must never be prescribed for these patients.

Drug delivery with a PCA device can be helpful. By using a PCA device, we can avoid potential conflicts between the patient and the clinician, who would otherwise have to admin-

ister each dose. Excessive dosing can be prevented by setting the PCA device to limit how much opioid the patient can self-administer.

PATIENT EDUCATION

Patient education is an integral part of cancer pain management. When education is successful, it can help reduce anxiety, dispel hopelessness, facilitate assessment, enhance compliance, decrease complications, provide a sense of control, and enable patients to take an active role in their care. All of these will promote pain relief.

General Issues

Common sense tells us that patient education should be accurate, comprehensive, and understandable. To reinforce communication, information should be presented at least twice and in more than one way. Major topics to discuss are (1) the nature and causes of pain, (2) assessment and the importance of honest self-reporting, and (3) plans for drug and nondrug therapy. Patients should be encouraged to express their fears and concerns about cancer, cancer pain, and pain treatment—and they should be reassured that pain can be effectively controlled in most cases. All patients should receive a written pain management plan. To facilitate ongoing education, patients should be invited to contact care providers whenever they feel the need—be it to discuss specific concerns with treatment or simply to acquire new information. Finally, patients should know when and how to contact the prescriber to report treatment failure, serious side effects, or new pain.

Drug Therapy

The goal in teaching patients about analgesic drugs is to maximize pain relief and minimize harm. To help achieve this goal, patients should know the following about each drug they take:

- Drug name and therapeutic category
- Dosage size and dosing schedule
- Route and technique of administration
- Expected therapeutic response and when it should develop
- Duration of treatment
- Method of drug storage
- Symptoms of major adverse effects and measures to minimize discomfort and harm
- Major adverse drug-drug and drug-food interactions
- Whom to contact in the event of therapeutic failure, severe adverse effects, or severe adverse interactions

The dosing schedule should be discussed. Patients should understand that PRN dosing is appropriate only if pain is intermittent. When pain is persistent, as it is for most patients, the objective is to *prevent* pain from returning. Hence, dosing should be done on a fixed schedule ATC, not PRN. However, even with ATC dosing, breakthrough pain can occur. Hence, patients should be taught what drug and dosage to use for rescue treatment.

Fears based on misconceptions about opioids can impair compliance, and can thereby impair pain control. The misconceptions that influence compliance the most relate to tolerance, physical dependence, addiction, and side effects. To correct

these misconceptions, and thereby dispel fears and improve compliance, the following topics should be discussed:

- *Tolerance*—Some patients fear that, because of tolerance, taking opioids now will decrease their effectiveness later. Hence, to help ensure pain relief in the future, they limit opioid use now, and thus suffer needless pain. These patients should be reassured that, if tolerance does develop, efficacy can be restored by increasing the dosage; tolerance does not mean that efficacy is lost.
- *Physical Dependence and Addiction*—Many patients fear opioid addiction, and hence are reluctant to take these drugs. This fear is based largely on the misconception that physical dependence (which eventually develops in all patients) equals addiction. Patients should be taught that physical dependence is not the same as addiction, and that physical dependence itself is nothing to fear. In addition, they should be taught that the behavior pattern that constitutes addiction rarely develops in people who take opioids in a therapeutic setting.
- *Fear of Severe Side Effects*—Some patients fear that opioids cannot relieve pain without causing severe side effects. These patients should be reassured that, when used correctly, opioids are both safe and effective. The most dangerous side effect—respiratory depression—is uncommon.

The rationale for using an adjuvant analgesic should be discussed. With all of the adjuvants, the objective is to *complement* the effects of opioid and nonopioid analgesics. Adjuvants are not intended to substitute for these drugs. Furthermore, because the drugs we use as adjuvants were originally developed to treat disorders other than pain, the rationale for prescribing specific adjuvants should be explained. For example, when imipramine is prescribed, the patient should understand that the objective is to relieve neuropathic pain and not depression, the disorder for which this drug was originally developed.

Basic issues related to patient education in drug therapy are discussed at length in Chapter 2.

Nondrug Therapy

Education regarding nondrug therapy focuses on psychosocial interventions. Patients should understand that these interventions are intended as complements to analgesics—not as alternatives. Techniques for imagery, relaxation, and distraction should be introduced early in treatment. Family caregivers should be taught how to apply heat and cold and how to give a therapeutic massage. Patients should be informed about the benefits of peer support groups and given assistance in locating one.

THE JOINT COMMISSION PAIN MANAGEMENT STANDARDS

Thanks to *The Joint Commission* (TJC)—formerly known as the *Joint Commission on Accreditation of Healthcare Organizations* (JCAHO)—undertreatment of pain will no longer be tolerated. For readers who may not know, TJC is the authority that accredits hospitals and other healthcare institutions in the United States. On January 1, 2001, TJC established a set of standards designed to make assessment and

management of pain a priority in the nation's healthcare system. Under the standards, accountability for pain management is shifted from individual practitioners to the institution as a whole. Compliance is mandatory: Healthcare organizations that fail to meet the standards will lose accreditation. This is serious. Why? Because loss of accreditation would mean loss of insurance reimbursement, and would disqualify teaching hospitals from offering training programs. Hence, thanks to the enforcement power wielded by TJC, healthcare institutions in the United States now have a very real incentive to correct the persistent problem of pain undertreatment. It should be noted that the standards are *not* a guideline on how to treat specific kinds of pain. Rather, they focus on (1) the rights of patients to receive appropriate assessment and management of pain and (2) ways for institutions to establish a formalized, systematic approach to pain management that involves interdisciplinary teams whose members have clearly identified responsibilities. Specific provisions include the following:

- Institutions must recognize assessment and management of pain as a right of all patients.
- Institutions must assess all patients for pain and, if pain is present, identify its nature and intensity.
- Pain must be regarded as a "fifth vital sign," and pain in-

- tensity must be quantified and recorded along with blood pressure, heart rate, respiration, and temperature.
- Institutions must educate patients and their families about pain management, and must provide ready access to educational materials.
- Institutions must educate clinical staff about assessment and management of pain and must document the education provided.
- Institutions must establish a system to monitor pain management, including a system of checks and balances in which individuals who assess and manage pain are monitored for compliance with standards set by the institution.
- Institutions must monitor patient satisfaction with pain management.
- Discharge planning must provide for continuing reassessment and management of pain.

Where can you find the new standards? Unfortunately, they don't exist as a separate document. Rather, TJC has inserted content related to pain management throughout existing manuals, including the *Comprehensive Accreditation Manual for Hospitals: The Official Handbook*. If you don't want to search through the manuals, a summary is available: *Pain Assessment and Management: An Organizational Approach*, published by Joint Commission Resources, Inc.

KEY POINTS

- Cancer pain can be relieved in 90% of patients.
- Despite the availability of effective treatments, cancer pain goes unrelieved in a large number of patients.
- Barriers to pain relief include inadequate prescriber training, fears of addiction, and a healthcare system that, until recently, has put a low priority on pain management.
- Pain is a personal, subjective experience that encompasses not only the sensory perception of pain but also the patient's emotional and cognitive responses to both the painful sensation and the underlying disease.
- Pain has two major forms: nociceptive pain, which results from injury to tissues, and neuropathic pain, which results from injury to peripheral nerves.
- Management of cancer pain is an ongoing process that involves repeated cycles of assessment, intervention, and reassessment. The goal is to create an individualized treatment plan that can meet the changing needs of the patient.
- The patient self-report is the cornerstone of assessment.
- Behavioral observation is a poor substitute for the patient self-report as a method of assessment.
- Analgesic drugs are the principal modality for treating cancer pain.
- Three groups of analgesics are employed: nonopioid analgesics (NSAIDs and acetaminophen), opioid analgesics, and adjuvant analgesics.
- Drug selection is guided by the WHO analgesic ladder: As pain intensity increases, treatment progresses from nonopioid analgesics to opioids of moderate strength (eg, oxycodone), and then to powerful opioids (eg, morphine). Adjuvant analgesics can be used at any time. If pain is already intense, treatment can start with an opioid, rather than trying a nonopioid first.
- Because nonopioids and opioids relieve pain by different mechanisms, combining an opioid with a nonopioid can be more effective than either drug alone.
- NSAIDs produce their effects by inhibiting cyclooxygenase (COX), an enzyme with two basic forms: COX-1 and COX-2.
- Most NSAIDs inhibit both COX-1 and COX-2. A few NSAIDs are COX-2 selective.
- Principal adverse effects of the NSAIDs are GI injury, acute renal failure, and bleeding. In addition, all NSAIDs except aspirin pose a risk of thrombotic events.
- The COX-2 inhibitors cause less GI injury than the nonselective NSAIDs, but they pose a greater risk of thrombotic events. Accordingly, long-term use of COX-2 inhibitors is not recommended.
- By inhibiting platelet aggregation, NSAIDs increase the risk of bruising and bleeding in patients with thrombocytopenia, a common side effect of cancer chemotherapy.
- In contrast to opioids, NSAIDs do not cause tolerance, physical dependence, or psychologic dependence.
- Acetaminophen relieves pain but, unlike the NSAIDs, does not suppress inflammation, inhibit platelet aggregation, or promote gastric ulceration or renal failure.
- Because acetaminophen does not affect platelets, the drug is safe for patients with thrombocytopenia.
- Combining acetaminophen with alcohol, even in moderate amounts, can result in potentially fatal liver damage.

- Opioids are the most effective analgesics available, and hence are the primary drugs for treating moderate to severe cancer pain.
- Opioids are especially effective against nociceptive pain; efficacy against neuropathic pain is limited.
- Opioid analgesics relieve pain by mimicking the actions of endogenous opioid peptides (enkephalins, dynorphins, endorphins), primarily at mu receptors in the CNS.
- The opioids fall into two major groups: pure (full) agonists (eg, morphine) and agonist-antagonists (eg, butorphanol).
- There is a ceiling to pain relief with the agonist-antagonists, but not with the pure agonists. Hence, for patients with cancer, pure agonists are generally preferred.
- For most patients, opioids should be given on a fixed schedule ATC, with additional doses provided for breakthrough pain. PRN dosing should be limited to patients with intermittent pain.
- Oral administration is preferred for most patients; transdermal administration is a good alternative.
- Intramuscular opioids are painful and should be avoided.
- PCA is a desirable method of opioid delivery because it gives patients more control over their treatment.
- An equianalgesia table can facilitate dosage selection when switching from one opioid to another or from one route to another.
- Over time, opioids cause tolerance, a state in which a specific dose produces a smaller effect than it could when treatment began.
- Tolerance develops to analgesia, euphoria, respiratory depression, and sedation, but not to constipation.
- Over time, opioids produce physical dependence, a state in which an abstinence syndrome will occur if the drug is abruptly withdrawn. *Note:* Physical dependence is NOT the same as addiction!
- Addiction is a behavior pattern characterized by continued use of a psychoactive substance despite physical, psychologic, or social harm. *Note:* Addiction is NOT the same as physical dependence!
- Addiction to opioids is very rare in people taking these drugs to relieve pain.
- Misconceptions about opioid addiction are a major cause for undertreatment of cancer pain. Accordingly, we must correct these misconceptions by teaching physicians, nurses, patients, and family members that (1) addiction is not the same as physical dependence and (2) addiction is very rare in therapeutic settings.
- Respiratory depression is the most dangerous side effect of the opioids. Fortunately, significant respiratory depression is rare.
- Respiratory depression is increased by other drugs with CNS-depressant actions (eg, alcohol, barbiturates, benzodiazepines). Accordingly, combining these agents with opioids should be avoided.
- Severe respiratory depression can be reversed with naloxone [Narcan], an opioid antagonist. However, because excessive naloxone will reverse opioid analgesia and precipitate withdrawal, dosage must be titrated carefully.
- Opioids cause constipation in most patients. No tolerance develops. Constipation can be minimized by increasing dietary fiber and fluids, and by taking one or more appropriate drugs: stool softener, stimulant laxative, osmotic laxative, peripherally acting opioid antagonist.
- Use of meperidine (a pure opioid agonist) should be limited to a few days because, with longer use, a toxic metabolite can accumulate.
- Agonist-antagonist opioids must not be given to patients taking pure opioid agonists because doing so could reduce analgesia and precipitate withdrawal.
- Adjuvant analgesics can enhance analgesia from opioids, help manage concurrent symptoms that exacerbate pain, and treat side effects caused by opioids. In addition, several adjuvants are effective against neuropathic pain.
- Adjuvant analgesics are given to complement the effects of opioids. Accordingly, these drugs are employed in combination with opioids—not as substitutes.
- Invasive therapies (nerve blocks, neurosurgical procedures, radiation) are the last resort for relieving intractable pain. All other options should be exhausted before these are tried.
- Physical interventions (eg, heat, cold, massage, acupuncture, TENS) and psychosocial interventions (eg, relaxation, imagery, cognitive distraction, peer support groups) can help reduce pain, but the degree of relief is limited. Accordingly, these interventions should be used only in conjunction with drug therapy—not as substitutes.
- Elderly patients are more sensitive to drugs than are younger adults. The principal reason is drug accumulation secondary to a decline in hepatic metabolism and renal excretion.
- Undertreatment of pain is especially common in the elderly. Undertreatment is inexcusable and must not be allowed.
- The elderly are at risk of increased side effects and adverse drug interactions. Careful drug selection and monitoring can minimize risk.
- Management of cancer pain in children is much like management in adults, except that assessment is more difficult.
- For children who can verbalize and are older than 4 years, self-reporting is the most reliable way to assess pain. The self-report can be supplemented with behavioral observation to enhance accuracy.
- Preverbal and nonverbal children cannot self-report pain, and hence a less reliable assessment method must be used. The principal option is behavioral observation, a method that carries a significant risk of underassessment.
- When opioid abusers get cancer, they feel pain and need relief like anyone else. If their pain is sufficient to justify opioids, then opioids should be used—nonopioids should not be substituted for opioids out of concern for addiction.
- Pain management standards from TJC are designed to make pain relief an institutional priority, and hence should greatly reduce the incidence of pain undertreatment.

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Drugs for Headache

MIGRAINE HEADACHE

Characteristics, Pathophysiology, and Overview of Treatment

Abortive Therapy

Analgesics

Ergot Alkaloids

Serotonin_{1B/1D} Receptor Agonists (Triptans)

Other Abortive Agents

Preventive Therapy

Beta Blockers

Antiepileptic Drugs

Tricyclic Antidepressants

Estrogens and Triptans for Menstrual Migraine

Other Drugs for Prophylaxis

CLUSTER HEADACHES

TENSION-TYPE HEADACHE

 Box 30-1. Medication Overuse Headache: Too Much of a Good Thing

Headache is a common symptom that can be triggered by a variety of stimuli, including stress, fatigue, acute illness, and sensitivity to alcohol. Many people experience mild, episodic headaches that can be relieved with over-the-counter medica-

tions, such as aspirin, acetaminophen [Tylenol, others], and ibuprofen [Motrin, Advil, others]. For these individuals, medical intervention is unnecessary. In contrast, some people experience severe, recurrent, debilitating headaches that are frequently unresponsive to aspirin-like drugs. For these individuals, medical attention is merited. In this chapter, we focus on severe forms of headache—specifically, migraine, cluster, and tension-type headaches. Defining characteristics of these headaches are summarized in Table 30-1.

When attempting to treat headache, we must differentiate between headaches that have an identifiable underlying cause (eg, severe hypertension; hyperthyroidism; tumors; infection; disorders of the eye, ear, nose, sinuses, and throat) and headaches that have no identifiable cause (eg, migraine and cluster headaches). Obviously, if there is a clear cause, it should be treated directly.

As we consider drugs for headache, keep three basic principles in mind. First, antiheadache drugs may be used in two ways: to abort an ongoing attack or to prevent an attack from occurring. Second, not all patients with a particular type of headache respond to the same drugs. Hence, therapy must be individualized. Third, several of the drugs employed to treat severe headaches (eg, ergotamine, opioids) can cause physical dependence. Accordingly, every effort should be made to keep dependence from developing. If dependence does develop, a withdrawal procedure is needed.

TABLE 30-1 ■ Characteristics of Major Headache Syndromes

	Migraine	Cluster Headache	Tension-type Headache
Pain Location	Unilateral (60%) Bilateral (40%)	Unilateral, behind the right or left eye	Bilateral, in “headband” configuration
Pain Quality	Throbbing	Throbbing, sometimes piercing	Nonthrobbing
Pain Severity	Moderate to severe	Severe	Mild to moderate
Duration	4 hr to 3 days	15 min to 2 hr*	30 min to 7 days [†]
Impact of Activity	Makes pain worse	None	None
Associated Symptoms	Nausea, vomiting, photophobia, phonophobia, neck pain	Conjunctival redness, lacrimation, nasal congestion, rhinorrhea, ptosis, miosis—all on the same side as the headache	Uncommon
Usual Time of Onset	Early morning	Nighttime	Daytime
Preceded by Aura	Yes, in 30% of cases	No	No
Triggers	Many (see Table 30-2)	Usually unidentified	Tension, anxiety
Gender Prevalence	More common in females	More common in males	Slightly more common in females
Family History	Likely	Unlikely	Unlikely
Impact on Daily Life	Often substantial	Usually substantial	Minimal

*Headaches occur in clusters that typically consist of one or more headaches (lasting 15 minutes to 2 hours) every day for 2 to 3 months, with a headache-free interval (months to years) between each cluster.

[†]Chronic tension headaches occur at least 15 days/month for 6 months or longer.

MIGRAINE HEADACHE

CHARACTERISTICS, PATHOPHYSIOLOGY, AND OVERVIEW OF TREATMENT

Characteristics

Migraine headache is characterized by throbbing head pain of moderate to severe intensity that may be unilateral (60%) or bilateral (40%). Most patients also experience nausea and vomiting, along with neck pain and sensitivity to light and sound. Physical activity intensifies the pain. During a prolonged attack, patients develop hyperalgesia (augmented responses to painful stimuli) and allodynia (painful responses to normally innocuous stimuli). Migraines usually develop in the morning after arising. Pain increases gradually and lasts 4 to 72 hours (median duration 24 hours). On average, attacks occur 1.5 times a month. Precipitating factors include anxiety, fatigue, stress, menstruation, alcohol, weather changes, and tyramine-containing foods (Table 30-2).

Migraine has two primary forms: migraine *with aura* and migraine *without aura*. In migraine with aura, the headache is preceded by visual symptoms (flashes of light, a blank area in the field of vision, zigzag patterns). Of the two forms, mi-

TABLE 30-2 ■ Factors That Can Precipitate Migraine Headache

Emotions

Stress
Anticipation
Anxiety
Depression
Excitement
Frustration

Foods That Contain:

Tyramine (eg, aged cheeses, Chianti wine)
Nitrates (eg, cured meat products)
Phenylethylamine (eg, chocolate)
Monosodium glutamate (eg, Chinese food, canned soups)
Aspartame (eg, diet sodas, artificial sweeteners)
Yellow food coloring

Drugs

Alcohol
Analgesics (excessive use or withdrawal)
Caffeine (excessive use or withdrawal)
Cimetidine
Cocaine
Estrogens (eg, oral contraceptives)
Nitroglycerin

Weather

Low temperature and low humidity
High temperature and high humidity
Major weather change over 1-2 days
High or low barometric pressure

Others

Carbon monoxide
Hormonal changes in females
Flickering lights
Glare
Loud noises
Hypoglycemia
Change in altitude

graine without aura is more common, affecting about 70% of migraineurs.

Migraine afflicts 29.5 million people in the United States and 324 million worldwide. The headaches are more common and more severe in females, with a lifetime incidence of 43%, compared with 18% in males. About 65% of migraineurs are women in their late teens, 20s, or 30s. With some women, migraine attacks are worse during menstruation but subside during pregnancy and cease after menopause, indicating a hormonal component to the attacks. A family history of the disease is typical.

Migraine is highly debilitating. An attack can prevent participation in social and leisure activities, and can result in lost productivity at home, school, and work. According to the World Health Organization, disability caused by a severe migraine attack equals that caused by quadriplegia, psychosis, or dementia.

Pathophysiology

Migraine headache is a *neurovascular* disorder that involves *dilation* and *inflammation* of intracranial blood vessels. Headache generation begins with neural events that trigger vasodilation. Vasodilation then leads to pain, which leads to further neural activation, thereby amplifying pain-generating signals. Neurons of the trigeminal vascular system, which innervate intracranial blood vessels, are key components.

The exact cause of migraine pain is not completely understood—although vasodilation and inflammation are clearly involved. Available data suggest that two compounds—*calcitonin gene-related peptide* (CGRP) and *serotonin* (5-hydroxytryptamine [5-HT])—play important roles. The role of CGRP is to *promote migraine*, and the role of 5-HT is to *suppress* migraine. Data that implicate CGRP as a cause of migraine include the following:

- Plasma levels of CGRP rise during a migraine attack.
- Stimulation of neurons of the trigeminal vascular system promotes release of CGRP, which in turn promotes vasodilation and release of inflammatory neuropeptides.
- Dosing with sumatriptan, a drug that relieves migraine, lowers elevated levels of CGRP.
- Sumatriptan can suppress release of CGRP from cultured trigeminal neurons.

Data that support a protective role for 5-HT include the following:

- Plasma levels of 5-HT drop by 50% during a migraine attack.
- Depletion of 5-HT with reserpine can precipitate an attack in migraine-prone individuals.
- Administration of 5-HT or sumatriptan, both of which activate 5-HT receptors, can abort an ongoing attack.

Overview of Treatment

Drugs for migraine are employed in two ways: to abort an ongoing attack and to prevent attacks from occurring. Drugs used to abort an attack fall into two groups: nonspecific analgesics (aspirin-like drugs and opioid analgesics) and migraine-specific drugs (ergot alkaloids and serotonin_{1B/1D} receptor agonists [triptans]). Drugs employed for prophylaxis include beta blockers (eg, propranolol), tricyclic antidepressants (eg, amitriptyline), and antiepileptic drugs (eg, divalproex).

Nondrug measures can help. Patients should try to control or eliminate triggers (see Table 30-2) and should maintain a regular pattern of eating, sleeping, and exercise. Why? Because, in people with migraine, the brain seems to have a low tolerance for the ups and downs of life. Once an attack has begun, the migraineur should retire to a dark, quiet room. Placing an ice pack on the neck and scalp can help.

ABORTIVE THERAPY

The objective of abortive therapy is to eliminate headache pain and suppress associated nausea and vomiting. Treatment should commence at the earliest sign of an attack. Because migraine causes GI disturbances (nausea, vomiting, and gastric stasis), oral therapy may be ineffective once an attack has begun. Hence, for treatment of an established attack, a drug that can be administered by injection, nasal spray, or rectal suppository may be best. As noted, two types of drugs are used: nonspecific analgesics and migraine-specific agents. Representative drugs are listed in Table 30-3.

Drug selection depends on the intensity of the attack. For mild to moderate symptoms, an *aspirin-like drug* (eg, aspirin, naproxen, acetaminophen) may be sufficient. For moderate to severe symptoms, patients should take a migraine-specific drug—either an *ergot alkaloid* (ergotamine or dihydroergotamine) or a *serotonin_{1B/1D}* agonist. If these agents fail to relieve pain, an *opioid analgesic* (eg, butorphanol, meperidine) may be needed.

Use of abortive medications (both nonspecific and migraine specific) should be limited to 1 or 2 days a week. Why? Because more frequent use can lead to *medication overuse headache* (MOH), also known as drug-induced headache or drug-rebound headache (Box 30-1).

Antiemetics are important adjuncts to migraine therapy. By reducing nausea and vomiting, these drugs can (1) make the patient more comfortable and (2) permit therapy with oral antimigraine drugs. Two antiemetics—*metoclopramide* [Reglan] and *prochlorperazine* (formerly available as *Compazine*)—are used most often. Of the two, metoclopramide is preferred. Why? Because, in addition to suppressing nausea and vomiting, metoclopramide can reverse gastric stasis caused by the attack, and can thereby facilitate absorption of oral antimigraine drugs. Like metoclopramide, prochlorperazine suppresses nausea and vomiting. However, because of its anticholinergic actions, prochlorperazine can make gastric stasis even worse.

Analgesics

Aspirin-like Drugs

Aspirin, acetaminophen, naproxen, diclofenac, and other aspirin-like analgesics can provide adequate relief of mild to moderate migraine attacks. In fact, when combined with metoclopramide (to enhance absorption), aspirin may work as well as sumatriptan, a highly effective antimigraine drug. Moreover, the combination of aspirin plus metoclopramide costs less than sumatriptan and causes fewer adverse effects.

Acetaminophen should be used only in combination with other drugs, not alone. One effective combination, marketed as *Excedrin Migraine*, consists of acetaminophen, aspirin, and caffeine. An older and less effective combination—acetaminophen, isometheptene (a sympathomimetic drug), and dichlo-

TABLE 30-3 ■ Migraine Headache: Drugs for Abortive Therapy

NONSPECIFIC ANALGESICS

Aspirin-like Drugs

Nonsteroidal anti-inflammatory drugs (eg, aspirin, naproxen, diclofenac)

Acetaminophen + Aspirin + Caffeine [Excedrin Migraine]

Opioid Analgesics

Butorphanol

Meperidine [Demerol]

MIGRAINE-SPECIFIC DRUGS

Ergot Alkaloids

Dihydroergotamine [D.H.E. 45, Migranal]

Ergotamine [Ergomar]

Ergotamine + Caffeine [Cafergot, Migergot]

Selective Serotonin_{1B/1D} Receptor Agonists (Triptans)

Almotriptan [Axert]

Frovatriptan [Frova]

Naratriptan [Amerge]

Eletriptan [Relpax]

Rizatriptan [Maxalt]

Sumatriptan [Imitrex, Sumavel DosePro]

Zolmitriptan [Zomig]

ralphenazone (a sedative)—marketed as *Midrin*, has been withdrawn.

Opioid Analgesics

Opioid analgesics are reserved for severe migraine that has not responded to first-line medications. The agents used most often are *meperidine* [Demerol] and *butorphanol nasal spray* (formerly available as *Stadol NS*). Of the two, butorphanol is preferred. Why? Because meperidine can cause all of the adverse effects associated with other pure opioid agonists (eg, respiratory depression, sedation, constipation) and also has significant abuse potential. These drawbacks are less pronounced with butorphanol.

Ergot Alkaloids

Ergotamine

Mechanism of Antimigraine Action. Ergotamine [Ergomar] has complex actions, and the precise mechanism by which it aborts migraine is unknown. Ergotamine can alter transmission at serotonergic, dopaminergic, and alpha-adrenergic junctions. Current evidence suggests that antimigraine effects are related to agonist activity at subtypes of serotonin receptors, specifically 5-HT_{1B} and 5-HT_{1D} receptors. Additional evidence indicates that ergotamine can block inflammation associated with the trigeminal vascular system, perhaps by suppressing release of CGRP. Relief may also be related to vascular effects. In cranial arteries, ergotamine acts directly to promote constriction and reduce the amplitude of pulsations. In addition, the drug can affect blood flow by depressing the vasomotor center.

Therapeutic Uses. Ergotamine is a drug of choice for stopping an ongoing migraine attack. Owing to the risk of dependence (see below), ergotamine should not be taken daily on a long-term basis.

Si

MEDICATION OVERUSE HEADACHE: TOO MUCH OF A GOOD THING

People who take headache medicine every day often develop medication overuse headaches (MOHs), also known as drug-rebound headaches or drug-induced headaches. What's a MOH? A chronic headache that develops in response to frequent use of headache medicines, and that resolves days to weeks after the overused drug is withdrawn. The stage for MOH is set when headache drugs are taken too often—especially if the dosage is high. Once the stage has been set, discontinuing the medication brings on the MOH, which causes the patient to resume taking medicine—thereby setting up a repeating cycle of MOH, followed by medication use and discontinuation, followed by another MOH, and so on. One reason the cycle gets established is that patients don't realize that the drugs they're taking to *treat* headache can, if taken too often, become the *cause* of headache. Failing to recognize MOH for what it is, patients take more and more medicine to make their headaches go away—but only succeed in making MOH worse.

Which drugs can cause MOH? Almost all of the medicines used for abortive headache therapy. Hence, MOH can be caused by overuse of analgesics (aspirin-like drugs, opioids), ergotamine (but not dihydroergotamine), triptans, and caffeine.

How can MOH be treated? The only hope is to stop taking all headache medicines. Unfortunately, when medication is withdrawn, headaches will increase for a while. Their duration and intensity depend on the drug that was overused. With triptans, withdrawal headaches are relatively mild and often resolve in a few days. In contrast, with analgesics or ergots, withdrawal headaches are more intense and may persist for 2 weeks or more.

Pharmacokinetics. Administration may be oral, sublingual, or rectal. Bioavailability with oral and sublingual administration is low. Bioavailability with rectal administration is higher. Although the half-life of ergotamine is only 2 hours, pharmacologic effects can still be observed 24 hours after dosing. Ergotamine undergoes metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450) followed by excretion in the bile.

Adverse Effects. Ergotamine is well tolerated at usual therapeutic doses. The drug can stimulate the chemoreceptor trigger zone, causing *nausea and vomiting* in about 10% of patients, thereby augmenting nausea and vomiting caused by the migraine itself. Concurrent treatment with metoclopramide or a phenothiazine antiemetic (eg, prochlorperazine) can help reduce these responses. Other common side effects include *weakness in the legs, myalgia, numbness and tingling in the fingers and toes, angina-like pain, and tachycardia or bradycardia.*

Overdose. Acute or chronic overdose can cause serious toxicity referred to as *ergotism*. In addition to the adverse effects seen at therapeutic doses, overdose can cause ischemia secondary to constriction of peripheral arteries and arterioles: the extremities become cold, pale, and numb; muscle pain develops; and gangrene may eventually result. Patients should be informed about these responses and instructed to seek immediate medical attention if they develop. The risk of ergotism is highest in patients with sepsis, peripheral vascular disease, and renal or hepatic impairment. Management consists of discontinuing ergotamine, followed by measures to maintain circula-

tion (treatment with anticoagulants, low-molecular-weight dextran, and/or intravenous nitroprusside as appropriate).

Is there a way to make withdrawal more comfortable? Yes. In 2010, Italian researchers published a new protocol, consisting of abrupt discontinuation of the overused drug, plus 7 to 15 days of the following treatment:

- IV hydration (1000 to 1500 mL of saline solution)
- IV dexamethasone (8 mg/day)
- IV metoclopramide (10 mg/day)
- IV benzodiazepines (eg, diazepam, 5 to 15 mg/day)

If a severe withdrawal headache occurred during the procedure, patients were allowed a single rescue medication, but always a drug different from the one they had overused. Not only did this procedure reduce the discomfort of medication withdrawal, it produced a sustained reduction in medication use.

Several measures can decrease the risk of developing MOH. The most important is to limit the use of abortive medicines. If possible, patients should take these drugs no more than 2 or 3 times a week—and doses should be no higher than actually needed. Alternating headache medicines may help too, since this would limit exposure to any one drug. If headaches begin to occur more than 2 or 3 times a month, prophylactic therapy should be tried. Implementing nondrug measures—stress reduction, avoidance of triggers, getting sufficient sleep, relaxation techniques, and biofeedback—can reduce the need for headache medicines, and can thereby decrease exposure to the drugs that cause MOH.

Drug Interactions. **Triptans.** Ergotamine should not be combined with triptans (eg, sumatriptan, zolmitriptan) because a prolonged vasospastic reaction could occur. To avoid this problem, dosing with ergotamine and serotonin agonists should be separated by at least 24 hours.

CYP3A4 Inhibitors. Potent inhibitors of CYP3A4 can raise ergotamine to dangerous levels, posing a risk of intense vasospasm. Cerebral and/or peripheral ischemia can result. Accordingly, concurrent use with CYP3A4 inhibitors is contraindicated. Drugs to avoid include certain HIV protease inhibitors (eg, ritonavir, nelfinavir), azole antifungal drugs (eg, ketoconazole, itraconazole), and macrolide antibiotics (eg, erythromycin, clarithromycin). Less potent inhibitors (eg, saquinavir, nefazodone, fluconazole, grapefruit juice) should be used with caution.

Physical Dependence. Regular daily use of ergotamine, even in moderate doses, can cause physical dependence. The withdrawal syndrome is characterized by headache, nausea, vomiting, and restlessness. That is, withdrawal resembles a migraine attack. Patients who experience these symptoms are likely to resume taking the drug, thereby perpetuating the cycle of dependence. Hospitalization may be required to break the cycle. To avoid dependence, dosage and duration of treatment must be restricted (see dosing guidelines below).

Contraindications. Ergotamine is contraindicated for patients with hepatic or renal impairment, sepsis (gangrene has re-

sulted), coronary artery disease (CAD), and peripheral vascular disease, and for those taking potent inhibitors of CYP3A4. In addition, the drug should not be taken during pregnancy. Why? Ergotamine can promote uterine contractions, and hence might cause fetal harm or abortion. In fact, because of its effects on the uterus, ergotamine is classified in Food and Drug Administration (FDA) Pregnancy Risk Category X: The risk of use by pregnant women clearly outweighs any possible benefits. Warn women of child-bearing age to avoid pregnancy while using this drug.

Preparations, Dosage, and Administration. Ergotamine by itself is available in tablets for sublingual use. In addition, ergotamine is available in combination with caffeine for oral and rectal dosing.

Sublingual. Ergotamine tartrate [Ergomar] is supplied in 2-mg tablets for sublingual use. One tablet should be placed under the tongue immediately after onset of aura or headache. If needed, additional tablets can be administered at 30-minute intervals—up to a maximum of 3 tablets/24 hr or 5 tablets/wk.

Oral. Tablets for oral dosing, sold as *Caférgot*, contain 1 mg ergotamine tartrate and 100 mg caffeine. Two tablets are taken immediately after onset of aura or headache. One additional tablet can be administered every 30 minutes—up to a maximum of 6 per attack or 10 per week.

Rectal. Suppositories for rectal dosing, sold as *Migergot*, contain 2 mg ergotamine tartrate and 100 mg caffeine. No more than 2 suppositories should be administered per attack.

Dihydroergotamine

Therapeutic Uses. Parenteral dihydroergotamine [D.H.E. 45, Migranal]—given IM, IV, or subQ—is a drug of choice for terminating a migraine attack. The drug also may be given by intranasal spray. A formulation for oral inhalation is in development. Intranasal dihydroergotamine is less effective than intranasal sumatriptan (see below), but is associated with a lower rate of migraine recurrence.

Pharmacologic Effects. The actions of dihydroergotamine are similar to those of ergotamine. Like ergotamine, dihydroergotamine alters transmission at serotonergic, dopaminergic, and alpha-adrenergic junctions. In contrast to ergotamine, dihydroergotamine causes little nausea and vomiting, no physical dependence, and minimal peripheral vasoconstriction (when used alone). Diarrhea, however, is prominent.

Pharmacokinetics. Dihydroergotamine may be administered parenterally or by nasal spray—but not by mouth (owing to extensive first-pass metabolism). In the liver, the drug is metabolized by CYP3A4. An active metabolite (8'-hydroxydihydroergotamine) contributes to therapeutic effects. The half-life of dihydroergotamine plus the active metabolite is about 21 hours.

Drug Interactions. As with ergotamine, dihydroergotamine should not be combined with potent inhibitors of CYP3A4, and should not be administered within 24 hours of a serotonin agonist (eg, sumatriptan).

Contraindications. Like ergotamine, dihydroergotamine is contraindicated for patients with CAD, peripheral vascular disease, sepsis, pregnancy, and hepatic or renal impairment, and for patients taking triptans or potent inhibitors of CYP3A4.

Parenteral Administration. Dihydroergotamine mesylate [D.H.E. 45] is available in solution (1 mg/mL) for IM, IV, and subQ administration.

Intramuscular and Subcutaneous. The initial dose is 1 mg immediately after symptom onset. Additional 1-mg doses may be given hourly—but the total dose should not exceed 3 mg/24 hr for IM or subQ administration, or 2 mg/24 hr for IV administration. With all routes, the total dose should not exceed 6 mg/wk.

Intravenous. One milligram is given initially, followed by 1 mg an hour later if needed. Dosage should not exceed 2 mg/24 hr or 6 mg/wk.

Intranasal Administration. The nasal spray device [Migranal] delivers 0.5 mg of dihydroergotamine per actuation. The dosage is 1 spray in each

nostril, repeated in 15 minutes, for a total of 2 mg. Pain is relieved in 60% of patients within 2 hours. The 24-hour recurrence rate is 15%.

Oral Inhalation. Dihydroergotamine for oral inhalation, using the breath-activated *Tempo* inhaler, is in development. In clinical trials, the dosage has been 0.5 or 1 mg, inhaled once after migraine onset.

Serotonin_{1B/1D} Receptor Agonists (Triptans)

The serotonin_{1B/1D} receptor agonists, also known as *triptans*, are first-line drugs for terminating a migraine attack. These agents relieve pain by constricting intracranial blood vessels and suppressing release of inflammatory neuropeptides. All are well tolerated. Rarely, they cause symptomatic coronary vasospasm.

Sumatriptan

Sumatriptan [Imitrex, Sumavel DosePro] was the first triptan available and will serve as our prototype for the group. The drug can be administered by mouth, nasal inhalation, or subQ injection. A transdermal patch [Zelrix] is in development.

Mechanism of Action. Sumatriptan, an analog of 5-HT, causes selective activation of 5-HT_{1B} and 5-HT_{1D} receptors (5-HT_{1B/1D} receptors). The drug has no affinity for 5-HT₂ or 5-HT₃ receptors, nor does it bind to adrenergic, dopaminergic, muscarinic, or histaminergic receptors. Binding to 5-HT_{1B/1D} receptors on intracranial blood vessels causes vasoconstriction. Binding to 5-HT_{1B/1D} receptors on sensory nerves of the trigeminal vascular system suppresses release of CGRT, a compound that promotes release of inflammatory neuropeptides. As a result, sumatriptan reduces release of inflammatory neuropeptides, and thereby diminishes perivascular inflammation. Both actions—vasoconstriction and decreased perivascular inflammation—help relieve migraine pain.

Therapeutic Use. Sumatriptan is taken to abort an ongoing migraine attack. The drug relieves headache and associated symptoms (nausea, neck pain, photophobia, phonophobia). In clinical trials, sumatriptan gave complete relief to the majority of patients. Beneficial effects begin about 15 minutes after subQ or intranasal dosing, and 30 to 60 minutes after oral dosing. Complete relief occurs in 70% to 80% of patients 2 hours after subQ dosing, in 60% of patients 2 hours after intranasal dosing, and in 50% to 60% of patients 4 hours after oral dosing. Unfortunately, headache returns in about 40% of patients within 24 hours. In comparison, the 24-hour recurrence rate with dihydroergotamine is only 18%. In patients who respond to subQ sumatriptan, subsequent administration of oral sumatriptan can delay recurrence but does not prevent it. In addition to migraine, sumatriptan is approved for cluster headaches.

Pharmacokinetics. With oral or intranasal dosing, bioavailability is low (about 15%), whereas with subQ dosing, bioavailability is high (97%). As a result, oral and intranasal doses are considerably higher than subQ doses. Sumatriptan undergoes extensive hepatic metabolism, primarily by monoamine oxidase (MAO), followed by excretion in the urine. The half-life is short—about 2.5 hours.

Adverse Effects. Sumatriptan is generally well tolerated. Most side effects are transient and mild. Coronary vasospasm is the biggest concern.

Chest Symptoms. About 50% of patients experience unpleasant chest symptoms, usually described as “heavy arms” or “chest pressure” rather than pain. These symptoms are transient and *not* related to ischemic heart disease. Possible causes are

Table 30-4 ■ Clinical Pharmacology of the Triptans

Generic Name [Trade Name]	Route	Bioavailability	Onset (min)	Duration	Half-Life (hr)
Sumatriptan [Imitrex]	Oral	15%	30–60	Short	2.5
[Imitrex]	Nasal spray	17%	15–20		
[Imitrex]	SubQ, with needle	97%	10–15		
[Sumavel DosePro]	SubQ, needle-free	97%	10		
Almotriptan [Axert]	Oral	70%	30–120	Short	3–4
Eletriptan [Relpax]	Oral	50%	60	Short	4
Frovatriptan [Frova]	Oral	20%–30%	120–180	Long	26
Naratriptan [Amerge]	Oral	70%	60–180	Intermediate	6
Rizatriptan [Maxalt, Maxalt MLT]	Oral	45%	30–120	Short	2–3
Zolmitriptan [Zomig, Zomig ZMT]	Oral	40%	45	Short	3
[Zomig]	Nasal spray	41%	15		

CYP3A4 = the 3A4 isozyme of cytochrome P450, MAOIs = monoamine oxidase inhibitors, SNRIs = serotonin/norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors.

pulmonary vasoconstriction, esophageal spasm, intercostal muscle spasm, and bronchoconstriction. Patients should be forewarned of these symptoms and reassured they are not dangerous.

Coronary Vasospasm. Very rarely, sumatriptan and other triptans can cause angina secondary to coronary vasospasm. Electrocardiographic changes have been observed in patients with CAD or Prinzmetal's (vasospastic) angina. To reduce the risk of angina, avoid sumatriptan in patients with risk factors for CAD until CAD has been ruled out. These patients include postmenopausal women, men over 40, smokers, and patients with hypertension, hypercholesterolemia, obesity, diabetes, or a family history of CAD. Owing to the risk of coronary vasospasm, sumatriptan is contraindicated for patients with a history of ischemic heart disease, myocardial infarction (MI), uncontrolled hypertension, or other heart disease.

Teratogenesis. *Sumatriptan should be avoided during pregnancy.* When given daily to pregnant rabbits, the drug was embryolethal at blood levels only 3 times higher than those achieved with a 6-mg subQ injection in humans (a typical dose). Accordingly, unless the prescriber directs otherwise, women should be instructed to avoid the drug if they are preg-

nant or think they might be, if they are trying to become pregnant, or if they are not using an adequate form of contraception. Sumatriptan is classified in FDA Pregnancy Risk Category C.

Other Adverse Effects. Mild reactions include *vertigo, malaise, fatigue, and tingling sensations.* Transient pain and redness may occur at sites of subQ injection. The intranasal formulation tastes bad and may irritate the nose and throat.

Drug Interactions. Ergot Alkaloids and Other Triptans. Sumatriptan, other triptans, and ergot alkaloids (eg, ergotamine, dihydroergotamine) all cause vasoconstriction. Accordingly, if one triptan is combined with another or with an ergot alkaloid, excessive and prolonged vasospasm could result. Accordingly, sumatriptan should not be used within 24 hours of an ergot derivative or another triptan.

Monoamine Oxidase Inhibitors. Monoamine oxidase inhibitors (MAOIs) can suppress hepatic degradation of sumatriptan, causing its plasma level to rise. Toxicity can result. Accordingly, sumatriptan should not be combined with an MAOI, and should not be used within 2 weeks of stopping an MAOI.

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs).

Dosage	Contraindicated Drugs			Comments
	SSRIs, SNRIs, Triptans, Ergots	MAOIs	CYP3A4 Inhibitors	
25, 50, or 100 mg; may repeat in 2 hr (max. 200 mg/24 hr)	✓	✓		First triptan available and best understood. Available in three fast-acting formulations: nasal spray, an auto-injector for subQ dosing (using a needle), and a needle-free device for subQ dosing [Sumavel DosePro].
5 or 20 mg; may repeat in 2 hr (max. 40 mg/24 hr)				
6 mg; may repeat in 1 hr (max. 12 mg/24 hr)				
6 mg; may repeat in 1 hr (max. 12 mg/24 hr)				
6.25 or 12.5 mg; may repeat in 2 hr (max. 25 mg/24 hr)	✓			Incidence of chest discomfort (pain, tightness, pressure) is lower than with other triptans. Decrease dosage if combined with a CYP3A4 inhibitor.
20 or 40 mg; may repeat in 2 hr (max. 40 mg/24 hr)	✓		✓	Bioavailability increased by high-fat meal. Good balance between fast onset and long duration.
2.5 mg; may repeat in 2 hr	✓			Slowest onset, longest half-life, and lowest rate of headache recurrence. Decrease dose if combined with propranolol.
1 or 2.5 mg; may repeat in 4 hr (max. 5 mg/24 hr)	✓			Slower onset and longer duration than most triptans.
5 or 10 mg; may repeat in 2 hours (max. 30 mg/24 hr)	✓	✓		May be the most consistently effective triptan. Decrease dose if combined with propranolol. Available in melt-in-the-mouth wafers [Maxalt MLT] that can be taken without water.
2.5 or 5 mg; may repeat in 2 hr (max. 10 mg/24 hr)	✓	✓		Available in a fast-acting nasal spray, and in melt-in-the-mouth wafers [Zomig ZMT] that can be taken without water.
5 mg; may repeat in 2 hr (max. 10 mg/24 hr)				

As discussed in Chapter 32 (Antidepressants), the SSRIs (eg, fluoxetine [Prozac]) and SNRIs (eg, duloxetine [Cymbalta]) indirectly activate serotonin receptors in the brain (by increasing the availability of serotonin at brain synapses). If receptor activation is excessive, serotonin syndrome can occur. Signs and symptoms include altered mental status (agitation, confusion, disorientation, anxiety, hallucinations, poor concentration) as well as incoordination, myoclonus, hyperreflexia, excessive sweating, tremor, and fever. Deaths have occurred. Since the triptans *directly* activate serotonin receptors, and the SSRIs and SNRIs *indirectly* activate serotonin receptors, you can see how combining these drugs could lead to excessive receptor activation. Accordingly, these combinations should not be used.

Preparations, Dosage, and Administration. *Subcutaneous, Using a Needle.* Sumatriptan succinate [Imitrex] for subQ injection is available in two strengths: 4 mg and 6 mg. The 4-mg strength is supplied in a STATdose Pen for self-injection. The 6-mg strength is supplied in single-dose vials as well as in a STATdose Pen. The maximum single dose is 6 mg. The maximum that may be given in 24 hours is two 6-mg doses, separated by at least 1 hour.

Subcutaneous, Using a Needle-Free Device. The sumatriptan needle-free device [Sumavel DosePro] uses pressurized nitrogen to push a sumatriptan solution (6 mg) through the skin into the subcutaneous tissue. Injections are made into the thigh or abdomen. Bioavailability and dosage are the same as when using a needle. Injection pain is the same too.

Oral. Sumatriptan [Imitrex], by itself, is available in 25-, 50-, and 100-mg tablets. The usual dose is 25 mg, but doses as high as 100 mg may be tried. If, after 2 hours, the response to the first dose is unsatisfactory, a second dose may be given.

Oral sumatriptan is also available with naproxen in fixed-dose combination tablets marketed as *Treximet* (see below).

Nasal Spray. Sumatriptan [Imitrex] is available in 5- and 20-mg unit-dose spray devices. The initial dose is 5 or 20 mg, which can be repeated in 2 hours if needed. The maximum 24-hour dose is 40 mg.

Transdermal. An investigational transdermal patch [Zelrix] uses a mild electrical current to transport sumatriptan into the skin. This process, known as iontophoresis, delivers the drug steadily over several hours, after which the patch can be replaced if needed.

Other Serotonin_{1B/1D} Receptor Agonists

In addition to sumatriptan, the triptan family includes six other drugs: naratriptan [Amerge], rizatriptan [Maxalt], zolmitriptan [Zomig], almotriptan [Axert], frovatriptan [Frova], and eletriptan [Relpax]. All six are administered orally, and one—zolmitriptan—is also given by nasal spray. All six are essentially equal to sumatriptan with respect to efficacy and safety, and all have the same mechanism of action: activation of 5-HT_{1B/1D} receptors with subsequent intracranial vasoconstriction and decreased perivascular inflammation. All are in FDA Pregnancy Risk Category C. Because the triptans are very similar, selection among them is based on differences in kinetics, side effects, and drug interactions. Dosage and time course are summarized in Table 30-4.

Zolmitriptan. Zolmitriptan [Zomig, Zomig ZMT] is indicated for terminating an ongoing migraine attack. The drug is similar to sumatriptan with regard to mechanism, efficacy, time course, side effects, and interactions.

Zolmitriptan is formulated for oral and intranasal use. Two oral preparations are available: tablets (2.5 and 5 mg), sold as *Zomig*, and melt-in-the-mouth wafers (2.5 mg), sold as *Zomig ZMT*. *Zomig ZMT* dissolves in saliva on the tongue. Since no water is needed, the drug can be taken conveniently as soon as an aura is perceived. Be aware, however, that onset of effects is no faster than with standard *Zomig* tablets. With either formulation, a 2.5-mg dose produces the most favorable response/tolerability ratio. Intranasal zolmitriptan, sold as *Zomig*, is available in a 5-mg single-dose spray device. Effects begin in 15 minutes, compared with 45 minutes for the oral products. However, although the nasal spray is faster, it does have two drawbacks: It tastes bad (albeit not as bad as sumatriptan nasal spray) and only one strength (5 mg/spray) is available. If a smaller dose is needed, an oral formulation must be used. Regardless of the formulation, about 65% of patients respond within 2 hours. If headache persists, dosing can be repeated 2 hours after the initial dose. The maximum dose per 24 hours is 10 mg. Headache recurs in 8% to 32% of patients. Adverse effects are generally mild and transient. Like sumatriptan, zolmitriptan causes harmless, transient chest discomfort. Of much greater concern, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. Like sumatriptan, zolmitriptan should not be administered within 24 hours of an ergot alkaloid or another triptan, or within 2 weeks of stopping an MAOI. To avoid serotonin syndrome, zolmitriptan should not be combined with an SSRI or SNRI.

Naratriptan. Naratriptan [Amerge] is indicated for oral therapy of an ongoing migraine attack. Compared with most other triptans, naratriptan has a slower onset and longer duration. Because effects persist, the 24-hour migraine recurrence rate may be reduced. Naratriptan is available in 1- and 2.5-mg tablets. The 2.5-mg strength is more effective but causes more side effects. The initial dose is 1 or 2.5 mg. Dosing may be repeated in 4 hours if needed. The maximum daily dose is 5 mg. Like other triptans, naratriptan causes transient chest discomfort. Also like other triptans, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, naratriptan should not be administered within 24 hours of an ergot alkaloid or another triptan. Like other triptans, naratriptan should not be combined with an SSRI or SNRI, owing to the risk of serotonin syndrome. In contrast to some triptans, naratriptan can be used safely with an MAOI.

Rizatriptan. Rizatriptan [Maxalt, Maxalt MLT] may be the most consistently effective triptan for terminating an ongoing migraine attack. The drug is similar to sumatriptan with regard to mechanism, efficacy, time course, side effects, and interactions. Rizatriptan is available in two oral formulations: standard tablets [Maxalt] and melt-in-the-mouth wafers [Maxalt MLT] that can be taken without water. Both formulations come in 5- and 10-mg strengths. The initial dose is 5 or 10 mg. Dosing may be repeated in 2 hours if needed. No more than 30 mg should be taken per day. Adverse effects are generally mild and transient. Like other triptans, rizatriptan causes harmless, transient chest discomfort. Also like other triptans, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, rizatriptan should not be administered within 24 hours of an ergot alkaloid or another triptan, or within 2 weeks of stopping an MAOI. Like other triptans, rizatriptan should not be combined with an SSRI or SNRI, owing to the risk of serotonin syndrome. Propranolol can raise levels of rizatriptan, and hence a dosage reduction may be needed. Rizatriptan may harm the developing fetus: In rats, the drug increased perinatal mortality, reduced learning capacity, and decreased pre- and post-weaning weight. However, postmarketing surveillance data suggest that, in humans, rizatriptan may not increase the risk of congenital anomalies or spontaneous abortion. Until more is known, the drug should be used with caution in pregnant women.

Almotriptan. Almotriptan [Axert] is indicated for oral therapy of an ongoing migraine attack. The drug is similar to sumatriptan with regard to mechanism, efficacy, and time course—and is better tolerated. Almotriptan is available in 6.25- and 12.5-mg tablets. The initial dose is 6.25 or 12.5 mg. Dosing can be repeated in 2 hours if headache persists. The maximum dose per 24 hours is 25 mg. Adverse effects are minimal. Like other triptans, almotriptan can cause harmless, transient chest discomfort—but the incidence is very low (only 0.3%). Also like other triptans, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. Almotriptan is metabolized by CYP3A4, and hence a dosage reduction is recommended if the drug is combined with a potent CYP3A4 inhibitor (eg, ketoconazole, itraconazole, clarithromycin, ritonavir). To avoid excessive vasospasm, almotriptan should not be administered within 24 hours of an ergot alkaloid or another triptan. Like other triptans, almotriptan should not be combined with an SSRI or

SNRI, owing to a risk of serotonin syndrome. In contrast to some triptans, almotriptan can be combined safely with an MAOI.

Frovatriptan. Frovatriptan [Frova] is indicated for oral therapy of an ongoing migraine attack. The drug is similar to other triptans with regard to mechanism and side effects—but is less effective and has very different kinetics. Effects begin slowly, but are sustained—thanks to the drug's long half-life (26 hours). Although the number of patients responding at 2 hours is low (37% to 46%), rates of headache recurrence are low too (7% to 23%)—lower than with any other triptan. Frovatriptan is available in 2.5-mg tablets. The initial dose is 2.5 mg. If headache recurs after initial relief, dosing can be repeated—but no sooner than 2 hours after the first dose. If there was no response to the first dose, repeat dosing is unlikely to help. The maximum dose per 24 hours is 7.5 mg. Adverse effects are mild and transient. Like sumatriptan, frovatriptan can cause harmless, transient chest discomfort. In addition, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, frovatriptan should not be administered within 24 hours of an ergot alkaloid or another triptan. However, it can be used concurrently with an MAOI. Like other triptans, frovatriptan should not be combined with an SSRI or SNRI, owing to the risk of serotonin syndrome. Dosage should be reduced in patients receiving propranolol.

Eletriptan. Eletriptan [Relpax] is indicated for oral therapy of an ongoing migraine attack. The drug is at least as effective as oral sumatriptan, and may have a faster onset. Eletriptan is available in 20- and 40-mg tablets. The initial dose is 20 or 40 mg, which can be repeated in 2 hours if needed. The total dose in 24 hours should not exceed 80 mg. Like other triptans, eletriptan can cause transient chest discomfort. Also like other triptans, it can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, eletriptan should not be administered within 24 hours of an ergot alkaloid or another triptan. However, the drug may be used concurrently with an MAOI. Eletriptan is metabolized in the liver by CYP3A4, and hence strong inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, clarithromycin, ritonavir) may cause toxicity by raising eletriptan levels. Accordingly, eletriptan should not be used within 72 hours of these drugs. Eletriptan levels may also be raised by verapamil, a moderate CYP3A4 inhibitor used for migraine prophylaxis; caution is advised. Like other triptans, eletriptan should not be combined with an SSRI or SNRI, owing to the risk of serotonin syndrome.

Other Abortive Agents

Sumatriptan/Naproxen. Sumatriptan and naproxen (a nonsteroidal anti-inflammatory drug) are available in a fixed-dose combination under the trade name *Treximet*. Each tablet contains 85 mg sumatriptan and 500 mg naproxen. In clinical trials, the combination was better than either agent alone at relieving the pain of a migraine attack. In addition, the combination effectively reduced nausea and sensitivity to both light and sound. Presumably, the superior benefits of the combination derive from attacking migraine by multiple mechanisms: naproxen reduces pain and inflammation, while sumatriptan causes vasoconstriction and inhibits release of inflammatory neuropeptides.

Haloperidol. Haloperidol [Haldol], a neuroleptic drug developed for schizophrenia, can relieve pain of migraine. In a small, placebo-controlled trial, 5 mg of intravenous haloperidol decreased migraine pain dramatically. As measured on a visual analog scale, pain intensity dropped from 7.7 to 2.2 with haloperidol, versus only 7.2 to 6.3 with placebo. Furthermore, the relapse rate with haloperidol was low—only 3%. The effects of haloperidol are even more impressive considering that most of the patients in this trial had been unresponsive to conventional antimigraine drugs. The major adverse effects of haloperidol were sedation and akathisia (a sense of restlessness and a compelling need to be in motion). The basic pharmacology of haloperidol is discussed in Chapter 31 (Antipsychotic Agents and Their Use in Schizophrenia).

Telcagepant. Telcagepant, an experimental CGRP receptor antagonist, has the same efficacy as zolmitriptan—and is better tolerated. In a randomized, double-blind, placebo-controlled trial that enrolled 1388 patients with moderate to severe migraine, 300 mg of telcagepant produced the same reduction in pain, phonophobia, photophobia, and nausea as did 5 mg of zolmitriptan. Furthermore, side effects with telcagepant—which were limited to dry mouth, fatigue, and vomiting—occurred only slightly more often than with placebo.

PREVENTIVE THERAPY

Prophylactic therapy can reduce the frequency, intensity, and duration of migraine attacks, and can improve responses to abortive drugs. Preventive treatment is indicated for patients

who have frequent attacks (three or more a month), attacks that are especially severe, or attacks that do not respond adequately to abortive agents. Preferred drugs for prophylaxis include propranolol, divalproex, and amitriptyline. All three are effective and well tolerated, and with all three, benefits take 4 to 6 weeks to develop. Major preventive agents are listed in Table 30-5.

Beta Blockers

Beta blockers are first-line drugs for migraine prevention. Of the available beta blockers, *propranolol* is used most often. Treatment can reduce the number and intensity of attacks in 70% of patients. Benefits take a few weeks to develop. The most common side effects are extreme tiredness and fatigue, which occur in about 10% of patients. In addition, the drug can exacerbate symptoms of asthma, and might promote depression. If rizatriptan is used for abortive therapy, its dosage must be reduced. The usual maintenance dosage for propranolol is 80 to 240 mg/day, taken either as a single dose (using a long-acting formulation) or in two divided doses (using a short-acting formulation). In addition to propranolol, four other beta blockers—*timolol*, *atenolol*, *metoprolol*, and *nadolol*—can help prevent migraine attacks. In contrast, beta blockers that possess intrinsic sympathomimetic activity (eg, acebutolol, pindolol) are *not* effective. The basic pharmacology of the beta blockers is discussed in Chapter 18.

Antiepileptic Drugs

Several drugs that were developed for epilepsy can reduce migraine attacks. Proof of efficacy is strongest for divalproex [Depakote ER] and topiramate [Topamax]. Gabapentin [Neurontin] and tiagabine [Gabitril] appear promising, although extensive proof of efficacy is lacking.

Divalproex. Divalproex [Depakote ER], employed first for epilepsy and later for bipolar disorder (manic-depressive illness), is now approved for prophylaxis of migraine too. The drug is a form of valproic acid (see Chapter 24). Divalproex reduces the incidence of attacks by 50% or more in 30% to 50% of patients. However, when attacks do occur, their intensity and duration are not diminished. In migraineurs, the most common side effect is nausea. Other side effects include fatigue, weight gain, tremor, bone loss, and reversible hair loss. Potentially fatal pancreatitis and hepatitis occur rarely. Divalproex can cause neural tube defects in the developing fetus, and hence is contraindicated during pregnancy. The drug is available in immediate-release and extended-release (ER) tablets. Only the ER tablets are approved for preventing migraine. The dosage range is 800 to 1500 mg once a day.

Topiramate. Topiramate [Topamax], originally developed for epilepsy, was approved for migraine prophylaxis in 2004. Benefits take several weeks to develop, and appear equal to those of beta blockers, tricyclic antidepressants, or divalproex. However, topiramate costs much more than these drugs. In clinical trials, topiramate reduced migraine frequency by at least 50% in 83% of adolescents and about 50% of adults. The drug also reduced the need for rescue medication. Unfortunately, side effects are common, especially paresthesias, fatigue, and cognitive dysfunction (psychomotor slowing, word-finding difficulty, impairment of concentration and memory). Other side effects include metabolic acidosis

TABLE 30-5 ■ Migraine Headache: Drugs for Preventive Therapy

Beta-Adrenergic Blocking Agents

Propranolol [Inderal]

Timolol [Blocadren]

Antiepileptic Drugs

Divalproex [Depakote ER]

Topiramate [Topamax]

Tricyclic Antidepressants

Amitriptyline [Elavil]

Estrogens (for menstrual migraine)

Estrogen gel

Estrogen patch [Alora, Climara, Esclim, Estraderm, Vivelle]

and moderate weight loss (owing to anorexia, nausea, and diarrhea). To minimize side effects, dosage should be low initially and then gradually increased. The recommended titration schedule is 25 mg in the evening the first week, 25 mg in the morning and evening the second week, 25 mg in the morning and 50 mg in the evening the third week, and 50 mg in the morning and evening thereafter. The basic pharmacology of topiramate is discussed in Chapter 24.

Tricyclic Antidepressants

Tricyclic antidepressants can prevent migraine and tension-type headaches in some patients. The underlying mechanism has not been established, but may involve inhibiting reuptake of serotonin, making more of the transmitter available for action. The tricyclic agent used most often is *amitriptyline* [Elavil]. Benefits equal those of propranolol. The dosage range is 25 to 150 mg once daily at bedtime. Since amitriptyline is effective in patients who are not depressed, it would seem that benefits do not depend on elevation of mood. Like other tricyclic antidepressants, amitriptyline can cause hypotension and anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision, tachycardia). Excessive doses can cause dysrhythmias. The basic pharmacology of amitriptyline is discussed in Chapter 32.

Estrogens and Triptans for Menstrual Migraine

Menstrual migraine is defined as migraine that routinely occurs within 2 days of the onset of menses. An important trigger is the decline in estrogen levels that precedes menstruation. For many women, menstrual migraine can be prevented by taking estrogen supplements, which compensate for the premenstrual estrogen drop. Topical preparations—estrogen gel and estrogen patches [eg, Climara, Estraderm]—work well. Effective dosages are 1.5 mg/day for the gel and 100 mcg/day for the patches. Dosing is done for 7 days each month, beginning 2 days before the expected attack.

Perimenstrual triptans can also help. For example, both frovatriptan (2.5 mg twice daily) and eletriptan (20 mg thrice daily) can reduce the frequency, intensity, and duration of menstrual migraine. Dosing is done for 6 days each month, beginning 2 days before the expected onset of menses.

TABLE 30-6 ■ Drugs Used for Prophylaxis of Cluster Headache

Drug*	Usual Daily Dosage (mg)
Calcium Channel Blockers	
Verapamil [Calan, others]	240–420
Neurostabilizers	
Divalproex [Depakote]	500–1500
Topiramate [Topamax]	50–200
Lithium [Lithobid]	600–1200 [†]
Nonsteroidal Anti-inflammatory Drugs	
Indomethacin	100–150
Naproxen	1000–1500
Glucocorticoids	
Prednisone	40–80
Ergot Alkaloids	
Ergotamine	1.2

*None of the drugs listed is approved by the FDA for cluster headache prophylaxis.

[†]Dosage is adjusted on the basis of serum lithium levels.

Other Drugs for Prophylaxis

Calcium Channel Blockers

Of the calcium channel blockers (CCBs) evaluated for migraine prevention, two appear especially useful: *verapamil* and *flunarizine* (a drug not yet available in the United States). Both agents are less effective than propranolol or divalproex, and their effects develop slowly, reaching a maximum in 1 to 2 months. Although CCBs can relieve vasospasm, it is not clear that vasodilation explains antimigraine effects. Another possible mechanism is modulation of neurotransmitter release, a calcium-dependent process that CCBs are known to affect. It is noteworthy that benefits take several weeks to develop, suggesting benefits may result from central nervous system *adaptation* to CCBs, and not directly from blockade of calcium channels on blood vessels or neurons. When used for prophylaxis, CCBs cause side effects in 20% to 60% of patients. Constipation and orthostatic hypotension are most common. The basic pharmacology of CCBs is discussed in Chapter 45.

Botulinum Toxin

In 2010, the FDA approved injections of botulinum toxin A [Botox] for prevention of headaches in adults with *chronic* migraine (defined as having 15 or more headache days per month), but not for patients with less frequent headaches. Treatment consists of 31 injections, made into muscles of the scalp, neck, and upper back. Treatment is expensive and benefits are modest: On average, patients experience about 2 fewer headache days a month. The basic pharmacology of botulinum toxin and its cosmetic use are discussed in Chapter 105 (Box 105-1).

Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs)

For prophylaxis of migraine, ACEIs and ARBs are considered second- or third-line drugs. Benefits are limited to a 25% reduction in migraine days. Side effects include hyperkalemia, hypotension, volume depletion, and angioedema. When used during pregnancy, these drugs can injure the developing fetus. How ACEIs and ARBs reduce migraine attacks is unknown. The basic pharmacology of these drugs is discussed in Chapter 44.

Supplements

Riboflavin. Riboflavin (vitamin B₂) can reduce the number and severity of migraine attacks, but benefits are modest and develop slowly. In one study, migraineurs with frequent attacks took 400 mg of riboflavin a day. After 3 months, the number of attacks was decreased by 37%. In addition, the average duration of each attack also declined. Side effects were minimal.

Coenzyme Q-10. In a preliminary study, daily therapy with coenzyme Q-10 (CoQ-10) produced a significant reduction in the occurrence of

migraine attacks. Subjects took 150 mg of CoQ-10 each morning. After 3 months, the number of days on which headaches occurred declined by at least 50% in 61% of study participants. However, although headache frequency declined, headache intensity was not affected. CoQ-10 was well tolerated.

Butterbur. Extracts made from the root of *Petasites hybridus*, a plant whose common name is butterbur, can reduce the frequency of migraine attacks. In a double-blind, placebo-controlled trial, about 1 in 5 patients taking 75 mg of extract twice daily experienced a 50% or greater reduction in migraine frequency. The only side effects were mild GI symptoms (eg, nausea, burping, stomach pain). However, butterbur root contains pyrrolizidine alkaloids, which, if not removed during processing, can cause liver damage and cancer. In the study noted, the preparation employed, sold as Petadolex, is pyrrolizidine free.

CLUSTER HEADACHES

Characteristics

Cluster headaches occur in a series or “cluster” of attacks. Each attack lasts 15 minutes to 2 hours and is characterized by severe, throbbing, unilateral pain in the orbital-temporal area (ie, near the eye). A typical cluster consists of one or two such attacks every day for 2 to 3 months. An attack-free interval of months to years separates each cluster. Along with headache, patients usually experience lacrimation, conjunctival redness, nasal congestion, rhinorrhea, ptosis (drooping eyelid), and miosis (constriction of the pupil)—all on the same side as the headache. Although related to migraine, cluster headaches differ in several ways: (1) they are not preceded by an aura, (2) they do not cause nausea and vomiting, (3) they can be more debilitating, (4) they are less common and occur mostly in males (5:1), (5) they are not associated with a family history of attacks, and (6) management is different.

Drug Therapy

Prophylaxis. Primary therapy is directed at prophylaxis. Effective agents include *prednisone*, *verapamil*, and *lithium*. High-dose prednisone (40 to 80 mg/day) acts rapidly, producing results in 48 hours. However, because long-term use of glucocorticoids carries serious risks (see Chapter 72), treatment should stop in 1 to 2 months. Verapamil is a first-line agent for preventing chronic cluster headache. This drug is effective, easy to use, and safe. Lithium is considered a second-line drug for prophylaxis. The drug is effective, but can cause multiple adverse effects, and dosing is difficult. To ensure therapeutic effects and minimize toxicity, blood levels of lithium must be monitored; the target range is 0.66 to 1.2 mEq/L. With all of these drugs, prophylactic therapy should be limited to the cluster cycle, and then discontinued when the current cycle is over. Drugs for prophylaxis are listed in Table 30-6.

Treatment. If an attack occurs despite preventive therapy, it can be aborted with *sumatriptan* or *oxygen*. Sumatriptan (6 mg subQ) is the treatment of choice for cluster headache. Inhaling 100% oxygen (7 to 10 L/min for 15 to 20 minutes) is also highly effective, and has virtually no adverse effects. In the past, *ergot preparations* (eg, intravenous dihydroergotamine, sublingual ergotamine) were commonly used. However, their use today is limited.

TENSION-TYPE HEADACHE

Characteristics

Tension-type headaches (formerly called muscle-contraction headaches) are the most common headache type. These headaches are characterized by moderate, nonthrobbing pain, usually located in a “headband” distribution. Headache is often associated with scalp formication and a sense of tightness or pressure in the head and neck. Precipitating factors include eye strain, aggravation, frustration, and life’s daily stresses. Depressive symptoms (sleep disturbances, including early and frequent awakening) are often present. Tension headaches may be episodic or chronic. By definition, chronic tension-type headaches occur 15 or more days per month for at least 6 months.

Treatment

An acute attack of mild to moderate intensity can be relieved with a nonopioid analgesic: acetaminophen or a nonsteroidal anti-inflammatory drug (eg, aspirin, ibuprofen, naproxen). An analgesic-sedative combination (eg, aspirin-butalbital) may also be used. However, because of their potential for

dependence and abuse, these combinations should be reserved for acute therapy of episodic attacks; they are inappropriate for patients with chronic daily headaches.

For prophylaxis, *amitriptyline* [Elavil], a tricyclic antidepressant, is the drug of choice. Dosing at bedtime will help relieve any depression-related sleep disturbances in addition to protecting against headache. Amitriptyline

can cause anticholinergic side effects (eg, dry mouth, constipation) and poses a risk of cardiotoxicity at high doses (see Chapter 32).

In addition to receiving drugs, patients should be taught how to manage stress. Instruction should include cognitive coping skills and information on relaxation techniques (eg, massage, hot baths, biofeedback, deep muscle relaxation).

KEY POINTS

- Migraine is a neurovascular disorder involving dilation and inflammation of intracranial arteries.
- Antimigraine drugs are used in two ways: abortive and prophylactic.
- The goal of abortive therapy is to eliminate headache pain and associated nausea and vomiting.
- The goal of prophylactic therapy is to reduce the incidence and intensity of migraine attacks.
- There are two kinds of drugs for abortive therapy: non-specific analgesics (aspirin-like drugs and opioids) and migraine-specific drugs (ergot alkaloids and triptans).
- Aspirin-like analgesics (eg, acetaminophen, aspirin, naproxen) are effective for abortive therapy of mild to moderate migraine.
- Opioid analgesics (eg, butorphanol, meperidine) are reserved for severe migraine that has not responded to other drugs.
- Ergotamine is a first-line drug for abortive therapy of severe migraine.
- Overdose with ergotamine can cause ergotism, a serious condition characterized by severe tissue ischemia secondary to generalized constriction of peripheral arteries.
- Ergotamine must not be taken routinely because physical dependence will occur.
- Ergotamine can cause uterine contractions and must not be taken during pregnancy.
- Ergotamine must not be combined with potent inhibitors of CYP3A4, owing to a risk of intense vasoconstriction and associated ischemia.
- Triptans (eg, sumatriptan) are first-line drugs for abortive therapy of moderate to severe migraine.
- Triptans activate 5-HT_{1B/1D} receptors and thereby constrict intracranial blood vessels and suppress release of inflammatory neuropeptides.
- All triptans are available in oral formulations, which have a relatively slow onset. Two triptans—sumatriptan and zolmitriptan—are available in fast-acting formulations (either nasal spray, subQ injection, or both).
- Triptans can cause coronary vasospasm, and hence are contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension.
- Triptans should not be combined with one another or with ergot derivatives because excessive vasoconstriction could occur.
- Triptans should not be combined with SSRIs or SNRIs because serotonin syndrome could occur.
- Prophylactic therapy is indicated for migraineurs who have frequent attacks (two or more a month), especially severe attacks, or attacks that do not respond adequately to abortive agents.
- Propranolol, divalproex, and amitriptyline are preferred drugs for migraine prophylaxis.
- Estrogen supplements can help prevent menstrual-associated migraine.

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Summary of Major Nursing Implications*

ERGOTAMINE AND DIHYDROERGOTAMINE

Preadministration Assessment

Therapeutic Goal

Termination of migraine or cluster headache.

Baseline Data

Determine the age at onset, frequency, location, intensity, and quality (throbbing or nonthrobbing) of headaches as well as the presence or absence of a prodromal aura. Assess for trigger factors (eg, stress, anxiety, fatigue) and for a family history of severe headache.

Assess for possible underlying causes of headache (eg, severe hypertension; hyperthyroidism; infection; tumors; disorders of the eye, ear, nose, sinuses, or throat), which should be treated if present.

*Patient education information is highlighted as blue text.

Identifying High-Risk Patients

Ergot alkaloids are *contraindicated* in patients with hepatic or renal impairment, sepsis, CAD, or peripheral vascular disease, and for patients who are pregnant, taking triptans, or taking potent inhibitors of CYP3A4.

Implementation: Administration

Routes

Ergotamine Alone. Sublingual.

Ergotamine Plus Caffeine. Oral, rectal.

Dihydroergotamine. Nasal spray, IM, IV, and subQ.

Dosage and Administration

Instruct patients to commence dosing immediately upon onset of symptoms.

Summary of Major Nursing Implications*—cont'd

Nausea and vomiting from the headache and from ergotamine itself may prevent complete absorption of oral ergotamine. Concurrent treatment with metoclopramide or another antiemetic can minimize these effects. (Nausea and vomiting are minimal with dihydroergotamine.)

Ergotamine (but not dihydroergotamine) can cause physical dependence and serious toxicity if dosage is excessive. **Inform patients about the risks of dependence and toxicity and the importance of not exceeding the prescribed dosage.**

Implementation: Measures to Enhance Therapeutic Effects

Educate patients in ways to control, avoid, or eliminate trigger factors (eg, stress, fatigue, anxiety, alcohol, tyramine-containing foods).

Teach patients about relaxation techniques (eg, biofeedback, deep muscle relaxation). Advise patients to rest in a quiet, dark room for 2 to 3 hours after drug administration and to apply an ice pack to the neck and scalp.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Determine the size and frequency of doses used and the extent to which therapy has reduced the intensity and duration of attacks.

Minimizing Adverse Effects

Nausea and Vomiting. Ergotamine promotes nausea and vomiting. Minimize these by concurrent therapy with metoclopramide or a phenothiazine-type antiemetic.

Ergotism. Toxicity (ergotism) can result from acute or chronic overdose. **Teach patients the early manifestations of ergotism (muscle pain; paresthesias in fingers and toes; extremities become cold, pale, and numb) and instruct them to seek immediate medical attention if they develop.** Treat by withdrawing ergotamine and administering drugs (anticoagulants, low-molecular-weight dextran, intravenous nitroprusside) as appropriate to maintain circulation.

Physical Dependence. Ergotamine can cause physical dependence. **Warn patients not to overuse the drug, since physical dependence can result. Teach patients the signs and symptoms of withdrawal (headache, nausea, vomiting, restlessness) and instruct them to inform the prescriber if these develop during a drug-free interval.** Patients who become dependent may require hospitalization to bring about withdrawal.

Abortion. Ergot alkaloids are uterine stimulants that can cause abortion in high doses. **Warn women of child-bearing age to avoid pregnancy while using these drugs.**

Minimizing Adverse Interactions

Inhibitors of CYP3A4. Ergotamine and dihydroergotamine must not be combined with potent inhibitors of CYP3A4, which can raise these drugs to toxic levels, thereby posing a risk of intense vasoconstriction and associated ischemia. Drugs to avoid include certain HIV protease

inhibitors (eg, ritonavir, nelfinavir), azole antifungal drugs (eg, ketoconazole, itraconazole), and macrolide antibiotics (eg, erythromycin, clarithromycin).

SEROTONIN_{1B/1D} RECEPTOR AGONISTS (TRIPTANS)

Almotriptan
Eletriptan
Frovatriptan
Naratriptan
Rizatriptan
Sumatriptan
Zolmitriptan

Preadministration Assessment

Therapeutic Goal

Termination of migraine headache.

Baseline Data

See *Ergotamine and Dihydroergotamine*.

Identifying High-Risk Patients

All triptans are *contraindicated* for patients with ischemic heart disease, prior MI, or uncontrolled hypertension, and for patients taking ergot alkaloids, other triptans, SSRIs, or SNRIs. *Sumatriptan, rizatriptan, and zolmitriptan* are *contraindicated* for patients taking MAOIs. *Eletriptan* is *contraindicated* for patients taking strong inhibitors of CYP3A4.

Implementation: Administration

Routes

Oral. All triptans.

Subcutaneous. Sumatriptan.

Intranasal. Sumatriptan and zolmitriptan.

Dosage and Administration

Instruct patients to administer triptans immediately after onset of symptoms.

Teach patients how to use the sumatriptan auto-injector and the needle-free injection device.

Implementation: Measures to Enhance Therapeutic Effects

Educate patients in ways to control, avoid, or eliminate trigger factors (eg, stress, fatigue, anxiety, alcohol, tyramine-containing foods).

Teach patients biofeedback or another relaxation technique. Advise patients to rest in a quiet, dark room for 2 to 3 hours after drug administration and to apply an ice pack to the neck and scalp.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Determine the size and frequency of doses used and the extent to which therapy has reduced the intensity and duration of attacks.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Minimizing Adverse Effects

Coronary Vasospasm. All triptans can cause coronary vasospasm with resultant anginal pain. Avoid these drugs in patients with ischemic heart disease, prior MI, or uncontrolled hypertension. In patients with risk factors for CAD, rule out CAD before giving triptans.

Teratogenesis. *Sumatriptan* can cause birth defects in laboratory animals, and hence must not be used during pregnancy. *Rizatriptan* may also pose fetal risk.

Minimizing Adverse Interactions

Ergot Alkaloids and Other Triptans. Combining a triptan with an ergot alkaloid (eg, ergotamine, dihydroergotamine) or another triptan can cause prolonged vasospasm. Do not administer a triptan within 24 hours of an ergot alkaloid or another triptan.

SSRIs and SNRIs. These drugs should not be combined with a triptan, owing to the risk of serotonin syndrome.

MAOIs. MAOIs can intensify the effects of *sumatriptan*, *rizatriptan*, and *zolmitriptan*. Patients should not combine these drugs with an MAOI, or use them within 2 weeks of stopping an MAOI.

CYP3A4 Inhibitors. Ketoconazole, ritonavir, and other strong inhibitors of CYP3A4 can raise levels of *eletriptan* and *almotriptan*. Toxicity can result. Eletriptan must not be combined with these inhibitors. Almotriptan can be combined with a CYP3A4 inhibitor, but almotriptan dosage must be reduced.

Propranolol. Propranolol can raise levels of *frovatriptan* and *rizatriptan*. Dosage of the triptan should be reduced.

*Patient education information is highlighted as blue text.

Antipsychotic Agents and Their Use in Schizophrenia

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The antipsychotic agents are a chemically diverse group of compounds used for a broad spectrum of psychotic disorders. Specific indications include schizophrenia, delusional disorders, bipolar disorder, depressive psychoses, and drug-induced psychoses. In addition to their psychiatric applications, the antipsychotics are used to suppress emesis and to treat Tourette's syndrome and Huntington's chorea. As a rule, antipsychotics should not be used to treat dementia-related psychosis in the elderly, owing to a risk of increased mortality.

Since their introduction in the early 1950s, the antipsychotic agents have catalyzed revolutionary change in the management of psychotic illnesses. Before these drugs were available, psychoses were largely untreatable and patients were fated to a life of institutionalization. With the advent of antipsychotic medications, many patients with schizophrenia and other severe psychotic disorders have been able to leave psychiatric hospitals and return to the community. Others have been spared hospitalization entirely. For those who must be institutionalized, antipsychotic drugs have at least reduced suffering.

The antipsychotic drugs fall into two major groups: (1) *first-generation antipsychotics* (FGAs), also known as *conventional antipsychotics*, and (2) *second-generation antipsy-*

chotics (SGAs), also known as *atypical antipsychotics*. Both groups are equally effective. All of the FGAs produce strong blockade of dopamine in the central nervous system (CNS). As a result, they all can cause serious movement disorders, known as *extrapyramidal symptoms* (EPS). The SGAs produce moderate blockade of receptors for dopamine and much stronger blockade of receptors for serotonin. Because dopamine receptor blockade is only moderate, the risk of EPS is lower than with the FGAs. However, although the SGAs carry a reduced risk of EPS, they carry a significant risk of *metabolic effects*—weight gain, diabetes, and dyslipidemia—that can cause cardiovascular events and early death.

In 2009, antipsychotic drugs were the top-selling medications in the United States, with total sales of \$14.6 billion, up from \$9.6 billion in 2004. Of note, the SGAs outsold the FGAs by a factor of 10. Why? Good question, given that the SGAs are no more effective than the FGAs, and carry significant risks that the FGAs don't have. Then why are SGAs so widely prescribed? The main reason is inappropriate off-label use, such as controlling agitation in nursing home residents. In addition, aggressive marketing has created the *perception* of clinical superiority, even though the FGAs are just as good.

SCHIZOPHRENIA: CLINICAL PRESENTATION AND ETIOLOGY

Clinical Presentation

Schizophrenia is a chronic psychotic illness characterized by disordered thinking and a reduced ability to comprehend reality. Symptoms usually emerge during adolescence or early adulthood. In the United States, about 3.2 million people are affected. Diagnostic criteria for schizophrenia are presented in Table 31-1.

Three Types of Symptoms

Symptoms of schizophrenia can be divided into three groups: positive symptoms, negative symptoms, and cognitive symptoms. Positive and negative symptoms are summarized in Table 31-2.

Positive Symptoms and Negative Symptoms. Positive symptoms can be viewed as an exaggeration or distortion of normal function, whereas negative symptoms can be viewed as a loss or diminution of normal function. Positive symptoms include hallucinations, delusions, agitation, tension, and paranoia. Negative symptoms include lack of motivation, poverty of speech, blunted affect, poor self-care, and social withdrawal. Positive and negative symptoms respond equally to FGAs and SGAs.

TABLE 31-1 ■ DSM-5 Diagnostic Criteria for Schizophrenia**A. Characteristic Symptoms**

At least two of the following are present for a significant time during a 1-month period (or less if successfully treated), and at least one of these should be delusions, hallucinations, or disorganized speech:

1. Delusions
2. Hallucinations
3. Disorganized speech
4. Grossly abnormal psychomotor behavior, such as catatonia
5. Negative symptoms (restricted affect or avolition/asociality)

B. Social/Occupational Dysfunction

For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration

Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).

D. Schizoaffective and Mood Disorder Exclusion

Schizoaffective Disorder and Mood Disorder with Psychotic Features have been ruled out because either (1) no Major Depressive or Manic Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/General Medical Condition Exclusion

The disturbance is not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.

F. Relationship to a Pervasive Developmental Disorder

If there is a history of Autistic Disorder or another Pervasive Developmental Disorder or other communication disorder of childhood onset, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Modified from the proposed diagnostic criteria for Schizophrenia, to be published in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on June 20, 2011.

Table 31-2 ■ Positive and Negative Symptoms of Schizophrenia

Positive Symptoms	Negative Symptoms
Hallucinations	Social withdrawal
Delusions	Emotional withdrawal
Disordered thinking	Lack of motivation
Disorganized speech	Poverty of speech
Combativeness	Blunted affect
Agitation	Poor insight
Paranoia	Poor judgment
	Poor self-care

Cognitive Symptoms. Cognitive symptoms include disordered thinking, reduced ability to focus attention, and prominent learning and memory difficulties. Subtle changes may appear years before symptoms become florid, when thinking and speech may be completely incomprehensible to others. Cognitive symptoms may respond equally to FGAs and SGAs.

Acute Episodes

During an acute schizophrenic episode, delusions (fixed false beliefs) and hallucinations are frequently prominent. Delusions are typically religious, grandiose, or persecutory. Auditory hallucinations, which are more common than visual hallucinations, may consist of voices arguing or commenting on one's behavior. The patient may feel controlled by external influences. Disordered thinking and loose association may render rational conversation impossible. Affect may be blunted or labile. Misperception of reality may result in hostility and lack of cooperation. Impaired self-care skills may leave the patient disheveled and dirty. Patterns of sleeping and eating are usually disrupted.

Residual Symptoms

After florid symptoms (eg, hallucinations, delusions) of an acute episode remit, less vivid symptoms may remain. These include suspiciousness, poor anxiety management, and diminished judgment, insight, motivation, and capacity for self-care. As a result, patients frequently find it difficult to establish close relationships, maintain employment, and function

independently in society. Suspiciousness and poor anxiety management contribute to social withdrawal. Inability to appreciate the need for continued drug therapy may cause non-adherence, resulting in relapse and perhaps hospital readmission.

Long-Term Course

The long-term course of schizophrenia is characterized by episodic acute exacerbations separated by intervals of partial remission. As the years pass, some patients experience progressive decline in mental status and social functioning. However, many others stabilize, or even improve. Maintenance therapy with antipsychotic drugs reduces the risk of acute relapse, but may fail to prevent long-term deterioration.

Etiology

Although there is strong evidence that schizophrenia has a biologic basis, the exact etiology is unknown. Genetic, perinatal, neurodevelopmental, and neuroanatomic factors may all be involved. Possible primary defects include excessive activation of CNS receptors for dopamine, and insufficient activation of CNS receptors for glutamate. Although psychosocial stressors can precipitate acute exacerbations in susceptible patients, they are not considered causative.

FIRST-GENERATION (CONVENTIONAL) ANTIPSYCHOTICS

The FGAs have been in use for over 50 years, and their pharmacology is well understood. Accordingly, it seems appropriate to begin with these drugs, even though their use has greatly declined. Besides, since the pharmacology of the FGAs and SGAs is very similar, once you understand the FGAs, you will know a great deal about the SGAs as well.

GROUP PROPERTIES

In this section we discuss pharmacologic properties shared by all FGAs. Much of our attention focuses on adverse effects. Of these, extrapyramidal side effects are of particular concern. Because of these neurologic side effects, the FGAs are also known as *neuroleptics*.

Classification

The FGAs can be classified by potency or chemical structure. From a clinical viewpoint, classification by potency is more helpful.

Classification by Potency

First-generation antipsychotics can be classified as *low potency*, *medium potency*, or *high potency* (Table 31-3). The low-potency drugs, represented by chlorpromazine, and the high-potency drugs, represented by haloperidol, are of particular interest.

It is important to note that, although the FGAs differ from one another in potency, they all have the same ability to relieve symptoms of psychosis. Recall that the term *potency* refers only to the size of the dose needed to elicit a given re-

sponse; potency implies nothing about the maximal effect a drug can produce. Hence, when we say that haloperidol is more potent than chlorpromazine, we only mean that the dose of haloperidol required to relieve psychotic symptoms is smaller than the required dose of chlorpromazine. We do not mean that haloperidol can produce greater effects. When administered in therapeutically equivalent doses, both drugs elicit an equivalent antipsychotic response.

If low-potency and high-potency neuroleptics are equally effective, why distinguish between them? The answer is that, although these agents produce identical *antipsychotic* effects, they differ significantly in *side effects*. Hence, by knowing the potency category to which a particular neuroleptic belongs, we can better predict its undesired responses. This knowledge is useful in drug selection and providing patient care and education.

Chemical Classification

The FGAs fall into five major chemical categories (Table 31-4). One of these categories, the phenothiazines, has three subgroups. Drugs in all groups are equivalent with respect to antipsychotic actions, and hence chemical classification is not emphasized in this chapter.

Two chemical categories—*phenothiazines* and *butyrophenones*—deserve attention. The phenothiazines were the first modern antipsychotic agents. Chlorpromazine, our prototype of the low-potency neuroleptics, belongs to this family. The butyrophenones stand out because they are the family to which haloperidol belongs. Haloperidol is the prototype of the high-potency FGAs.

Mechanism of Action

The FGAs block a variety of receptors within and outside the CNS. To varying degrees, they block receptors for dopamine, acetylcholine, histamine, and norepinephrine. There is little question that blockade at these receptors is responsible for the major *adverse effects* of the antipsychotics. However, since the etiology of psychotic illness is unclear, the relationship of receptor blockade to *therapeutic effects* can only be guessed. The current dominant theory suggests that FGA drugs suppress symptoms of psychosis by blocking dopamine₂ (D₂) receptors in the mesolimbic area of the brain. In support of this theory is the observation that all of the FGAs produce D₁ receptor blockade. Furthermore, there is a close correlation between the clinical potency of these drugs and their potency as D₂ receptor antagonists.

Therapeutic Uses

Schizophrenia. Schizophrenia is the primary indication for antipsychotic drugs. These agents effectively suppress symptoms during acute psychotic episodes and, when taken chronically, can greatly reduce the risk of relapse. Initial effects may be seen in 1 to 2 days, but substantial improvement usually takes 2 to 4 weeks, and full effects may not develop for several months. Positive symptoms (eg, delusions, hallucinations) may respond somewhat better than negative symptoms (eg, social and emotional withdrawal, blunted affect, poverty of speech) or cognitive dysfunction (eg, disordered thinking, learning and memory difficulties). All of the FGA agents are equally effective, although individual patients may

Table 31-3 • Antipsychotic Drugs: Relative Potency and Incidence of Selected Side Effects

Drug	Trade Name	Equivalent Oral Dose (mg)*	Incidence of Side Effects										Metabolized by CYP3A4
			Extrapyramidal Effects†	Sedation	Orthostatic Hypotension	Anticholinergic Effects	Metabolic Effects: Weight Gain, Diabetes Risk, Dyslipidemia	Significant QT Prolongation	Prolactin Elevation				
FIRST-GENERATION (CONVENTIONAL) ANTIPSYCHOTICS													
Low Potency													
Chlorpromazine	generic only	100	Moderate	High	High	Moderate	Moderate	Moderate	Yes	Low	—		
Thioridazine	generic only	100	Low	High	High	High	Moderate	Moderate	Yes	Low	—		
Medium Potency													
Loxapine	Loxitane	13	Moderate	Moderate	Low	Low	Low	Low	No	Moderate	—		
Perphenazine	generic only	8	Moderate	Moderate	Low	Low	Low	—	No	Low	—		
High Potency													
Fluphenazine	generic only	1	Very high	Low	Low	Low	Low	—	No	Moderate	—		
Haloperidol	Haldol	2	Very high	Low	Low	Low	Moderate	Moderate	Yes	Moderate	—		
Pimozide	Orap	1	High	Moderate	Low	Moderate	—	—	Yes	Moderate	—		
Thiothixene	Navane	2	High	Low	Moderate	Low	Moderate	Moderate	No	Moderate	—		
Trifluoperazine	generic only	1	High	Low	Low	Low	Low	—	No	Moderate	—		
SECOND-GENERATION (ATYPICAL) ANTIPSYCHOTICS													
Aripiprazole	Abilify	2	Very low	Low	Low	None	None	None/low	No	Low	Yes		
Asenapine	Saphris	4	Moderate	Moderate	Moderate	Low	Low	Low	Yes	Low	Slightly		
Clozapine	Clozaril, FazaClo	75	Very low	High	Moderate	High	High	High	No	Low	Yes		
Iloperidone	Fanapt	4	Very low	Moderate	Moderate	Moderate	Moderate	Moderate	Yes	Low	Yes		
Lurasidone	Latuda	10	Moderate	Moderate	Low	None	None	None/low	No	Low	Yes		
Olanzapine	Zyprexa	3	Low	Moderate	Moderate	Moderate	Moderate	High	No	Low	No		
Paliperidone	Invega	2	Moderate	Low	Low	None	None	Moderate	Yes	High	Slightly		
Quetiapine	Seroquel	95	Very low	Moderate	Moderate	None	None	Moderate/high	Yes	Low	Yes		
Risperidone	Risperdal	1	Moderate	Low	Low	None	None	Moderate	No	High	No		
Ziprasidone	Geodon, Zeldox♦	20	Low	Moderate	Moderate	None	None	None/low	Yes	Low	Yes		

*Doses listed are the therapeutic equivalent of 100 mg of oral chlorpromazine.

†Incidence here refers to *early* extrapyramidal reactions (acute dystonia, parkinsonism, akathisia). The incidence of *late* reactions (tardive dyskinesia) is the same for all traditional antipsychotics.

Table 31-4 • Antipsychotic Drugs: Routes and Dosages

Chemical Group and Generic Name	Trade Name	Route	Usual Total Daily Dose for Schizophrenia (mg)	
			Short Term	Maintenance
FIRST-GENERATION (CONVENTIONAL) ANTIPSYCHOTICS				
Phenothiazine: Aliphatic				
Chlorpromazine	generic only	PO, IM, IV	200–1000	50–400
Phenothiazine: Piperidine				
Thioridazine	generic only	PO	200–800	50–400
Phenothiazine: Piperazine				
Fluphenazine	generic only	PO, IM	5–30	1–15
Perphenazine	generic only	PO	12–64	8–24
Trifluoperazine	generic only	PO, IM	10–60	4–30
Thioxanthene				
Thiothixene	Navane	PO	10–60	6–30
Butyrophenone				
Haloperidol	Haldol	PO, IM	5–50	1–5
Dibenzoxazepine				
Loxapine	Loxitane	PO	20–160	20–60
Diphenylbutylpiperidine				
Pimozide	Orap	PO	1–2*	10*
SECOND-GENERATION (ATYPICAL) ANTIPSYCHOTICS				
Aripiprazole	Abilify	PO	10–15	10–15
Asenapine	Saphris	Sublingual	10	10
Clozapine	Clozaril, FazaClo	PO	300–900	300–600
Iloperidone	Fanapt	PO	12–24	12–24
Lurasidone	Latuda	PO	40–80	40–80
Olanzapine	Zyprexa	PO, IM	5–10	10–20
Paliperidone	Invega	PO	6	6
Quetiapine	Seroquel	PO	50	300–400
Risperidone	Risperdal	PO, IM	2–4	4–6
Ziprasidone	Geodon, Zeldox♦	PO, IM	40	80–120

*Dosage for Tourette's syndrome.

respond better to one FGA than to another. Consequently, selection among these drugs is based primarily on their side effect profiles, rather than on therapeutic effects. It must be noted that antipsychotic drugs do not alter the underlying pathology of schizophrenia. Hence, treatment is not curative—it offers only symptomatic relief. Management of schizophrenia is discussed in depth later in the chapter.

Bipolar Disorder (Manic-Depressive Illness). Most patients with bipolar disorder are managed with a mood-stabilizing agent (eg, lithium, valproic acid). Neuroleptics may be employed acutely, usually in combination with lithium or valproic acid, to help manage patients going through a severe manic phase. Bipolar disorder and its treatment are the subject of Chapter 33.

Tourette's Syndrome. This rare inherited disorder is characterized by severe motor tics, barking cries, grunts, and outbursts of obscene language, all of which are spontaneous and beyond control of the patient. In addition to these core symptoms, patients frequently have symptoms resembling those of obsessive-compulsive disorder (OCD) or attention-deficit/hyperactivity disorder (ADHD). Neuroleptic drugs (eg, pimozide, fluphenazine, haloperidol) are the most effective agents for managing core symptoms. When core symptoms are mild, clonidine is the drug of choice. Symptoms of OCD can be managed with a selective serotonin reuptake inhibitor (eg, fluoxetine [Prozac]). Symptoms of ADHD can be controlled with a CNS stimulant (eg, methylphenidate [Ritalin]).

Prevention of Emesis. Neuroleptics suppress emesis by blocking dopamine receptors in the chemoreceptor trigger zone of the medulla. These drugs can be employed to suppress vomiting associated with cancer chemotherapy, gastroenteritis, uremia, and other conditions.

Other Applications. Neuroleptics can be used for *delusional disorders*, *schizoaffective disorder*, and *dementia and other organic mental syndromes* (ie, psychiatric syndromes resulting from organic causes, such as infection, metabolic disorders, poisoning, and structural injury to the brain). In addition, neuroleptics can relieve symptoms of *Huntington's chorea*.

Adverse Effects

The antipsychotic drugs block several kinds of receptors, and hence produce an array of side effects. Side effects associated with blockade of specific receptors are summarized in Table 31-5.

Although antipsychotic agents produce a variety of undesired effects, these drugs are, on the whole, very safe; death from overdose is practically unheard of. Among the many side effects FGAs can produce, the most troubling are the extrapyramidal reactions—especially tardive dyskinesia (TD).

Table 31-5 ■ Receptor Blockade and Side Effects of Antipsychotic Drugs

Receptor Type	Consequence of Blockade
D ₂ dopaminergic	EPS; prolactin release
H ₁ histaminergic	Weight gain, sedation
Muscarinic cholinergic	Dry mouth, blurred vision, urinary retention, constipation, tachycardia
Alpha ₁ -adrenergic	Orthostatic hypotension; reflex tachycardia

EPS = extrapyramidal symptoms.

Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) are movement disorders resulting from effects of antipsychotic drugs on the extrapyramidal motor system. The extrapyramidal system is the same neuronal network whose malfunction is responsible for the movement disorders of Parkinson's disease (PD). Although the exact cause of EPS is unclear, blockade of D₂ receptors is strongly suspected.

Four types of EPS occur. They differ with respect to time of onset and management. Three of these reactions—acute dystonia, parkinsonism, and akathisia—occur early in therapy and can be managed with a variety of drugs. The fourth reaction—tardive dyskinesia—occurs late in therapy and has no satisfactory treatment. Characteristics of EPS are summarized in Table 31-6.

The *early* reactions occur *less frequently* with *low-potency* agents (eg, chlorpromazine) than with *high-potency* agents (eg, haloperidol). In contrast, the risk of TD is equal with all FGAs.

Acute Dystonia. Acute dystonia can be both disturbing and dangerous. The reaction develops within the first few days of therapy, and frequently within hours of the first dose. Typically, the patient develops severe spasm of the muscles of the tongue, face, neck, or back. Oculogyric crisis (involuntary

upward deviation of the eyes) and opisthotonus (tetanic spasm of the back muscles causing the trunk to arch forward, while the head and lower limbs are thrust backward) may also occur. Severe cramping can cause joint dislocation. Laryngeal dystonia can impair respiration.

Intense dystonia is a crisis that requires rapid intervention. Initial treatment consists of an anticholinergic medication (eg, benztropine, diphenhydramine) administered IM or IV. As a rule, symptoms resolve within 5 minutes of IV dosing and within 15 to 20 minutes of IM dosing.

It is important to differentiate between acute dystonia and psychotic hysteria. Why? Because misdiagnosis of acute dystonia as hysteria could result in giving bigger antipsychotic doses, thereby causing the acute dystonia to become even worse.

Parkinsonism. Antipsychotic-induced parkinsonism is characterized by bradykinesia, mask-like facies, drooling, tremor, rigidity, shuffling gait, cogwheeling, and stooped posture. Symptoms develop within the first month of therapy and are indistinguishable from those of idiopathic PD.

Neuroleptics cause parkinsonism by blocking dopamine receptors in the striatum. Since idiopathic PD is also due to reduced activation of striatal dopamine receptors (see Chapter 21), it is no wonder that PD and neuroleptic-induced parkinsonism share the same symptoms.

Neuroleptic-induced parkinsonism is treated with some of the drugs used for idiopathic PD. Specifically, centrally acting *anticholinergic drugs* (eg, benztropine, diphenhydramine) and *amantadine* [Symmetrel] may be employed. Levodopa and direct dopamine agonists (eg, bromocriptine) should be avoided. Why? Because these drugs activate dopamine receptors, and might thereby counteract the beneficial effects of antipsychotic treatment.

Use of antiparkinsonism drugs should not continue indefinitely. Antipsychotic-induced parkinsonism tends to resolve spontaneously, usually within months of its onset. Accordingly, antiparkinsonism drugs should be withdrawn after a few months to determine if they are still needed.

Table 31-6 ■ Extrapyramidal Side Effects of Antipsychotic Drugs

Type of Reaction	Time of Onset	Features	Management
Early Reactions			
Acute dystonia	A few hours to 5 days	Spasm of muscles of tongue, face, neck, and back; opisthotonus	Anticholinergic drugs (eg, benztropine) IM or IV.
Parkinsonism	5–30 days	Bradykinesia, mask-like facies, tremor, rigidity, shuffling gait, drooling, cogwheeling, stooped posture	Anticholinergics (eg, benztropine, diphenhydramine), amantadine, or both. For severe symptoms, switch to a second-generation antipsychotic.
Akathisia	5–60 days	Compulsive, restless movement; symptoms of anxiety, agitation	Reduce dosage or switch to a low-potency antipsychotic. Treat with a benzodiazepine, beta blocker, or anticholinergic drug.
Late Reaction			
Tardive dyskinesia	Months to years	Oral-facial dyskinesias, choreoathetoid movements	Best approach is prevention; no reliable treatment. Discontinue all anticholinergic drugs. Give benzodiazepines. Reduce antipsychotic dosage. For severe TD, switch to a second-generation antipsychotic.

If parkinsonism is severe, switching to an SGA is likely to help. As discussed below, the risk of parkinsonism with the SGAs is much lower than with FGAs.

Akathisia. Akathisia is characterized by pacing and squirming brought on by an uncontrollable need to be in motion. This profound sense of restlessness can be very disturbing. The syndrome usually develops within the first 2 months of treatment. Like other early EPS, akathisia occurs most frequently with high-potency FGAs.

Three types of drugs have been used to suppress symptoms: *beta blockers*, *benzodiazepines*, and *anticholinergic drugs*. Although these drugs can help, reducing antipsychotic dosage or switching to a low-potency FGA may be more effective.

It is important to differentiate between akathisia and exacerbation of psychosis. If akathisia were to be confused with anxiety or psychotic agitation, it is likely that antipsychotic dosage would be increased, thereby making akathisia more intense.

Tardive Dyskinesia. Tardive dyskinesia, the most troubling EPS, develops in 15% to 20% of patients during long-term therapy with FGAs. The risk is related to duration of treatment and dosage size. For many patients, symptoms are irreversible.

Tardive dyskinesia is characterized by involuntary choreo-athetoid (twisting, writhing, worm-like) movements of the tongue and face. Patients may also present with lip-smacking movements, and their tongues may flick out in a "fly-catching" motion. One of the earliest manifestations of TD is slow, worm-like movement of the tongue. Involuntary movements that involve the tongue and mouth can interfere with chewing, swallowing, and speaking. Eating difficulties can result in malnutrition and weight loss. Over time, TD produces involuntary movements of the limbs, toes, fingers, and trunk. For some patients, symptoms decline following a dosage reduction or drug withdrawal. For others, TD is irreversible.

The cause of TD is complex and incompletely understood. One theory suggests that symptoms result from excessive *activation* of dopamine receptors. It is postulated that, in response to chronic receptor blockade, dopamine receptors of the extrapyramidal system undergo a functional change such that their sensitivity to activation is increased. Stimulation of these "supersensitive" receptors produces an imbalance in favor of dopamine, and thereby produces abnormal movement. In support of this theory is the observation that symptoms of TD can be reduced (temporarily) by *increasing* antipsychotic dosage, which increases dopamine receptor blockade. (Since symptoms eventually return even though antipsychotic dosage is kept high, dosage elevation cannot be used to treat TD.)

There is no reliable management for TD. Measures that may be tried include gradually withdrawing anticholinergic drugs, giving benzodiazepines, and reducing the dosage of the offending FGA. For patients with severe TD, switching to an SGA agent may help. Why? Because SGAs are less likely to promote TD.

Since TD has no reliable means of treatment, prevention is the best approach. Antipsychotic drugs should be used in the lowest effective dosage for the shortest time required. After 12 months, the need for continued therapy should be assessed. If drug use must continue, a neurologic evaluation should be done at least every 3 months to detect early signs of TD. For

patients with chronic schizophrenia, dosage should be tapered periodically (at least annually) to determine the need for continued treatment.

Other Adverse Effects

Neuroleptic Malignant Syndrome. Neuroleptic malignant syndrome (NMS) is a rare but serious reaction that carries a 4% risk of mortality—down from 30% in the past, thanks to early diagnosis and intervention. Primary symptoms are "lead pipe" rigidity, sudden high fever (temperature may exceed 41°C), sweating, and autonomic instability, manifested as dysrhythmias and fluctuations in blood pressure. Level of consciousness may rise and fall, the patient may appear confused or mute, and seizures or coma may develop. Death can result from respiratory failure, cardiovascular collapse, dysrhythmias, and other causes. NMS is more likely with high-potency FGAs than with low-potency FGAs.

Treatment consists of supportive measures, drug therapy, and immediate withdrawal of antipsychotic medication. Hyperthermia should be controlled with cooling blankets and antipyretics (eg, aspirin, acetaminophen). Hydration should be maintained with fluids. Benzodiazepines may relieve anxiety and help reduce blood pressure and tachycardia. Two drugs—*dantrolene* and *bromocriptine*—may be especially helpful. Dantrolene is a direct-acting muscle relaxant (see Chapter 25). In patients with NMS, this drug reduces rigidity and hyperthermia. Bromocriptine is a dopamine receptor agonist (see Chapter 21) that may relieve CNS toxicity.

Resumption of antipsychotic therapy carries a small risk of NMS recurrence. The risk can be minimized by (1) waiting at least 2 weeks before resuming antipsychotic treatment, (2) using the lowest effective dosage, and (3) avoiding high-potency agents. If a second episode occurs, switching to an SGA may help.

Anticholinergic Effects. First-generation agents produce varying degrees of muscarinic cholinergic blockade (see Table 31-3), and can elicit the full spectrum of anticholinergic responses (dry mouth, blurred vision, photophobia, urinary hesitancy, constipation, tachycardia). Patients should be informed about these responses and taught how to minimize danger and discomfort. As indicated in Table 31-3, anticholinergic effects are more likely with low-potency FGAs than with high-potency FGAs. Anticholinergic effects and their management are discussed in detail in Chapter 14.

Orthostatic Hypotension. Antipsychotic drugs promote orthostatic hypotension by blocking α_1 -adrenergic receptors on blood vessels. Alpha-adrenergic blockade prevents compensatory vasoconstriction when the patient stands, thereby causing blood pressure to fall. Patients should be informed about signs of hypotension (lightheadedness, dizziness) and advised to sit or lie down if these occur. In addition, patients should be informed that hypotension can be minimized by moving slowly when assuming an erect posture. With hospitalized patients, blood pressure and pulses should be checked before dosing and 1 hour after. Measurements should be made while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes. If blood pressure is low, or if pulse rate is high, the dose should be withheld and the prescriber consulted. Hypotension is more likely with low-potency FGAs than with the high-potency FGAs (see Table 31-3). Tolerance to hypotension develops in 2 to 3 months.

Sedation. Sedation is common during the early days of treatment but subsides within a week or so. Neuroleptic-induced sedation is thought to result from blockade of histamine receptors in the CNS. Daytime sedation can be minimized by giving the entire daily dose at bedtime. Patients should be warned against participating in hazardous activities (eg, driving) until sedative effects diminish.

Neuroendocrine Effects. Antipsychotics increase levels of circulating prolactin by blocking the inhibitory action of dopamine on prolactin release. Elevation of prolactin levels promotes gynecomastia (breast growth) and galactorrhea in up to 57% of women. Up to 97% of women experience menstrual irregularities. Gynecomastia and galactorrhea can also occur in males. Since prolactin can promote growth of prolactin-dependent carcinoma of the breast, neuroleptics should be avoided in patients with this form of cancer. (It should be noted that, although FGAs can promote the growth of cancers that already exist, there is no evidence that FGAs actually cause cancer.)

Seizures. First-generation agents can reduce seizure threshold, thereby increasing the risk of seizure activity. The risk of seizures is greatest in patients with epilepsy and other seizure disorders. These patients should be monitored, and, if loss of seizure control occurs, the dosage of their antiseizure medication must be increased.

Sexual Dysfunction. First-generation agents can cause sexual dysfunction in women and men. In women, these drugs can suppress libido and impair the ability to achieve orgasm. In men, FGAs can suppress libido and cause erectile and ejaculatory dysfunction; the incidence is 25% to 60%. Drug-induced sexual dysfunction can make treatment unacceptable to sexually active patients, thereby leading to poor compliance. A reduction in dosage or switching to a high-potency FGA may reduce adverse sexual effects. Patients should be counseled about possible sexual dysfunction and encouraged to report any problems.

Agranulocytosis. Agranulocytosis is a rare but serious reaction. Among the FGAs, the risk is highest with chlorpromazine and certain other phenothiazines. Since agranulocytosis severely compromises the ability to fight infection, a white blood cell (WBC) count should be done whenever signs of infection (eg, fever, sore throat) appear. If agranulocytosis is diagnosed, the neuroleptic should be withdrawn. Agranulocytosis will then reverse.

Severe Dysrhythmias. Four FGAs—*chlorpromazine*, *haloperidol*, *thioridazine*, and *pimozide*—pose a risk of fatal cardiac dysrhythmias. The mechanism is prolongation of the QT interval, an index of cardiac function that can be measured with an electrocardiogram (ECG). As discussed in Chapter 7 (Adverse Drug Reactions and Medication Errors), drugs that prolong the QT interval increase the risk of torsades de pointes, a dysrhythmia that can progress to fatal ventricular fibrillation. To reduce the risk of dysrhythmias, patients should undergo an ECG and serum potassium determination prior to treatment and periodically thereafter. In addition, they should avoid other drugs that cause QT prolongation (see Chapter 7, Table 7-2), as well as drugs that can increase levels of the drugs under consideration.

Effects in Elderly Patients with Dementia. When used off-label to treat elderly patients with dementia-related psychosis, all antipsychotics (FGAs and SGAs) about double the rate of mortality. Most deaths result from heart-related events (eg, heart failure, sudden death) or from infection (mainly

pneumonia). Since antipsychotics are not approved for treating dementia-related psychosis, and since doing so increases the risk of death, it would seem that such use is ill advised.

Signs of Withdrawal and Extrapyramidal Symptoms in Neonates. In 2011, the Food and Drug Administration (FDA) notified healthcare professionals that neonates exposed to antipsychotic drugs (first or second generation) during the third trimester of pregnancy may experience EPS and/or signs of withdrawal. Symptoms include tremor, agitation, sleepiness, difficulty feeding, severe breathing difficulty, and altered muscle tone (increased or decreased). Fortunately, the risk appears low: As of October 29, 2008, only 69 cases of neonatal EPS or withdrawal had been reported to the Adverse Event Reporting System. Neonates who present with EPS or signs of withdrawal should be monitored. Some will recover within hours or days, but others may require prolonged hospitalization. Despite the risk to the infant, women who become pregnant should not discontinue their medication without consulting the prescriber.

Dermatologic Effects. Drugs in the phenothiazine class can sensitize the skin to ultraviolet light, thereby increasing the risk of severe sunburn. Patients should be warned against excessive exposure to sunlight and advised to apply a sunscreen and wear protective clothing. Phenothiazines can also produce pigmentary deposits in the skin as well as the cornea and lens of the eye.

Handling antipsychotics can cause contact dermatitis in patients and healthcare workers. Dermatitis can be prevented by avoiding direct contact with these drugs.

Physical and Psychologic Dependence

Development of physical and psychologic dependence is rare. Patients should be reassured that addiction and dependence are not likely.

Although physical dependence is minimal, abrupt withdrawal of FGAs can precipitate a mild abstinence syndrome. Symptoms, which are related to chronic cholinergic blockade, include restlessness, insomnia, headache, gastric distress, and sweating. The syndrome can be avoided by withdrawing FGAs gradually.

Drug Interactions

Anticholinergic Drugs. Drugs with anticholinergic properties will intensify anticholinergic responses to neuroleptics. Patients should be advised to avoid all drugs with anticholinergic actions, including antihistamines and certain over-the-counter sleep aids.

CNS Depressants. Neuroleptics can intensify CNS depression caused by other drugs. Patients should be warned against using alcohol and all other drugs with CNS-depressant actions (eg, antihistamines, benzodiazepines, barbiturates).

Levodopa and Direct Dopamine Receptor Agonists. Levodopa (a drug for Parkinson's disease) may counteract the antipsychotic effects of neuroleptics. Conversely, neuroleptics may counteract the therapeutic effects of levodopa. These interactions occur because levodopa and neuroleptics have opposing effects on receptors for dopamine: Levodopa activates dopamine receptors, whereas neuroleptics cause receptor blockade. Like levodopa, the direct dopamine receptor agonists (eg, bromocriptine) activate dopamine receptors, and hence have interactions with neuroleptics identical to those of levodopa.

Toxicity

First-generation antipsychotics are very safe; death by overdose is extremely rare. With chlorpromazine, for example, the therapeutic index is about 200. That is, the lethal dose is 200 times the therapeutic dose.

Overdose produces hypotension, CNS depression, and extrapyramidal reactions. Extrapyramidal reactions can be treated with antiparkinsonism drugs. Hypotension can be treated with IV fluids plus an alpha-adrenergic agonist (eg, phenylephrine). There is no specific antidote to CNS depression. Excess drug should be removed from the stomach by gastric lavage. Emetics cannot be used because their effects would be blocked by the antiemetic action of the neuroleptic.

PROPERTIES OF INDIVIDUAL AGENTS

All of the FGAs are equally effective at alleviating symptoms of schizophrenia, although individual patients may respond better to one FGA than to another. Differences among these agents relate primarily to side effects (see Table 31-3). Because the high-potency agents produce fewer side effects than the low-potency agents, high-potency agents are used more often.

High-Potency Agents

Compared with the low-potency FGAs, the high-potency FGAs cause more early EPS, but cause less sedation, orthostatic hypotension, and anticholinergic effects. Because they cause fewer side effects, high-potency agents are generally preferred for initial therapy.

Haloperidol

Actions and Uses. Haloperidol [Haldol], a member of the *butyrophenone* family, is the prototype of the high-potency FGAs. Principal indications are schizophrenia and acute psychosis. In addition, haloperidol is a preferred agent for Tourette's syndrome. The drug can also be used to control severe behavioral problems in children (eg, combative, explosive hyperexcitability unrelated to any immediate provocation), but only as a last resort. Haloperidol is used more than other FGAs.

Pharmacokinetics. Haloperidol may be administered PO or IM. Oral bioavailability is about 60%. Hepatic metabolism is extensive. Parent drug and metabolites are excreted in the urine.

Adverse Effects. As indicated in Table 31-3, early extrapyramidal reactions (acute dystonia, parkinsonism, akathisia) occur frequently, whereas sedation, hypotension, and anticholinergic effects are uncommon. Note that the incidence of these reactions is opposite to that seen with the low-potency agents. However, the incidence of TD is the same as with all other FGAs. Neuroendocrine effects—galactorrhea, gynecomastia, menstrual irregularities—are seen occasionally. NMS, photosensitivity, convulsions, and impotence are rare.

Haloperidol can prolong the QT interval, and hence may pose a risk of *serious dysrhythmias*, especially when given IV and/or in high doses. The drug should be used with caution in patients with dysrhythmia risk factors, including long QT syndrome, hypokalemia or hyperkalemia, or a history of dysrhythmias, heart attack, or severe heart failure. Combined use with other QT-prolonging drugs (eg, amiodarone, erythromycin, quinidine) should be avoided.

Preparations. Haloperidol for oral use is available in tablets (0.5, 1, 2, 5, 10, and 20 mg) and a liquid concentrate (2 mg/mL), both sold generically. Two injectable forms—*haloperidol lactate* in a 5-mg/mL solution [Haldol] and *haloperidol decanoate* in a 100-mg/mL oily suspension [Haldol Decanoate 100]—are available for IM dosing. Haloperidol lactate is employed for acute therapy. Haloperidol decanoate is a depot preparation used for long-term therapy.

Dosage and Administration. Oral. The initial dosage for adults is 0.5 to 2 mg taken 2 or 3 times a day. For severe illness, daily doses up to 100 mg have been employed. Once symptoms have been controlled, the dosage should be reduced to the lowest effective amount.

Intramuscular. For *acute therapy* of severe psychosis, haloperidol lactate is administered IM in doses of 2 to 5 mg. Dosing may be repeated as often as every 60 minutes, although intervals of 4 to 8 hours may be satisfactory. Once symptoms are under control, the patient should be switched to oral therapy.

For *long-term therapy*, haloperidol decanoate is given once every 4 weeks by deep IM injection—but only to patients already stabilized on oral haloperidol. The initial dose is 10 to 20 times the current oral dose—but no greater than 100 mg. Maintenance doses are 10 to 15 times the previous oral dose.

Other High-Potency Agents

Fluphenazine. Fluphenazine, formerly available as *Prolixin*, is a high-potency agent indicated for schizophrenia and other psychotic disorders. The drug belongs to the piperazine subclass of phenothiazines. As with other high-potency agents, the most common adverse effects are early EPS: acute dystonia, parkinsonism, and akathisia. The risk of TD equals that of other FGAs. Effects seen occasionally include sedation, orthostatic hypotension, anticholinergic effects, gynecomastia, galactorrhea, and menstrual irregularities. NMS, convulsions, and agranulocytosis are rare.

Fluphenazine may be given PO or IM. For oral use, the drug is available in tablets (1, 2.5, 5, and 10 mg), an elixir (2.5 mg/5 mL), and an oral concentrate (5 mg/5 mL). The initial *oral* dosage is 2.5 to 10 mg/day, given in divided doses every 6 to 8 hours. Daily dosages greater than 3 mg are rarely needed, although some patients may require as much as 30 mg. Once symptoms have been controlled, the dosage should be reduced to the lowest effective amount, typically 1 to 5 mg/day taken as a single dose.

Two injectable preparations are available: *fluphenazine hydrochloride* (2.5 mg/mL) and *fluphenazine decanoate* (25 mg/mL). Both are given IM. Fluphenazine hydrochloride is a fast-acting preparation used for acute therapy. The usual dosage is 2.5 to 10 mg/day, given in divided doses every 6 to 8 hours. Fluphenazine decanoate is a depot preparation used for long-term therapy—but only in patients already stabilized on oral fluphenazine (or another phenothiazine antipsychotic). Intramuscular doses are based on the oral dosage. A reasonable conversion ratio is 12.5 mg of IM fluphenazine every 3 weeks for each 10 mg of oral fluphenazine taken daily.

Trifluoperazine. Trifluoperazine is a high-potency agent used for schizophrenia and other psychotic disorders. The drug belongs to the piperazine subclass of phenothiazines. The most common adverse effects are early extrapyramidal reactions (acute dystonia, parkinsonism, akathisia). Effects seen occasionally include sedation, orthostatic hypotension, anticholinergic effects, gynecomastia, galactorrhea, menstrual irregularities, and TD. NMS, convulsions, and agranulocytosis are rare. Trifluoperazine is available in tablets (1, 2, 5, and 10 mg) for oral use. Dosing is begun at 2 to 5 mg twice daily, and then increased until an optimal response has been produced, usually with 15 to 20 mg/day.

Thiothixene. Thiothixene [Navane] is a high-potency agent approved only for schizophrenia. The most common adverse effects are early extrapyramidal reactions (acute dystonia, parkinsonism, akathisia) and anticholinergic effects. Side effects seen occasionally include galactorrhea, gynecomastia, menstrual irregularities, sedation, orthostatic hypotension, and TD. Agranulocytosis, NMS, and convulsions are rare. Thiothixene is available in capsules (1, 2, 5, 10, and 20 mg) for oral use. The initial dosage is 2 mg 3 times daily. Dosage is increased until an optimal response has been achieved, usually with 20 to 30 mg/day.

Pimozide. Pimozide [Orap] is a high-potency FGA approved only for treating *Tourette's syndrome*, a rare disorder characterized by severe motor tics and uncontrollable grunts, barking cries, and outbursts of obscene language. Like other neuroleptics, pimozide can cause sedation, postural hypotension, and extrapyramidal reactions (acute dystonia, parkinsonism, akathisia, TD).

Pimozide can prolong the QT interval, and hence poses a risk of *fatal cardiac dysrhythmias*. Sertraline [Zoloft] increases this risk by raising pimozide levels, and hence the two drugs should not be combined. Similarly,

combining citalopram [Celexa] or escitalopram [Lexapro] with pimozide can prolong the QT interval (by an unknown mechanism), and hence these combinations should be avoided.

Pimozide is available in tablets (1 and 2 mg) for oral therapy. The initial dosage is 1 to 2 mg/day in divided doses. Dosage should be slowly increased to a maintenance level of 10 mg/day or 0.2 mg/kg/day (whichever is less).

Medium-Potency Agents

Loxapine. Loxapine [Loxitane] is a medium-potency agent indicated only for schizophrenia. The side effect profile is similar to that of fluphenazine. The drug is available in capsules (5, 10, 25, and 50 mg) for oral use. The initial dosage is 10 mg twice a day. Dosage is increased until symptoms are controlled, typically with 60 to 100 mg/day in divided doses. The dosage should be reduced for maintenance therapy; the usual range is 20 to 60 mg/day.

Perphenazine. Perphenazine, formerly available as *Trilafon*, is a medium-potency agent used for schizophrenia and other psychotic disorders. Its side effect profile is like that of fluphenazine. The drug is available in tablets (2, 4, 8, and 16 mg) for oral use. The initial dosage is 4 to 8 mg 3 times daily. Once symptoms have been controlled, the dosage should be reduced to the lowest effective amount.

Low-Potency Agents

Chlorpromazine

Chlorpromazine, formerly available as *Thorazine*, was the first modern antipsychotic medication. None of the newer FGAs is superior at relieving symptoms of psychotic illnesses. Chlorpromazine is a low-potency FGA and belongs to the phenothiazine family.

Therapeutic Uses. Principal indications are schizophrenia and other psychotic disorders. Additional psychiatric indications are schizoaffective disorder and the manic phase of bipolar disorder. Other uses include suppression of emesis, relief of intractable hiccups, and control of severe behavioral problems in children.

Pharmacokinetics. Chlorpromazine may be administered PO, IM, or IV. Following oral administration, the drug is well absorbed but undergoes extensive first-pass metabolism. As a result, oral bioavailability is only 30%. When chlorpromazine is given IM or IV, peak plasma levels are 10 times those achieved with an equal oral dose. Excretion is renal, almost entirely as metabolites.

Adverse Effects. The most common adverse effects are sedation, orthostatic hypotension, and anticholinergic effects (dry mouth, blurred vision, urinary retention, photophobia, constipation, tachycardia). Neuroendocrine effects (galactorrhea, gynecomastia, menstrual irregularities) are seen on occasion. Photosensitivity reactions are possible, and patients should be advised to minimize unprotected exposure to sunlight. Because chlorpromazine is a low-potency neuroleptic, the risk of early extrapyramidal reactions (dystonia, akathisia, parkinsonism) is relatively low. However, the risk of TD is the same as with all other FGAs. Chlorpromazine lowers seizure threshold. Accordingly, patients with seizure disorders should be especially diligent about taking antiseizure medication. Like haloperidol, chlorpromazine can prolong the QT interval, and hence may pose a risk of fatal dysrhythmias, especially in patients with dysrhythmia risk factors (e.g., long QT syndrome, hypokalemia, hyperkalemia, history of cardiac dysrhythmias). Agranulocytosis and NMS occur rarely.

Drug Interactions. Chlorpromazine can intensify responses to CNS depressants (eg, antihistamines, benzodiazepines, barbiturates) and anticholinergic drugs (eg, antihistamines, tricyclic antidepressants, atropine-like drugs).

Preparations, Dosage, and Administration. Chlorpromazine is available in two formulations: tablets (10, 25, 50, 100, and 200 mg) and solution for injection (25 mg/mL).

Oral Therapy. The initial dosage for adults is 25 mg 3 times a day. Dosage should be gradually increased until symptoms are controlled. The usual maintenance dosage is 400 mg/day. Elderly patients require less drug than younger patients.

Parenteral Therapy. Parenteral therapy is indicated for acutely psychotic, hospitalized patients. Intramuscular administration is preferred to IV administration. (Intravenous chlorpromazine is highly irritating and generally avoided.) The initial dose is 25 to 50 mg. Dosage may be increased gradually to a maximum of 400 mg every 4 to 6 hours. Once symptoms are controlled, oral therapy should be substituted for parenteral therapy.

Thioridazine

Thioridazine, formerly available as *Mellaril*, is a low-potency FGA that prolongs the QT interval, and hence can cause fatal cardiac dysrhythmias. Because of this danger, the drug should be reserved for treating schizophrenia in patients who have not responded to safer agents. The most common ad-

verse effects are sedation, orthostatic hypotension, anticholinergic effects, weight gain, and inhibition of ejaculation. Effects seen occasionally include extrapyramidal reactions (dystonia, parkinsonism, akathisia, TD), galactorrhea, gynecomastia, menstrual irregularities, and photosensitivity reactions. NMS, convulsions, agranulocytosis, and pigmentary retinopathy occur rarely. Principal interactions are with anticholinergic drugs and CNS depressants. Thioridazine is available in tablets (10, 15, 25, 50, 100, 150, and 200 mg) for oral dosing. The initial dosage is 50 to 100 mg 3 times a day. Dosage may be gradually increased until symptoms are controlled, but should not exceed 800 mg/day. The usual maintenance dosage is 200 to 800 mg/day in two to four divided doses.

SECOND-GENERATION (ATYPICAL) ANTIPSYCHOTICS

The second-generation antipsychotics (SGAs), also known as *atypical antipsychotics*, were introduced in the 1990s and quickly took over 90% of the market, owing to the perception of superior efficacy and greater safety. However, neither initial perception has held up. Thanks to two large, government-sponsored studies, one in the United States and the other in Great Britain, we now know that, in most cases, SGAs and FGAs are equally effective. As for major side effects, the SGAs are less likely to cause EPS, including TD. However, the SGAs carry an even greater risk of their own, namely, serious metabolic effects—weight gain, diabetes, and dyslipidemia—that can lead to cardiovascular events and premature death. Furthermore, like the FGAs, the SGAs can cause sedation and orthostatic hypotension, and can increase the risk of death when used to treat dementia-related psychosis in the elderly. Lastly, even though SGAs have no clear clinical advantage over FGAs, the SGAs cost 10 to 20 times as much.

In addition to their use in schizophrenia, all of the SGAs are approved for bipolar disorder (see Chapter 33).

Clozapine

Clozapine [Clozaril, FazaClo] was the first SGA and will serve as our prototype for the group—even though other SGAs are now used more widely. This drug is our most effective agent for schizophrenia, the only indication it has. However, because clozapine can cause agranulocytosis, it should be reserved for patients who have not responded to safer alternatives.

Mechanism of Action

Antipsychotic effects result from blockade of receptors for dopamine and serotonin (5-hydroxytryptamine [5-HT]). Like the FGAs, clozapine blocks D₂ dopamine receptors, but its affinity for these receptors is relatively low. In contrast, the drug produces strong blockade of 5-HT₂ serotonin receptors. Combined blockade of D₂ receptors and 5-HT₂ receptors is thought to underlie therapeutic effects. Low affinity for D₂ receptors may explain why SGAs cause fewer EPS than do the FGAs. In addition to blocking receptors for dopamine and serotonin, clozapine blocks receptors for norepinephrine (alpha₁), histamine, and acetylcholine.

Therapeutic Use

Schizophrenia. Clozapine is approved for relieving general symptoms of schizophrenia and for reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder who are at chronic suicide risk. The drug is

highly effective, and often works when all other antipsychotics have failed. Unfortunately, clozapine can cause fatal agranulocytosis (see below), and hence should be reserved for patients with severe disease who have not responded to safer alternatives. Like the FGAs, clozapine improves positive, negative, and cognitive symptoms of schizophrenia. Because the incidence of EPS with clozapine is low, the drug is well suited for patients who have experienced severe EPS with an FGA.

Levodopa-Induced Psychosis. Psychosis is a common side effect of levodopa, a drug used for Parkinson's disease (PD). Clozapine is preferred to FGAs for treatment. As discussed in Chapter 21, the movement disorders of PD result from insufficient dopamine in the striatum, a component of the extrapyramidal system. Levodopa reduces symptoms of PD by increasing dopamine availability. Since FGAs cause profound blockade of dopamine receptors in the striatum, they will intensify symptoms of PD. In contrast, clozapine causes little or no blockade of striatal dopamine receptors, and hence can alleviate levodopa-induced psychosis without making symptoms of PD worse. The dosage of clozapine required is only 25 mg a day—about 20 times less than the dosage for schizophrenia.

Pharmacokinetics

Clozapine is rapidly absorbed following oral administration. Plasma levels peak in 3.2 hours. About 95% of the drug is bound to plasma proteins. Clozapine undergoes extensive metabolism by hepatic cytochrome P450 (CYP) enzymes (CYP1A2, CYP2D6, and CYP3A4), followed by excretion in the urine and feces. The half-life is approximately 12 hours.

Adverse Effects and Interactions

Common adverse effects include sedation and weight gain (from blocking H_1 histamine receptors); orthostatic hypotension (from blocking alpha-adrenergic receptors); and dry mouth, blurred vision, urinary retention, constipation, and tachycardia (from blocking muscarinic cholinergic receptors). Neuroendocrine effects (galactorrhea, gynecomastia, amenorrhea) and interference with sexual function are minimal. Compared with the FGAs, clozapine carries a low risk of extrapyramidal effects, including TD.

Agranulocytosis. Clozapine produces agranulocytosis in 1% to 2% of patients. The overall risk of death is about 1 in 5000. The usual cause is gram-negative septicemia. Agranulocytosis typically occurs during the first 6 months of treatment, and the onset is usually gradual. Why agranulocytosis occurs is unknown.

Because of the risk of fatal agranulocytosis, monitoring of the WBC count and absolute neutrophil count (ANC) is mandatory. Prior to starting clozapine, both the total WBC count and ANC must be in the normal range (ie, $3500/\text{mm}^3$ or greater and $2000/\text{mm}^3$ or greater, respectively). During treatment, the WBC count and ANC must be monitored weekly for the first 6 months, every 2 weeks for the next 6 months, and monthly thereafter. If the total WBC count falls below $3000/\text{mm}^3$ or if the ANC falls below $1500/\text{mm}^3$, treatment should be interrupted. When subsequent daily monitoring indicates that counts have risen above these values, clozapine can be resumed. If the total WBC count falls below $2000/\text{mm}^3$ or if the ANC falls below $1000/\text{mm}^3$, clozapine should be permanently discontinued. Blood counts should be monitored for 4 weeks after drug withdrawal.

Patients should be informed about the risk of agranulocytosis and told that clozapine will not be dispensed if the blood tests have not been done. Also, patients should be informed about early signs of infection (fever, sore throat, fatigue, mucous membrane ulceration) and instructed to report these immediately.

Metabolic Effects: Weight Gain, Diabetes, and Dyslipidemia. Clozapine and the other SGAs can cause a group of closely linked metabolic effects—obesity, diabetes, and dyslipidemia—all of which increase the risk of cardiovascular events. As indicated in Table 31-3, risk is highest with clozapine and olanzapine, and lowest with aripiprazole, lurasidone, and ziprasidone.

Weight gain is the metabolic effect of greatest concern. Why? Because it seems to underlie development of diabetes and dyslipidemia. Among patients taking clozapine, weight gain can be significant. Increases in excess of 30 pounds have been reported. Patients should be informed about the possibility of weight gain and encouraged to get regular exercise, monitor their weight, and control caloric intake. Weight should be measured at baseline; 4, 8, and 12 weeks later; and every 3 months thereafter. In addition, waist circumference should be measured at baseline and annually thereafter. If significant weight gain occurs, it can be managed with a combination of lifestyle measures (diet and exercise) and metformin, an oral drug used for diabetes. In one study, metformin was more effective than lifestyle measures, and the combination of metformin plus lifestyle measures was more effective than either intervention alone. Why do antipsychotic drugs promote weight gain? Probably from blockade of histamine H_1 receptors in the brain.

Clozapine and all other SGAs can cause *new-onset diabetes*. Patients taking these drugs have developed typical diabetes symptoms, including hyperglycemia, polyuria, polydipsia, polyphagia, and dehydration. In extreme cases, hyperglycemia has led to ketoacidosis, hyperosmolar coma, and even death. Because of diabetes risk, fasting blood sugar should be measured before starting clozapine, 12 weeks later, and annually thereafter. Patients with documented diabetes at treatment onset should be monitored for worsening of glucose control. All patients should be informed about symptoms of diabetes and instructed to report them. If diabetes develops, it can be managed with insulin or an oral antidiabetic drug, such as metformin. Discontinuing clozapine is also an option. However, if the drug has produced control of psychotic symptoms, continuing clozapine and treating the diabetes would seem preferable.

Dyslipidemia associated with clozapine and other SGAs can manifest as increased total cholesterol, LDL cholesterol, and triglycerides, along with decreased HDL cholesterol. This lipid profile increases the risk of atherosclerosis and coronary heart disease. To monitor effects on lipids, a fasting lipid profile should be obtained at baseline, 12 weeks later, and every 5 years thereafter.

Seizures. Generalized tonic-clonic convulsions occur in 3% of patients. The risk of seizures is dose related. Patients should be warned not to drive or to participate in other potentially hazardous activities if a seizure has occurred. Patients with a history of seizure disorders should use the drug with great caution.

Extrapyramidal Symptoms. Although the risk of EPS with SGAs is relatively low, it is not zero. Hence, like the FGAs, clozapine and other SGAs can cause parkinsonism, acute dystonia, akathisia, and TD.

Myocarditis. Very rarely, clozapine has been associated with myocarditis (inflammation of the heart muscle), which can be fatal. If a patient develops signs and symptoms (eg, unexplained fatigue, dyspnea, tachypnea, chest pain, palpita-

ions), clozapine should be withheld until myocarditis has been ruled out. If myocarditis is diagnosed, clozapine should not be used again.

Orthostatic Hypotension. Clozapine can cause orthostatic hypotension, sometimes with fainting. Rarely, collapse is severe, and accompanied by respiratory and/or cardiac arrest. Hypotension is most likely during initial dosage titration, especially if dosage escalation is rapid.

Effects in Elderly Patients with Dementia. Like the FGAs, the SGAs about double the rate of mortality when used off-label to treat dementia-related psychosis in the elderly. Accordingly, since SGAs are not approved for this use, and since SGAs pose a risk to these patients, it is clear that SGAs should not be prescribed for this condition.

Drug Interactions. Because it can cause agranulocytosis, clozapine is contraindicated for patients taking other drugs that can suppress bone marrow function, including many anticancer drugs.

Drugs that induce P450 enzymes (eg, phenytoin, rifampin) can lower clozapine levels, and drugs that inhibit P450 enzymes (eg, ketoconazole, erythromycin) can raise clozapine levels. These inducers and inhibitors should be used with caution.

Preparations, Dosage, and Administration

Clozapine is available in standard tablets (12.5, 25, 50, 100, and 200 mg), sold as *Clozaril*, and in orally disintegrating tablets (12.5, 25, 100, and 200 mg), sold as *FazaClo*. To minimize side effects, treatment should begin with a 12.5-mg dose, followed by 25 mg once or twice daily. Dosage is then increased by 25 mg/day until it reaches 300 to 450 mg/day. Further increases can be made once or twice weekly in increments no larger than 100 mg. The usual maintenance dosage is 300 to 600 mg/day in three divided doses. The maximum dosage is 900 mg/day. If therapy is interrupted, it should resume with a 12.5-mg dose and then follow the original titration guidelines. Because of the risk of agranulocytosis, dispensing is normally limited to a 1-week supply.

Other Second-Generation Antipsychotics

Risperidone

Risperidone [Risperdal, Risperdal Consta] is a rapid-acting drug originally approved for schizophrenia and then later approved for acute bipolar mania. Most recently, the drug was approved for children with autism spectrum disorder, with the goal of reducing irritability-associated symptoms such as tantrums, aggression, mood swings, and self-injury. In patients with schizophrenia, risperidone improves positive symptoms, negative symptoms, and cognitive function. Like other SGAs, it causes fewer EPS than FGAs. Risperidone is structurally unrelated to clozapine.

Mechanism of Action. We know that risperidone binds to multiple receptors, but we don't know with certainty how clinical benefits are produced. Risperidone is a powerful antagonist at 5-HT₂ receptors and a less powerful antagonist at D₂ receptors. Antagonism at both sites probably underlies therapeutic effects. Risperidone does not block cholinergic receptors but does block H₁ receptors as well as alpha-adrenergic receptors.

Pharmacokinetics. Absorption is rapid and not affected by food. Plasma levels peak about 1 hour after oral dosing. Much of each dose is metabolized to 9-hydroxyrisperidone, whose activity equals that of risperidone itself. Parent drug and metabolite are excreted primarily in the urine. The effective half-life is 24 hours. In patients with hepatic or renal dysfunction, the half-life is prolonged.

Therapeutic Effects. Risperidone relieves positive and negative symptoms of schizophrenia and improves cognitive function. Significant improvement may be seen in 1 week. In patients with severe TD, risperidone may have an antidyskinetic effect.

Adverse Effects. Side effects are generally infrequent and mild, and only rarely require discontinuation of treatment. The incidence of EPS is very low at the recommended dosage. However, at dosages above 10 mg/day, there is a dose-related increase in EPS. With the long-acting IM formulation, the incidence of EPS is substantial (about 25%). Risperidone increases prolactin levels, but symptoms (gynecomastia, galactorrhea) are uncommon. Like

most other SGAs, risperidone can cause metabolic effects: weight gain, diabetes, and dyslipidemia. Adverse effects that have led to drug discontinuation include agitation, dizziness, somnolence, and fatigue. Excessive doses have caused sedation, difficulty concentrating, and disruption of sleep. When used off-label to treat elderly patients with dementia-related psychosis, risperidone doubles or triples the risk of stroke, and nearly doubles the risk of death (usually from cardiac events or pneumonia).

Preparations, Dosage, and Administration. Schizophrenia,

Oral Therapy. For oral therapy, risperidone is available in film-coated tablets (0.25, 0.5, 1, 2, 3, and 4 mg) and solution (1 mg/mL), both sold as *Risperdal*, and in orally disintegrating tablets (0.5, 1, 2, 3, and 4 mg), sold as *Risperdal M-TAB*. The recommended dosage is 1 mg twice daily the first day, 2 mg twice daily the second day, and 3 mg twice daily thereafter. Dosages above 2 or 3 mg twice daily do not increase therapeutic effects, but do increase the risk of EPS and other side effects. Dosage should be reduced in patients with renal or hepatic impairment.

Schizophrenia, Intramuscular Therapy. Intramuscular risperidone [Risperdal Consta] is a depot preparation used only for long-term therapy. In this formulation, risperidone is bound to a matrix that has been encapsulated within microspheres. Following IM injection, the matrix gradually breaks down to release free drug. Importantly, significant release doesn't begin until 2 to 3 weeks after the injection, producing therapeutic levels 4 to 6 weeks after the injection. Because effects are delayed, patients should take an oral antipsychotic during the first 3 weeks of Risperdal Consta use. The IM dosage range is 25 to 50 mg every 2 weeks. Risperdal Consta is supplied in a kit that contains 2 mL of diluent plus risperidone in microspheres (12.5, 25, 37.5, or 50 mg).

Bipolar Disorder. Dosage for bipolar disorder is presented in Chapter 33 (Table 33-5).

Irritability Associated with Autism Spectrum Disorder. The initial dosage is 0.25 mg/day (for children under 20 kg) and 0.5 mg/day (for children 20 kg and over). After a minimum of 4 days, dosage may be increased to the recommended maintenance level of 0.5 mg/day (for children under 20 kg) or 1 mg/day (for children 20 kg and over). If needed, dosage may be slowly titrated higher. For all children, the total daily dose can be administered as a single dose or as two divided doses of equal size.

Paliperidone

Paliperidone [Invega, Invega Sustenna] is approved for acute therapy of schizoaffective disorder, and for acute and maintenance therapy of schizophrenia. The drug is the active metabolite of risperidone (9-hydroxyrisperidone), and hence has the same adverse and therapeutic effects as risperidone itself. The two drugs differ primarily in that paliperidone is not extensively metabolized, and has no significant kinetic interactions with other drugs. Also, in contrast to risperidone, paliperidone is dosed just once a day, and doesn't require initial dosage titration. Paliperidone can prolong the QT interval, and hence should not be combined with other QT-prolonging drugs.

Paliperidone for oral therapy [Invega] is available in extended-release tablets (1.5, 3, 6, and 9 mg) that employ the so-called osmotic-release oral system (OROS) for delivery. Dosing is done once daily in the morning, with or without food. Patients should be instructed to swallow the tablets whole, without crushing, chewing, or dividing. Also, they should be informed that Invega tablets have a nonabsorbable shell that passes intact into the stool. For patients with normal renal function, the usual dosage is 6 mg/day. For patients with moderate renal impairment (creatinine clearance 50 to 80 mL/min), dosage must not exceed 6 mg/day. For patients with severe renal impairment (creatinine clearance 10 to 50 mL/min), dosage should not exceed 3 mg/day.

Paliperidone for parenteral therapy [Invega Sustenna] is available as an extended-release suspension (39, 79, 117, 156, and 234 mg) in pre-filled syringes. The usual dosing schedule is 234 mg on day 1 and 156 mg on day 8, both injected into the deltoid muscle, followed by monthly maintenance doses (117 mg) injected into either the deltoid or gluteal muscle. The maintenance range is 79 to 234 mg once a month.

Olanzapine

Olanzapine [Zyprexa] is an SGA approved for (1) schizophrenia, (2) maintenance therapy of bipolar disorder, (3) acute agitation associated with schizophrenia and bipolar mania, and (4) treatment-resistant major depression (in combination with fluoxetine). In addition, olanzapine is used off-label to suppress nausea and vomiting in cancer patients. The drug is similar to clozapine in structure and actions, but carries little or no risk of agranulocytosis (although it can cause leukopenia/neutropenia). The risk of metabolic effects is higher than with most other SGAs.

Mechanism of Action. Olanzapine blocks receptors for serotonin, dopamine, histamine, acetylcholine, and norepinephrine. Therapeutic effects

are believed to result from blocking 5-HT₂ receptors and D₂ receptors. Adverse effects result in part from blocking receptors for histamine, acetylcholine, and norepinephrine.

Pharmacokinetics. Olanzapine is well absorbed following oral administration. Food does not alter the rate or extent of absorption. Plasma levels peak 6 hours after dosing and decline with a half-life of 30 hours. Hepatic metabolism is extensive.

Therapeutic Uses. Schizophrenia. In patients with schizophrenia, olanzapine is at least as effective as haloperidol or risperidone and produces fewer EPS than either drug. Comparative trials with clozapine have not been done. Interestingly, olanzapine can relieve psychosis induced by drugs taken for Parkinson's disease, without reversing antiparkinsonism effects.

Bipolar Disorder. Olanzapine is approved for monotherapy of acute mania in patients with bipolar disorder. Benefits appear equal to those of lithium, a drug of choice for this condition (see Chapter 33).

Adverse Effects with Oral Olanzapine. Regarding serious adverse effects, olanzapine is a mixed blessing: the drug carries a low risk of EPS but carries a high risk of metabolic effects. Acute EPS are minimal when olanzapine is used at the recommended dosage. Among the SGAs, olanzapine (along with clozapine) poses the highest risk of serious metabolic effects: weight gain, diabetes, and dyslipidemia—all of which can lead to adverse cardiovascular events and premature death. Like all other antipsychotic drugs, olanzapine can increase mortality in elderly patients with dementia-related psychosis.

Olanzapine can cause *leukopenia/neutropenia*, and can thereby increase the risk of infection. Accordingly, for patients at high risk—including those with pre-existing low WBC counts and those with a history of drug-induced leukopenia/neutropenia—complete blood counts should be conducted often during the first few months of treatment. If the absolute neutrophil count falls below 1000/mm³, olanzapine should be discontinued, and the patient should be monitored for fever and other signs of infection. Neutrophil counts should be monitored until they return to normal.

Mild effects are relatively common. Olanzapine causes somnolence in 26% of patients, presumably by blocking H₁ receptors. Blockade of muscarinic receptors causes constipation and other anticholinergic effects. Alpha-adrenergic blockade causes orthostatic hypotension. In addition, case reports indicate that olanzapine can cause sleepwalking and writer's cramp. Following an overdose, the only signs are slurred speech and drowsiness.

Adverse Effects with Long-Acting IM Olanzapine. Overdose with long-acting IM olanzapine is dangerous. Principal concerns are CNS depression (ranging from mild sedation to coma) and/or delirium (confusion, disorientation, agitation, anxiety). Patients may also experience EPS, joint pain, ataxia, aggression, dizziness, weakness, hypertension, and convulsions. Symptoms typically develop within 1 to 3 hours of dosing, but may also develop later. After the injection, patients should be observed by a healthcare provider for at least 3 hours, and should be warned against driving and other hazardous activities for the remainder of the day.

Preparations. For oral therapy, olanzapine is available in standard tablets (2.5, 5, 7.5, 10, and 20 mg), sold as *Zyprexa*, orally disintegrating tablets (5, 10, 15, and 20 mg), sold as *Zyprexa Zydis*, and in capsules combined with fluoxetine (3 mg olanzapine/25 mg fluoxetine, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg), sold as *Symbyax*.

For IM therapy, olanzapine is available in two formulations: short acting and long acting. The *short-acting* formulation, sold as *Zyprexa Intramuscular*, is supplied as a powder (10 mg olanzapine) to be reconstituted with 2.1 mL of sterile water. The *long-acting* formulation, sold as *Zyprexa Relprevv*, is supplied as a powder (210, 300, and 405 mg olanzapine pamoate in single-use vials) to be reconstituted with the diluent supplied. The volume of diluent depends on the intended dose and the vial used.

Dosage and Administration. Schizophrenia. The recommended oral dosage is 5 to 10 mg once a day for the first few days, and 10 mg once a day thereafter. Dosages greater than 10 mg/day are not more effective, but do increase the risk of side effects. *Intramuscular* doses depend on the formulation. With the *short-acting* formulation, the usual dosage is 2.5 to 10 mg. With the *long-acting* formulation, the usual dosage is 150 to 300 mg every 2 weeks, or 405 mg every 4 weeks. After the injection, patients should be watched for at least 3 hours for signs of overdose (see above).

Bipolar Disorder. For bipolar disorder, we can use olanzapine alone [*Zyprexa*, *Zyprexa Zydis*] or olanzapine/fluoxetine [*Symbyax*]. The dosage for olanzapine alone is presented in Chapter 33 (Table 33-5). The dosage range for olanzapine/fluoxetine is 6 to 12 mg/day of olanzapine plus 25 to 50 mg/day of fluoxetine.

Treatment-Resistant Major Depression. Major depression is treated with olanzapine/fluoxetine [*Symbyax*], not with olanzapine alone. The initial dosage is olanzapine 6 mg/fluoxetine 25 mg given once daily in the evening. Daily dosages for maintenance range from 6 to 18 mg olanzapine plus 25 or 50 mg fluoxetine.

Ziprasidone

Ziprasidone [*Geodon*, *Zeldox* ♦] is an SGA indicated for schizophrenia and acute bipolar mania. In patients with schizophrenia, ziprasidone can improve positive symptoms, negative symptoms, and cognitive function, while causing fewer EPS than FGAs. Like some other SGAs, ziprasidone can cause significant prolongation of the QT interval, and can thereby cause potentially fatal dysrhythmias.

Mechanism of Action. Ziprasidone blocks multiple receptor types, including D₂, 5-HT₂, H₁, and alpha-adrenergic receptors. In addition, it blocks reuptake of two transmitters: serotonin and norepinephrine. As with other SGAs, therapeutic effects are believed to result from blockade of D₂ and 5-HT₂ receptors. Blockade of serotonin and norepinephrine uptake may provide antidepressant effects.

Pharmacokinetics. Oral ziprasidone is well absorbed, especially in the presence of food. Binding to plasma proteins is extensive. Ziprasidone undergoes hepatic metabolism, primarily by CYP3A4, followed by excretion in the urine and feces. The elimination half-life is about 7 hours.

Adverse Effects. Ziprasidone is generally well tolerated. The most common side effects are somnolence (perhaps from H₁ blockade), orthostatic hypotension (perhaps from alpha-adrenergic blockade), and rash (the side effect most responsible for discontinuing the drug). Extrapyramidal symptoms are seen in about 5% of patients. Like other SGAs, ziprasidone can promote weight gain, diabetes, and dyslipidemia. However, the risk is low. Like other antipsychotic drugs, ziprasidone may increase mortality in elderly patients with dementia-related psychosis.

Like olanzapine, ziprasidone can cause *leukopenia/neutropenia*, and can thereby increase the risk of infection. For patients at high risk (eg, those with pre-existing low WBC counts, those with a history of drug-induced leukopenia/neutropenia), complete blood counts should be conducted often during the first few months of treatment. If the absolute neutrophil count falls below 1000/mm³, ziprasidone should be discontinued, and the patient should be monitored for fever and other signs of infection. Neutrophil counts should be monitored until they return to normal.

Ziprasidone *prolongs the QT interval*, and thereby poses a risk of torsades de pointes, a dysrhythmia that can progress to fatal ventricular fibrillation. QT prolongation is greater than with haloperidol but less than with thioridazine [*Mellaril*]. Because of QT prolongation, ziprasidone should not be given to patients with risk factors for torsades de pointes, the most important being hypokalemia, hypomagnesemia, bradycardia, congenital QT prolongation, or a history of dysrhythmias, myocardial infarction, or severe heart failure.

Drug Interactions. Ziprasidone should not be combined with other drugs that prolong the QT interval. Among these are tricyclic antidepressants, thioridazine, several antidysrhythmic drugs (eg, amiodarone, dofetilide, quinidine), and certain antibiotics (eg, clarithromycin, erythromycin, moxifloxacin, gatifloxacin).

Drugs that induce CYP3A4 (eg, rifampin, phenytoin) can accelerate the metabolism of ziprasidone, and may thereby decrease its levels. Conversely, drugs that inhibit CYP3A4 (eg, ketoconazole) may increase ziprasidone levels.

Preparations. Ziprasidone [*Geodon*, *Zeldox* ♦] is available in capsules (20, 40, 60, and 80 mg) for oral dosing and 20-mg single-use vials for IM injection.

Dosage and Administration. Schizophrenia, Oral. The initial dosage is 20 mg twice daily taken with food. The maximum is 80 mg twice daily.

Schizophrenia, Intramuscular. Two dosing schedules may be employed: (1) 10-mg doses given at least 2 hours apart up to a maximum of 40 mg/day or (2) 20-mg doses administered at least 4 hours apart up to a maximum of 40 mg/day. Intramuscular therapy for more than 3 days has not been studied. If long-term treatment is indicated, switch to oral ziprasidone.

Bipolar Disorder. Dosage for bipolar disorder is presented in Chapter 33 (Table 33-5).

Quetiapine

Actions and Uses. Quetiapine [*Seroquel*] is an SGA indicated for schizophrenia, major depression, and acute episodes of mania and depression in patients with bipolar disorder. In patients with schizophrenia, the drug can improve positive symptoms, negative symptoms, and cognitive function. Like other SGAs, quetiapine produces strong blockade of 5-HT₂ receptors and weaker blockade of D₂ receptors. Blockade of both receptor types is believed responsible for beneficial effects. In addition to blocking receptors for serotonin and dopamine, quetiapine blocks H₁ receptors and alpha-adrenergic receptors, but does not block receptors for acetylcholine. Quetiapine was introduced in 1997, and has since become one of the top-selling drugs in the world, with sales of \$3.7 billion in the United States alone in 2010.

Pharmacokinetics. Quetiapine is well absorbed following oral administration. The drug undergoes extensive hepatic metabolism, mainly by CYP3A4 (the 3A4 isozyme of cytochrome P450), followed by excretion in the urine and feces. The half-life is 6 hours.

Adverse Effects. Quetiapine carries a moderate risk of serious metabolic effects (ie, weight gain, diabetes, and dyslipidemia). As with other SGAs, the risk of EPS is low at therapeutic doses. Despite structural similarity to clozapine, quetiapine does not pose a risk of agranulocytosis. Common side effects include sedation (from H₁ blockade) and orthostatic hypotension (from alpha blockade). Like other antipsychotics, quetiapine increases the risk of death in elderly patients with dementia-related psychosis.

Cataracts are a concern. Cataracts developed in dogs fed 4 times the maximum human dose for 6 or 12 months. Lens changes have also developed in patients; quetiapine may have been the cause. Because quetiapine may pose a risk of cataracts, the manufacturer recommends examining the lens for cataracts at baseline and every 6 months thereafter.

Like ziprasidone, quetiapine can prolong the QT interval, thereby posing a risk of torsades de pointes. Accordingly, quetiapine should not be given to patients with risk factors for torsades de pointes (eg, hypokalemia; hypomagnesemia; bradycardia; congenital QT prolongation; a history of dysrhythmias, myocardial infarction, or severe heart failure) or to patients taking drugs that prolong the QT interval.

Drug Interactions. Metabolism of quetiapine is accelerated by drugs that induce CYP3A4 (eg, phenytoin, rifampin). As a result, a larger dose of quetiapine may be needed to maintain antipsychotic effects. Conversely, drugs that inhibit CYP3A4 (eg, ketoconazole, itraconazole, fluconazole, erythromycin) may increase levels of quetiapine, and may thereby cause toxicity. Caution is advised.

As noted, quetiapine should not be combined with other drugs that prolong the QT interval. Agents to avoid include tricyclic antidepressants, thioridazine, certain antidysrhythmic drugs (eg, amiodarone, dofetilide, quinidine), and certain antibiotics (eg, clarithromycin, erythromycin, moxifloxacin, gatrifloxacin).

Preparations. Quetiapine is available in immediate-release tablets (25, 50, 100, 200, 300, and 400 mg), marketed as *Seroquel*, and in extended-release tablets (50, 150, 200, 300, and 400 mg), marketed as *Seroquel XR*.

Dosage and Administration. Schizophrenia. With the immediate-release tablets, the initial dosage is low—25 mg twice a day—to minimize orthostatic hypotension. Dosage is gradually increased over the next 3 days to a maintenance level of 400 to 800 mg/day, given in two or three divided doses. For patients who may be especially sensitive to quetiapine (eg, the elderly, those with hepatic impairment, those predisposed to hypotension), a slower titration rate and lower maintenance dosage may be advisable.

With the extended-release tablets, dosing begins at 300 mg once daily, and is later increased to a maintenance level of 400 to 800 mg once daily. Patients currently using immediate-release quetiapine may be switched to extended-release quetiapine at the equivalent total daily dosage.

Major Depression. The recommended dosage is 150 to 300 mg once daily, using the extended-release formulation.

Bipolar Disorder. Dosage for bipolar disorder is presented in Chapter 33 (Table 33-5).

Aripiprazole

Contrasts with Other Atypical Antipsychotic Agents. Aripiprazole [Abilify, Abilify Discmelt] is the first representative of a unique class of antipsychotic drugs, referred to by some as *dopamine system stabilizers* (DSSs). Approved indications are schizophrenia, acute bipolar mania, major depressive disorder, agitation associated with schizophrenia or bipolar mania, and irritability associated with autism spectrum disorder. Aripiprazole has a more favorable safety profile than any other SGA, but may be less effective than some. In patients with schizophrenia, aripiprazole is like other SGAs: it improves cognitive function, positive symptoms, and negative symptoms, while posing a low risk of EPS and TD. In contrast to other SGAs, aripiprazole is unlikely to cause significant metabolic effects, hypotension, or prolactin release, and poses no risk of anticholinergic effects or dysrhythmias. However, like all other antipsychotics, the drug may increase mortality in elderly patients with dementia-related psychosis.

Mechanism of Action. Like other antipsychotic drugs, aripiprazole can affect multiple receptor types. It blocks H₁, 5-HT₂, and alpha₁ receptors, and has mixed effects on 5-HT₁ and D₂ receptors. The drug does not block cholinergic receptors.

As with other SGAs, therapeutic effects are believed to result from interaction with dopamine and serotonin receptors. However, the nature of the interaction differs: Whereas other SGAs act as *pure antagonists* at dopamine and serotonin receptors, aripiprazole acts as a *partial agonist* at 5-HT₁ and D₂ receptors, and as a *pure antagonist* only at 5-HT₂ receptors. Because aripiprazole is a partial agonist at 5-HT₁ and D₂ receptors, net effects on receptor activity will depend on how much transmitter (dopamine or serotonin) is present. Specifically, at synapses where transmitter concentrations are low, aripiprazole will bind to receptors and thereby cause *moderate activation*.

Conversely, at synapses where transmitter concentrations are *high*, aripiprazole will compete with the transmitter for receptor binding, and hence will *reduce receptor activation*. Because of this ability to modulate the activity of dopamine receptors—rather than simply cause receptor activation or blockade—aripiprazole has been dubbed a DSS. Researchers suggest that dopamine system stabilization explains why aripiprazole can improve positive and negative symptoms of schizophrenia while having little or no effect on the extrapyramidal system or prolactin release.

Pharmacokinetics. Aripiprazole is well absorbed following oral administration, both in the presence and absence of food. Plasma levels peak 3 to 5 hours after dosing. Protein binding in blood is high—more than 99%. In the liver, aripiprazole undergoes metabolism by CYP3A4 and CYP2D6. Aripiprazole and its active metabolite—dehydro-aripiprazole—have prolonged half-lives: 75 hours and 94 hours, respectively. Because elimination is slow, (1) dosing can be done once a day and (2) about 14 days (four half-lives) are required to achieve steady-state (plateau) plasma drug levels.

Adverse Effects. Aripiprazole is generally well tolerated. The most common side effects are headache, agitation, nervousness, anxiety, insomnia, nausea, vomiting, dizziness, and somnolence. The incidence of EPS is very low. Only a few cases of NMS have been reported. Among the SGAs, aripiprazole (along with ziprasidone) poses the lowest risk of weight gain, diabetes, and dyslipidemia. Although aripiprazole can block alpha₁-adrenergic receptors, the incidence of orthostatic hypotension is low (1.9% vs. 1% in patients on placebo). Aripiprazole does not prolong the QT interval, and hence does not pose a risk of dysrhythmias. Also, the drug has little or no effect on prolactin levels, and hence does not cause gynecomastia or galactorrhea. Like other antipsychotic drugs, aripiprazole may increase mortality in elderly patients with dementia-related psychosis.

Drug Interactions. Drugs that induce CYP3A4 (eg, barbiturates, carbamazepine, phenytoin, rifampin) can accelerate metabolism of aripiprazole, and can thereby reduce its blood level. Conversely, drugs that inhibit CYP3A4 (eg, ketoconazole, itraconazole, fluconazole, erythromycin) can increase aripiprazole levels, as can drugs that inhibit CYP2D6 (eg, quinidine, fluoxetine, paroxetine).

Preparations. Aripiprazole for *oral therapy* is available in standard tablets (2, 5, 10, 15, 20, and 30 mg) and solution (1 mg/mL), both sold as *Abilify*, and in orally disintegrating tablets (10 and 15 mg) sold as *Abilify Discmelt*. Aripiprazole for IM therapy is available in single-use vials (7.5 mg/mL) sold as *Abilify*.

Dosage and Administration. Schizophrenia. The recommended dosage—both initial and maintenance—is 10 or 15 mg PO once a day, administered with or without food. Dosages above 15 mg/day do not increase therapeutic effects, but can intensify side effects. Dosage should be doubled for patients taking inducers of CYP3A4, and cut in half for patients taking inhibitors of CYP3A4 or CYP2D6.

Major Depressive Disorder. The recommended initial dosage is 2 to 5 mg PO a day. Dosage may be increased by up to 5 mg/day, but at intervals of no less than 1 week. Dosages above 15 mg/day have not been studied. As with oral therapy of schizophrenia, dosage should be doubled for patients taking inducers of CYP3A4, and cut in half for patients taking inhibitors of CYP3A4 or CYP2D6.

Bipolar Disorder. Dosage for bipolar disorder is presented in Chapter 33 (Table 33-5).

Irritability Associated with Autism Spectrum Disorder. The initial dosage is 2 mg/day, and the usual maintenance dosage is 5 to 15 mg/day.

Agitation Associated with Schizophrenia or Bipolar Mania. The recommended dosage is 9.75 mg IM once. As with oral therapy, dosage should be doubled for patients taking inducers of CYP3A4, and cut in half for patients taking inhibitors of CYP3A4 or CYP2D6.

Asenapine

Therapeutic Use. Asenapine [Saphris], approved in 2009, is an SGA indicated for (1) acute and maintenance therapy of schizophrenia in adults, and (2) acute monotherapy or acute adjunctive therapy (with lithium or valproate) of manic or mixed manic episodes associated with bipolar disorder. In clinical trials, benefits appeared modest. Asenapine is formulated as a sublingual tablet to allow absorption directly across the oral mucosa. The drug carries a low risk of weight gain, diabetes, or dyslipidemia, and has few interactions with other agents. Because of its unique properties, asenapine is well suited for patients who (1) have difficulty swallowing or (2) cannot tolerate the metabolic side effects of some other SGAs.

Mechanism of Action. Asenapine can block D₂, 5-HT₂, H₁, and alpha-adrenergic receptors, but has little effect on muscarinic receptors. As with other SGAs, clinical benefits appear to result from blockade of D₂ and 5-HT₂ receptors. Blockade of H₁ and alpha-adrenergic receptors contributes to side effects.

Pharmacokinetics. When asenapine is swallowed and absorbed from the intestine, it undergoes extensive first-pass metabolism, making bioavailability very low (less than 2%). In contrast, when the drug is administered sublingually, it gets absorbed directly across the oral mucosa, and thereby avoids first-pass metabolism. As a result, bioavailability is relatively high (about 35%). Prior to elimination in the urine, the drug undergoes metabolism by hepatic CYP1A2. The half-life is about 24 hours.

Adverse Effects. Asenapine is generally well tolerated. The risk of anticholinergic effects, prolactin elevation, and metabolic effects (weight gain, diabetes, dyslipidemia) is low. Blockade of H_1 receptors can promote drowsiness, and blockade of alpha-adrenergic receptors can promote hypotension. In clinical trials, higher doses were associated with extrapyramidal symptoms. Asenapine can prolong the QT interval, and hence should be avoided by patients with risk factors for QT prolongation, including use of other drugs that can prolong the QT interval. Asenapine has local anesthetic properties, and hence can numb the mouth when the sublingual tablets dissolve. Like other antipsychotic drugs, asenapine may increase mortality in elderly patients with dementia-related psychosis. Rarely, patients have experienced severe allergic reactions, including angioedema and life-threatening anaphylaxis.

Drug Interactions. Asenapine is largely devoid of significant drug interactions. In theory, drugs such as fluvoxamine (Luvox), which strongly inhibit CYP1A2, can increase serum levels of asenapine.

Preparations, Dosage, and Administration. Asenapine [Saphris] is formulated in 5- and 10-mg sublingual tablets. Instruct patients to place the tablet under the tongue, where it will dissolve in a few seconds. This dosing method has two benefits. First, it greatly increases absorption (by avoiding first-pass metabolism). Second, patients can't "cheek" the drug to avoid being medicated. Why? Because if asenapine is cheeked, it will simply dissolve and be absorbed across the oral mucosa. Warn patients not to swallow the tablets, and instruct them to avoid eating and drinking for 10 minutes after dosing. Also, tell them not to be alarmed if their mouth gets numb when the tablet dissolves (asenapine can act like a local anesthetic). The usual dosage is 5 mg twice daily for patients with schizophrenia, and 10 mg twice daily for patients with bipolar disorder. Increasing the dosage above 10 mg twice daily offers no clinical benefit, but will increase the risk of certain side effects. No dosage adjustment is needed in patients with renal impairment, or in patients with mild or moderate hepatic impairment. However, in patients with severe hepatic impairment, asenapine should be avoided.

Iloperidone

Actions and Therapeutic Use. Iloperidone [Fanapt], a chemical relative of risperidone, was approved in 2009 for treating schizophrenia. As with other SGAs, benefits derive from blocking D_2 and 5-HT₂ receptors. In clinical trials, efficacy equaled that of risperidone and haloperidol. Iloperidone is better tolerated than some other SGAs, but still carries a significant risk of weight gain, hypotension, and QT effects.

Pharmacokinetics. Iloperidone is administered by mouth, and plasma levels peak 2 to 4 hours after dosing. Metabolism is by two hepatic P450 enzymes: CYP2D6 and CYP3A4. The elimination half-life is 18 to 37 hours.

Adverse Effects. The most common adverse effects are dry mouth, somnolence, fatigue, nasal congestion, and orthostatic hypotension, which can be severe during initial therapy. The incidence of EPS is very low. Iloperidone carries a low risk of diabetes and dyslipidemia, but can cause significant weight gain. The drug prolongs the QT interval, and hence poses a risk of serious dysrhythmias. Like other antipsychotic drugs, iloperidone may increase mortality in elderly patients with dementia-related psychosis.

Drug Interactions. Strong inhibitors of CYP2D6 (eg, paroxetine) or CYP3A4 (eg, ketoconazole) can increase levels of iloperidone, and can thereby increase QT prolongation. Accordingly, in patients taking such inhibitors, dosage of iloperidone should be reduced. Iloperidone should not be combined with other drugs that prolong the QT interval (eg, amiodarone, quinidine).

Preparations, Dosage, and Administration. Iloperidone [Fanapt] is supplied in tablets (1, 2, 4, 6, 8, 10, and 12 mg) for oral dosing. A four-day titration pack (2 tablets each of 1, 2, 4, and 6 mg) is available to start treatment. The usual maintenance dosage is 6 to 12 mg twice daily. To minimize hypotension during initial therapy, dosage should be titrated as follows: on days 1, 2, 3, 4, 5, 6, and 7, give twice-daily doses of 1, 2, 4, 6, 8, 10, and 12 mg, respectively. Dosage should be reduced by 50% in patients taking strong inhibitors of CYP2D6 or CYP3A4. Patients with significant hepatic impairment should avoid this drug.

Lurasidone

Actions and Therapeutic Use. Lurasidone [Latuda], approved in 2010, is indicated only for schizophrenia. In clinical trials, dosages of 40 and 80 mg/day were clearly superior to placebo. As with other SGAs, benefits derive from blocking D_2 and 5-HT₂ receptors.

Pharmacokinetics. Administration is oral, and food greatly increases absorption. Plasma levels peak 1 to 3 hours after dosing. Protein binding in blood is high (about 99%). Lurasidone is metabolized in the liver, primarily by CYP3A4, and then excreted in the feces (80%) and urine (9%). The half-life is 18 hours.

Adverse Effects. In clinical trials, the most common adverse events were somnolence (22%), akathisia (15%), parkinsonism (11%), nausea (12%), agitation (6%), and anxiety (6%). Lurasidone does not cause anticholinergic effects or orthostatic hypotension, or prolong the QT interval, and the risk of metabolic effects (diabetes, weight gain, dyslipidemia) is low. Like other antipsychotic drugs, lurasidone may increase mortality in elderly patients with dementia-related psychosis.

Drug Interactions. Because lurasidone is metabolized by CYP3A4, its levels can be increased by CYP3A4 inhibitors and reduced by CYP3A4 inducers. Accordingly, use of the drug with strong inhibitors (eg, ketoconazole) or strong inducers (eg, rifampin) of CYP3A4 is contraindicated.

Preparations, Dosage, and Administration. Lurasidone [Latuda] is supplied in tablets (40 and 80 mg) for dosing with food (at least 350 calories). The usual initial dosage is 40 mg once daily. The maximum dosage is 80 mg once daily. Increasing the daily dose to 120 mg does not increase benefits, but does increase the risk of dystonia and other side effects. Dosage should not exceed 40 mg once daily in patients with moderate to severe liver impairment or moderate to severe renal impairment, or in patients taking a moderate inhibitor of CYP3A4. Patients taking a strong inhibitor of CYP3A4 should not use the drug.

DEPOT ANTIPSYCHOTIC PREPARATIONS

Depot antipsychotics are long-acting, injectable formulations used for long-term maintenance therapy of schizophrenia. The objective is to prevent relapse and maintain the highest possible level of functioning. As a rule, the rate of relapse is lower with depot therapy than with oral therapy. Depot preparations are valuable for all patients who need long-term treatment—not just for patients who have difficulty with adherence. There is no evidence that depot preparations pose an increased risk of side effects, including NMS and TD. In fact, because depot therapy permits a reduction in the total drug burden (the dose per unit time is lower than with oral therapy), the risk of TD is actually reduced.

Five depot preparations are currently available: *haloperidol decanoate* [Haldol Decanoate 100], *fluphenazine decanoate* (generic only), *risperidone microspheres* [Risperdal Consta], *paliperidone palmitate* [Invega Sustenna], and *olanzapine pamoate* [Zyprexa Relprevv]. Following the injection, active drug is slowly absorbed into the blood. Because of this slow, steady absorption, plasma levels remain relatively constant between doses. The dosing interval is 2 to 4 weeks. Typical maintenance dosages are presented in Table 31-7.

MANAGEMENT OF SCHIZOPHRENIA

Drug Therapy

Drug therapy of schizophrenia has three major objectives: (1) suppression of acute episodes, (2) prevention of acute exacerbations, and (3) maintenance of the highest possible level of functioning.

Drug Selection

Like all other drugs, antipsychotics should be selected on the basis of effectiveness, tolerability, and cost. Currently, SGAs are prescribed 10 times more often than FGAs, but that may change. When the SGAs were introduced, available data suggested they were more effective than FGAs and also safer. However, we now know otherwise. The *Clinical Antipsychotics*

Table 31-7 • Depot Antipsychotic Preparations

Generic Name [Trade Name]	Route	Typical Maintenance Dosage
Haloperidol decanoate [Haldol Decanoate 100]	IM	50–200 mg every 4 wk
Fluphenazine decanoate (generic only)	IM, subQ	12.5–50 mg every 2 wk
Risperidone microspheres [Risperdal Consta]	IM	25–50 mg every 2 wk
Paliperidone palmitate [Invega Sustenna]	IM	117 mg every 4 wk
Olanzapine pamoate [Zyprexa Relprevv]	IM	150–300 mg every 2 wk <i>or</i> 405 mg every 4 wk

Trials in Intervention Effectiveness (CATIE) study, published in 2005, compared four SGAs—olanzapine [Zyprexa], quetiapine [Seroquel], risperidone [Risperdal], and ziprasidone [Geodon, Zeldox]—with the FGA perphenazine. This result? The SGAs were no more effective than perphenazine. These data were confirmed by a second study, conducted in Great Britain, which again showed that perphenazine was just as effective as several SGAs. These two trials were the first large studies to directly compare FGAs and SGAs—and their surprising results were completely unexpected. Regarding serious side effects, SGAs were initially thought to be safer than FGAs. Why? Because SGAs posed a low risk of EPS. However, over time, it became clear that SGAs posed a serious risk of their own: potentially fatal metabolic effects. Hence, rather than being *free* of serious side effects, the SGAs simply substituted a new serious effect for the old one. As for cost, the FGAs are much cheaper. For example, whereas haloperidol costs only \$50 a year, risperidone costs about \$2000 a year, and olanzapine costs about \$4000. In summary, here's what we know:

- Most FGAs and SGAs are equally effective, except for clozapine, which is more effective than the rest.
- Whereas FGAs pose a greater risk of EPS, SGAs pose a significant risk of metabolic effects, which may be more detrimental than EPS.
- FGAs cost much less than SGAs.

Given this information, which drug should we choose? That's still hard to answer. With regard to efficacy and safety, no single agent is clearly superior to the others. So we're back to our initial selection criteria: efficacy, safety, and cost. For a patient who is treatment resistant, a trial with clozapine might be reasonable. For a patient with a history of diabetes or dyslipidemia, an FGA might be a good choice, as might aripiprazole or ziprasidone, two SGAs with a low risk of metabolic effects. If there's no clinical reason to select an SGA over an FGA, cost considerations would suggest choosing an FGA.

Dosing

Dosing with antipsychotics is highly individualized. Elderly patients require relatively small doses—typically 30% to 50% of those for younger patients. Poorly responsive patients may

need larger doses. However, very large doses should generally be avoided. Why? Because huge doses are probably no more effective than moderate doses, and will increase the risk of side effects.

Dosage size and timing are likely to change over the course of therapy. During the initial phase, antipsychotics should be administered in divided daily doses. Once an effective dosage has been determined, the entire daily dose can often be given at bedtime. Since antipsychotics cause sedation, bedtime dosing helps promote sleep while decreasing daytime drowsiness. Doses used early in therapy to gain rapid control of behavior are often very high. For long-term therapy, the dosage should be reduced to the lowest effective amount.

Routes

Oral. Oral dosing is preferred for most patients. Antipsychotics are available in tablets, capsules, and liquids for oral use.

The liquid formulations require special handling. These preparations are concentrated and must be diluted prior to use. Dilution may be performed with a variety of fluids, including milk, fruit juices, and carbonated beverages. Some oral liquids are light sensitive and must be stored in amber or opaque containers. Liquid formulations of *phenothiazines* can cause contact dermatitis; nurses and patients should take care to avoid skin contact with these preparations.

Sublingual. One SGA—*asenapine* [Saphris]—is administered as a sublingual tablet designed to be absorbed through the oral mucosa (to avoid first-pass hepatic metabolism). This route has the additional advantage of preventing “cheeking,” since doing so will simply cause the drug to be absorbed as intended.

Intramuscular. Intramuscular injection is generally reserved for patients with severe, acute schizophrenia and for long-term maintenance. Depot preparations are given every 2 to 4 weeks (see Table 31-7).

Initial Therapy

With adequate dosing, symptoms begin to resolve within 1 to 2 days. However, significant improvement takes 1 to 2 weeks, and a full response may not be seen for several months.

Some symptoms resolve sooner than others. During the first week, the goal is to reduce agitation, hostility, anxiety, and tension and to normalize patterns of sleeping and eating. Over the next 6 to 8 weeks, symptoms should continue to steadily improve. The goals over this interval are increased socialization and improved self-care, mood, and formal thought processes. Of the patients who have not responded within 6 weeks, 50% are likely to respond by the end of 12 weeks.

Maintenance Therapy

Schizophrenia is a chronic disorder that usually requires prolonged treatment. The purpose of long-term therapy is to reduce the recurrence of acute florid episodes and to maintain the highest possible level of functioning. Unfortunately, although long-term treatment can be very effective, it also carries a risk of adverse effects, especially TD.

Following control of an acute episode, antipsychotic therapy should continue for at least 12 months. Withdrawal of medication prior to this time is associated with a 55% incidence of relapse, compared with only 20% in patients who

continue drug use. Accordingly, patients must be convinced to continue therapy for the entire 12-month course, even though they may be symptom free and consider themselves “cured.”

After 12 months, an attempt should be made to discontinue drug use, provided symptoms are absent. About 25% of patients do not need drugs beyond this time. To avoid a withdrawal reaction, dosage should be tapered gradually. It is important that medication not be withdrawn at a time of stress (eg, when the patient is being discharged following hospitalization). If relapse occurs following withdrawal, treatment should be reinstated. For many patients, resumption of therapy controls symptoms and prevents further deterioration.

When long-term therapy is conducted, dosage should be adjusted with care. To reduce the risk of TD and other adverse effects, a minimum effective dosage should be established. Annual attempts should be made to lower the dosage or to discontinue treatment entirely.

Long-acting (depot) antipsychotics are especially well suited for prolonged treatment. Depot therapy has three major advantages over oral therapy: (1) the relapse rate may be lower, (2) drug levels are more stable between doses, and (3) the total dose per unit time is lower, thereby reducing the risk of adverse effects, including TD. In the United States, only 10% of patients receive depot therapy. This low rate is based in large part on the widely held (but unfounded) perception that depot therapy is for “losers”—patients who suffer recurrent relapse because of persistent nonadherence with oral therapy.

Adjunctive Drugs

Benzodiazepines (eg, lorazepam, alprazolam) can suppress anxiety and promote sleep. Whether they also improve core symptoms of schizophrenia is uncertain. In patients experiencing an acute psychotic episode, benzodiazepines can help suppress anxiety, irritability, and agitation. In addition, benzodiazepines may allow the dosage of antipsychotic medication to be reduced.

Antidepressants are appropriate when schizophrenia is associated with depressive symptoms. A tricyclic antidepressant (eg, imipramine) is usually chosen. Antidepressant dosage is the same as for major depression. The ideal duration is unknown.

Promoting Adherence

Poor adherence is a common cause of therapeutic failure, and underlies a significant proportion of hospital readmissions. Adherence can be difficult to achieve because treatment is

prolonged and because patients may fail to appreciate the need for therapy, or they may be unwilling or unable to take medicine as prescribed. In addition, side effects can discourage adherence. Adherence can be enhanced by

- Ensuring that the medication given to hospitalized patients is actually swallowed and not “cheeked”
- Encouraging family members to oversee medication for outpatients
- Providing patients with written and verbal instructions on dosage size and timing, and encouraging them to take their medicine exactly as prescribed
- Informing patients and their families that antipsychotics must be taken on a regular schedule to be effective, and hence should not be used PRN
- Informing patients about side effects of treatment and teaching them how to minimize undesired responses
- Assuring patients that antipsychotic drugs do not cause addiction
- Establishing a good therapeutic relationship with the patient and family
- Using an IM depot preparation (eg, fluphenazine decanoate, haloperidol decanoate) for long-term therapy

Nondrug Therapy

Although drugs can be of great benefit in schizophrenia, medication alone does not constitute optimal treatment. The acutely ill patient needs care, support, and protection; a period of hospitalization may be essential. Counseling can offer the patient and family insight into the nature of schizophrenia and can facilitate adjustment and rehabilitation. Although conventional psychotherapy is of little value in reducing symptoms of schizophrenia, establishing a good therapeutic relationship can help promote adherence and can help the prescriber evaluate the patient, which in turn can facilitate dosage adjustment and drug selection. Behavioral therapy can help reduce stress. Vocational training in a sheltered environment offers the hope of productivity and some measure of independence. Ideally, the patient will be provided with a comprehensive therapeutic program to complement the benefits of medication. Unfortunately, ideal situations don't always exist, leaving many patients to rely on drugs as their sole treatment modality.

KEY POINTS

- Schizophrenia is the principal indication for antipsychotic drugs, although many are also used for bipolar disorder.
- Schizophrenia is a chronic illness characterized by disordered thinking and reduced comprehension of reality. Positive symptoms include hallucinations, delusions, and agitation. Negative symptoms include blunted affect, poverty of speech, and social withdrawal. Cognitive dysfunction manifests as disordered thinking, reduced ability to focus attention, plus learning and memory difficulties.
- Antipsychotic drugs fall into two major groups: first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs).
- The drugs in both groups are equally effective at treating schizophrenia.
- Despite initial impressions, the SGAs are no safer than FGAs—they simply produce different dangerous effects: Whereas FGAs carry a high risk of extrapyramidal symptoms (EPS), the SGAs carry a high risk of metabolic effects.

- Drugs in both generations increase the risk of mortality in elderly patients with dementia-related psychosis.
- Therapeutic responses to antipsychotic drugs develop slowly, often taking several months to become maximal.
- First-generation antipsychotics are thought to relieve symptoms of schizophrenia by causing strong blockade of D₂ receptors.
- Second-generation antipsychotics are thought to relieve symptoms of schizophrenia by causing moderate blockade of D₂ receptors and strong blockade of 5-HT₂ receptors.
- The major concern with FGAs is production of EPS, which can occur early in treatment (acute dystonia, parkinsonism, and akathisia) or late in treatment (tardive dyskinesia).
- Acute dystonia and parkinsonism respond to anticholinergic drugs (eg, benztropine). Akathisia is harder to treat, but may respond to anticholinergic drugs, benzodiazepines, or beta blockers.
- Tardive dyskinesia has no reliable treatment. For patients with severe TD, switching to an SGA may help.
- The risk of early EPS is much greater with high-potency FGAs than with low-potency FGAs, whereas the risk of TD is equal with both groups.
- The risk of sedation, orthostatic hypotension, and anticholinergic effects is greater with the low-potency FGAs than with the high-potency FGAs.
- FGAs can cause neuroleptic malignant syndrome, characterized by muscular rigidity, high fever, and autonomic instability. Deaths have occurred. Dantrolene and bromocriptine are used for treatment.
- Antipsychotic drugs can increase levels of circulating prolactin. How? By blocking the inhibitory action of dopamine on prolactin release.
- Levodopa can counteract the beneficial effects of FGA drugs and vice versa. Why? Because levodopa activates dopamine receptors, whereas FGAs block dopamine receptors.
- Haloperidol [Haldol] is the prototype of the high-potency FGAs.
- Second-generation antipsychotics differ from FGAs in three important ways: (1) they block receptors for serotonin in addition to receptors for dopamine; (2) they carry a lower risk of EPS, including TD; and (3) they carry a higher risk of serious metabolic effects—weight gain, diabetes, and dyslipidemia—that can lead to adverse cardiovascular events and premature death.
- Among the SGAs, the risk of metabolic effects is greatest with clozapine and olanzapine.
- Clozapine, the first SGA, is the most effective antipsychotic drug available.
- Clozapine can cause potentially fatal agranulocytosis. Hence, regular blood tests are mandatory and the drug should be reserved for patients who have not responded to other antipsychotics.
- Antipsychotic depot preparations (eg, haloperidol decanoate, fluphenazine decanoate) are used for long-term maintenance therapy of schizophrenia.

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Summary of Major Nursing Implications*

FIRST-GENERATION (CONVENTIONAL) ANTIPSYCHOTICS

Chlorpromazine
Fluphenazine
Haloperidol
Loxapine
Perphenazine
Pimozide
Thioridazine
Thiothixene
Trifluoperazine

Except where indicated, the nursing implications below apply to all FGAs.

Preadministration Assessment

Therapeutic Goal

Treatment of schizophrenia has three goals: suppression of acute episodes, prevention of acute exacerbations, and maintenance of the highest possible level of functioning.

Baseline Data

Patients should receive a thorough mental status examination and a physical examination.

Observe and record such factors as overt behavior (eg, gait, pacing, restlessness, volatile outbursts), emotional state (eg, depression, agitation, mania), intellectual function (eg, stream of thought, coherence, hallucinations, delusions), and responsiveness to the environment.

Obtain a complete family and social history.

Determine vital signs and obtain complete blood counts, electrolytes, and evaluations of hepatic, renal, and cardiovascular function.

Identifying High-Risk Patients

First-generation antipsychotics are *contraindicated* for patients who are comatose or severely depressed and for patients with Parkinson's disease, prolactin-dependent carcinoma of the breast, bone marrow depression, and severe hypotension or hypertension. Use with *caution* in patients

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

with glaucoma, adynamic ileus, prostatic hypertrophy, cardiovascular disease, hepatic or renal dysfunction, and seizure disorders.

Avoid *chlorpromazine*, *thioridazine*, *haloperidol*, and *pimozide* in patients with risk factors for torsades de pointes (eg, hypokalemia, hypomagnesemia, bradycardia, congenital QT prolongation, or a history of dysrhythmias, myocardial infarction, or severe heart failure) and for those taking drugs that prolong the QT interval.

Generally *avoid all FGAs* in elderly patients with dementia-related psychosis.

Implementation: Administration

Routes

Oral, IM, IV, and subQ. Routes for individual agents are summarized in Tables 31-4 and 31-7.

Administration

Dosing. Divided daily doses are employed initially. Once an effective dosage has been determined, the entire daily dose is usually administered at bedtime, thereby promoting sleep and minimizing daytime sedation. For long-term therapy, the smallest effective dosage should be employed.

Oral Liquids. Oral liquid formulations must be protected from light. Concentrated formulations should be diluted just prior to use. Dilution in fruit juice improves palatability.

Oral liquids can cause contact dermatitis. **Warn patients against making skin contact with these drugs, and instruct them to flush the affected area with water if a spill occurs.** Take care to avoid skin contact with these preparations yourself.

Intramuscular. Make injections into the deltoid or gluteal muscle. Rotate the injection site. Depot preparations are administered every 2 to 4 weeks (see Table 31-7).

Implementation: Measures to Enhance Therapeutic Effects

Promoting Adherence

Poor adherence is a common cause of therapeutic failure and rehospitalization. To improve adherence:

- Ensure that medication is actually swallowed and not "cheeked."
- **Encourage family members to oversee medication for outpatients.**
- **Provide patients with written and verbal instructions on dosage size and timing, and encourage them to take their medicine as prescribed.**
- **Inform patients and their families that antipsychotic drugs must be taken on a regular schedule.**
- **Inform patients about side effects and teaching them how to minimize undesired responses.**
- **Assure patients that antipsychotic drugs do not cause addiction.**
- Establish a good therapeutic relationship with the patient and family.
- Use a depot preparation (eg, paliperidone palmitate) for long-term therapy.

Nondrug Therapy

Acutely ill patients need care, support, and protection; hospitalization may be essential. **Educate the patient and family about the nature of schizophrenia to facilitate adjustment and rehabilitation.** Behavioral therapy can help reduce stress. Vocational training in a sheltered environment offers the hope of productivity and some measure of independence.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Success is indicated by improvement in psychotic symptoms. Evaluate for suppression of hallucinations, delusions, agitation, tension, and hostility, and for improvement in judgment, insight, motivation, affect, self-care, social skills, anxiety management, and patterns of sleeping and eating.

Minimizing Adverse Effects

Early EPS: Acute Dystonia, Parkinsonism, and Akathisia. These reactions develop within hours to months after starting treatment. The risk is greatest with high-potency FGAs. Take care to differentiate these reactions from worsening of psychotic symptoms. **Inform patients and their families about symptoms (eg, muscle spasm of tongue, face, neck, or back; tremor; rigidity; restless movement), and instruct them to notify the prescriber if these appear.** Acute dystonia and parkinsonism respond to anticholinergic drugs (eg, benztropine). Akathisia may respond to anticholinergic drugs, beta blockers, or benzodiazepines. For severe parkinsonism, switch to an SGA.

Late EPS: Tardive Dyskinesia. TD develops after months or years of continuous therapy. The risk is equal with all FGAs. **Inform patients and their families about early signs (eg, fine, worm-like movements of the tongue), and instruct them to notify the prescriber if these develop.** Although there is no reliable treatment, the following measures are recommended: discontinue all anticholinergic drugs; give a benzodiazepine; and discontinue the antipsychotic, or at least reduce the dosage. For severe TD, switch to an SGA.

Neuroleptic Malignant Syndrome. NMS is a rare reaction that carries a 4% risk of death. Symptoms include rigidity, fever, sweating, dysrhythmias, and fluctuations in blood pressure. NMS is most likely with high-potency FGAs.

Treatment consists of supportive measures (use of cooling blankets, rehydration), drug therapy (dantrolene, bromocriptine), and immediate withdrawal of the neuroleptic. If neuroleptic therapy is resumed after symptoms subside, the lowest effective dosage of a low-potency drug should be employed. If a second episode occurs, switching to an SGA may help.

Anticholinergic Effects. Inform patients about possible anticholinergic effects (dry mouth, blurred vision, photophobia, urinary hesitancy, constipation, tachycardia, suppression of sweating), and teach them how to minimize discomfort. A complete summary of nursing implications for anticholinergic effects is given in Chapter 14. Anticholinergic effects are most likely with low-potency FGAs.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Orthostatic Hypotension. Inform patients about signs of hypotension (lightheadedness, dizziness) and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when assuming an erect posture. Orthostatic hypotension is most likely with low-potency FGAs.

In hospitalized patients, measure blood pressure and pulses before dosing and 1 hour after. Make these measurements while the patient is lying down and again after he or she has been sitting or standing for 1 to 2 minutes. If blood pressure is low, withhold medication and consult the prescriber.

Sedation. Sedation is most intense during the first weeks of therapy and declines with continued drug use. Warn patients about sedative effects, and advise them to avoid hazardous activity until sedation subsides. Sedation is most likely with low-potency FGAs.

Seizures. Neuroleptics reduce seizure threshold, thereby increasing the risk of seizures, especially in patients with epilepsy and other seizure disorders. For patients with seizure disorders, adequate doses of antiseizure medication must be employed. Monitor the patient for seizure activity; if loss of seizure control occurs, dosage of antiseizure medication must be increased.

Sexual Dysfunction. In women, FGAs can suppress libido and impair the ability to achieve orgasm. In men, FGAs can suppress libido and cause erectile and ejaculatory dysfunction. Counsel patients about possible sexual dysfunction and encourage them to report problems. Dosage reduction or switching to a high-potency FGA may help.

Dermatologic Effects. Inform patients that phenothiazines can sensitize the skin to ultraviolet light, thereby increasing the risk of sunburn. Advise them to avoid excessive exposure to sunlight, apply a sunscreen, and wear protective clothing.

Oral liquid formulations can cause contact dermatitis. Warn patients to avoid skin contact with these drugs.

Neuroendocrine Effects. Inform patients that FGAs can cause galactorrhea, gynecomastia, and menstrual irregularities.

Antipsychotics can promote growth of prolactin-dependent carcinoma of the breast and must not be used by patients with this cancer.

Agranulocytosis. Agranulocytosis greatly diminishes the ability to fight infection. Inform patients about early signs of infection (fever, sore throat), and instruct them to notify the prescriber if these develop. If blood tests indicate agranulocytosis, the antipsychotic should be withdrawn.

Severe Dysrhythmias. *Chlorpromazine*, *haloperidol*, *thioridazine*, and *pimozide* prolong the QT interval, and can thereby induce torsades de pointes, a dysrhythmia that can progress to fatal ventricular fibrillation. To reduce risk, (1) ensure that potassium and magnesium levels are normal, (2) avoid other drugs that cause QT prolongation, and (3) avoid drugs that can increase levels of the antipsychotic drug being used.

Signs of Withdrawal and Extrapyrarnidal Symptoms in Neonates. Neonates exposed to antipsychotic

drugs during the third trimester may experience EPS and/or signs of withdrawal. Symptoms include tremor, agitation, sleepiness, difficulty feeding, severe breathing difficulty, and altered muscle tone (increased or decreased). Neonates who develop EPS or signs of withdrawal should be monitored. Hospitalization may be required. Advise women who become pregnant not to discontinue their medication without consulting the prescriber.

Death in Elderly Dementia Patients. All FGAs increase the risk of mortality when used to treat dementia-related psychosis in elderly patients, an application use for which these drugs are not approved. Avoid FGAs in these patients.

Minimizing Adverse Interactions

Anticholinergics. Drugs with anticholinergic properties will intensify anticholinergic responses to FGAs. Instruct patients to avoid all drugs with anticholinergic properties, including the antihistamines and certain over-the-counter sleep aids.

CNS Depressants. First-generation agents will intensify CNS depression caused by other drugs. Warn patients against use of alcohol and all other drugs with CNS-depressant properties (eg, barbiturates, opioids, antihistamines, benzodiazepines).

Levodopa and Direct Dopamine Receptor Agonists. Levodopa and the dopamine receptor agonists (eg, bromocriptine) promote activation of dopamine receptors, and may thereby diminish the therapeutic effects of FGAs. Accordingly, patients taking FGAs should not use these drugs.

QT-Prolonging Drugs. Drugs that prolong the QT interval increase the risk of dysrhythmias in patients taking *thioridazine*, *haloperidol*, and *pimozide*, and hence must be avoided. Agents to avoid include tricyclic antidepressants, *thioridazine*, several antidysrhythmic drugs (eg, *amiodarone*, *dofetilide*, *quinidine*), and certain antibiotics (eg, *clarithromycin*, *erythromycin*, *moxifloxacin*, *gatifloxacin*).

SECOND-GENERATION (ATYPICAL) ANTIPSYCHOTICS

Aripiprazole
Asenapine
Clozapine
Iloperidone
Lurasidone
Olanzapine
Paliperidone
Quetiapine
Risperidone
Ziprasidone

Except where indicated, the nursing implications below apply to all SGAs.

Preadministration Assessment

Therapeutic Goal

See *First-Generation (Conventional) Antipsychotics*.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Baseline Data

See *First-Generation (Conventional) Antipsychotics*. Also, obtain baseline measurements of weight, waist circumference, fasting blood glucose, and fasting lipid levels. For patients taking *quetiapine*, examine the lens for cataracts. For patients taking *clozapine*, obtain baseline values for total WBC count and ANC.

Identifying High-Risk Patients

Use all SGAs, and especially *clozapine* and *olanzapine*, with *caution* in patients with diabetes.

Clozapine is *contraindicated* for patients with a history of bone marrow depression or clozapine-induced agranulocytosis, and for those taking myelosuppressive drugs (eg, many anticancer drugs).

Use *clozapine* with *caution* in patients with seizure disorders.

Ziprasidone is *contraindicated* for patients with risk factors for torsades de pointes (eg, hypokalemia, hypomagnesemia, bradycardia, congenital QT prolongation, or a history of dysrhythmias, myocardial infarction, or severe heart failure) and for those taking drugs that prolong the QT interval. Use *asenapine*, *iloperidone*, *quetiapine*, and *paliperidone* with caution in these patients.

Generally *avoid all SGAs* in elderly patients with dementia-related psychosis.

Implementation: Administration

Routes

Oral, IM, and sublingual. Routes for individual agents are summarized in Tables 31-4 and 31-7.

Dosing

To minimize side effects, dosage should be low initially and then gradually increased.

Implementation: Measures to Enhance Therapeutic Effects

Promoting Adherence

See *First-Generation (Conventional) Antipsychotics*.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See *First-Generation (Conventional) Antipsychotics*.

Minimizing Adverse Effects

Compared with the FGAs, the SGAs carry a low risk of sexual dysfunction, neuroendocrine effects, and extrapyramidal reactions, including TD—but they carry a high risk of metabolic effects.

Orthostatic Hypotension and Anticholinergic Effects. See *First-Generation (Conventional) Antipsychotics*.

Agranulocytosis. *Clozapine* produces agranulocytosis in 1% to 2% of patients, typically during the first 6 months of treatment. Deaths from gram-negative septicemia have occurred.

Regular hematologic monitoring is mandatory: WBC count and ANC must be determined weekly for the first

6 months, every 2 weeks for the next 6 months, and monthly thereafter. If the total WBC count falls below 3000/mm³ or if the ANC falls below 1500/mm³, treatment should be interrupted. When subsequent *daily* monitoring indicates that cell counts have risen above these values, clozapine can be resumed. If the total WBC count falls below 2000/mm³ or if the ANC falls below 1000/mm³, clozapine should be permanently discontinued. Continue monitoring blood counts for 4 weeks.

Warn patients about the risk of agranulocytosis, and inform them that clozapine will not be dispensed without repeated proof of blood counts. Inform patients about early signs of infection (fever, sore throat, fatigue, mucous membrane ulceration), and instruct them to report these immediately.

Leukopenia/Neutropenia. *Olanzapine* and *ziprasidone* can cause *leukopenia/neutropenia*, and can thereby increase the risk of infection. For patients at high risk (eg, those with pre-existing low WBC count, those with a history of drug-induced leukopenia/neutropenia), conduct complete blood counts frequently during the first few months of treatment. If the ANC falls below 1000/mm³, these drugs should be discontinued, and the patient monitored for fever and other signs of infection. Neutrophil counts should be monitored until they return to normal.

Metabolic Effects: Weight Gain, Diabetes, and Dyslipidemia. All SGAs—and especially *clozapine* and *olanzapine*—can promote weight gain, which can lead to diabetes and dyslipidemia. To monitor weight gain, determine weight at baseline; 4, 8, and 12 weeks later; and every 3 months thereafter. Also, determine waist circumference at baseline and annually thereafter. **Inform patients about the risk of weight gain and encourage them to control caloric intake and get regular exercise.** If significant weight gain occurs, it can be managed with a combination of diet, exercise, and metformin.

To monitor for diabetes, measure fasting blood glucose at baseline, 12 weeks later, and annually thereafter. In patients with documented diabetes at baseline, monitor for worsening of glucose control. **Inform all patients about symptoms of diabetes—hyperglycemia, polyuria, polydipsia, polyphagia, dehydration—and instruct them to tell the prescriber if they occur.** If diabetes develops, it can be managed with insulin or an oral antidiabetic drug (eg, metformin).

To monitor for *dyslipidemia*, obtain a fasting lipid profile at baseline, 12 weeks later, and every 5 years thereafter.

Seizures. *Clozapine* causes generalized tonic-clonic seizures in 3% of patients. **Warn patients against driving and other hazardous activities if seizures have occurred.**

Sedation. All SGAs—and especially *clozapine* and *olanzapine*—can cause sedation. **Warn patients against driving and participating in other hazardous activities if impairment is significant.**

Extrapyramidal Symptoms. Like the FGAs, the SGAs can cause acute dystonia, parkinsonism, akathisia, and tardive dyskinesia—although the risk is lower than with the FGAs. For nursing implications, see *First-Generation (Conventional) Antipsychotics*.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Myocarditis. Very rarely, *clozapine* causes myocarditis. Inform patients about signs and symptoms (eg, unexplained fatigue, dyspnea, tachypnea, chest pain, palpitations), and advise them to seek immediate medical attention if these develop. Withhold *clozapine* until myocarditis has been ruled out. If myocarditis is diagnosed, the drug should never be used again.

Dysrhythmias. Five SGAs—*asenapine*, *iloperidone*, *paliperidone*, *quetiapine*, and *ziprasidone*—may prolong the QT interval, posing a risk of torsades de pointes, a potentially fatal dysrhythmia. To reduce the risk of dysrhythmias (1) ensure that potassium and magnesium levels are normal, (2) avoid other drugs that cause QT prolongation, and (3) avoid drugs that can increase levels of *ziprasidone*.

Signs of Withdrawal and Extrapyramidal Symptoms in Neonates. Neonates exposed to antipsychotic drugs during the third trimester may experience EPS and/or signs of withdrawal. Symptoms include tremor, agitation, sleepiness, difficulty feeding, severe breathing difficulty, and altered muscle tone (increased or decreased). Neonates who present with EPS or signs of withdrawal should be monitored. Hospitalization may be required. Advise women who become pregnant not to discontinue their medication without consulting the prescriber.

Death in Elderly Dementia Patients. All SGAs increase the risk of mortality when used to treat dementia-related psychosis in elderly patients, an application for which these drugs are not approved. Avoid SGAs in these patients.

Cataracts. *Quetiapine* may pose a risk of cataracts. Examine the lens for cataracts at baseline and every 6 months thereafter.

Minimizing Adverse Interactions

CNS Depressants. Second-generation antipsychotics may intensify CNS depression caused by other drugs. Warn patients against use of alcohol and all other drugs with CNS-depressant properties (eg, barbiturates, opioids, antihistamines, benzodiazepines).

Levodopa and Direct Dopamine Receptor Agonists. Levodopa and the dopamine receptor agonists (eg, bromocriptine) promote activation of dopamine receptors, and may thereby diminish therapeutic effects of the SGAs. Patients taking antipsychotics should not use these drugs.

Myelosuppressive Drugs. *Clozapine* must not be given to patients taking other drugs that can suppress bone marrow function (eg, many anticancer agents).

QT-Prolonging Drugs. Drugs that prolong the QT interval increase the risk of dysrhythmias in patients taking *asenapine*, *iloperidone*, *paliperidone*, *quetiapine*, and *ziprasidone*, and hence must be avoided. Agents to avoid include tricyclic antidepressants, thioridazine, several antidysrhythmic drugs (eg, amiodarone, dofetilide, quinidine), and certain antibiotics (eg, clarithromycin, erythromycin, moxifloxacin, gatifloxacin).

Inducers and Inhibitors of CYP3A4. Drugs that induce CYP3A4 (eg, barbiturates, carbamazepine, phenytoin, rifampin) can reduce levels of *aripiprazole*, *iloperidone*, *lurasidone*, *quetiapine*, and *ziprasidone*, and may thereby cause therapeutic failure. Conversely, drugs that inhibit CYP3A4 (eg, ketoconazole, itraconazole, fluconazole, erythromycin) can increase levels of these five drugs, and may thereby increase toxicity. Use caution if these combinations are employed. Use of *lurasidone* with strong CYP3A4 inhibitors or inducers is contraindicated.

*Patient education information is highlighted as blue text.

MAJOR DEPRESSION: CLINICAL FEATURES, PATHOGENESIS, AND TREATMENT OVERVIEW**DRUGS USED FOR DEPRESSION**

Basic Considerations

Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine

Other SSRIs

Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

Venlafaxine

Desvenlafaxine

Duloxetine

Tricyclic Antidepressants (TCAs)

Monoamine Oxidase Inhibitors (MAOIs)

Oral MAOIs

Transdermal MAOI: Selegiline

Atypical Antidepressants

Bupropion

Mirtazapine

Other Atypical Antidepressants

Nonconventional Drugs for Depression

Ketamine

St. John's Wort

S-Adenosylmethionine

SOMATIC (NONDRUG) THERAPIES FOR DEPRESSION

Electroconvulsive Therapy

Transcranial Magnetic Stimulation

Vagus Nerve Stimulation

Light Therapy

**BOX 32-1. Postpartum Depression**

Our principal focus in this chapter is drugs used to treat major depression. In addition, we consider four somatic (non-drug) therapies. We begin the chapter by discussing depression itself and the basic approach to treatment. After that, we discuss the antidepressant drugs and the somatic therapies.

MAJOR DEPRESSION: CLINICAL FEATURES, PATHOGENESIS, AND TREATMENT OVERVIEW

Depression is the most common psychiatric disorder. In the United States, about 30% of the population will experience some form of depression during their lives. At any given time, about 5% of the adult population is depressed. The incidence in women is twice that in men. The risk of suicide among

TABLE 32-1 ■ DSM-5 Diagnostic Criteria for Major Depression**Diagnostic Criteria for Major Depressive Episode**

- A. Presence of a single *Major Depressive Episode* (as described below)
- B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.
- C. There has never been a Manic Episode or a Hypomanic Episode. (*Note:* This exclusion does not apply if all of the manic-like or hypomanic-like episodes are due to a substance (eg, drug of abuse, medication) or the direct physiologic effects of a general medical condition.)

Criteria for a Major Depressive Episode

- A. At least five of the following criteria must be present for 2 weeks or more, and must represent a change from previous functioning. Furthermore, at least one symptom must be (1) depressed mood or (2) loss of interest or pleasure. (*Note:* Do not include symptoms that are clearly due to a medical condition.)
 1. Depressed mood most of the day, nearly every day. (*Note:* In children and adolescents, can be irritable mood.)
 2. Markedly diminished interest or pleasure in all or almost all activities.
 3. Significant weight loss or weight gain without dieting or decrease or increase in appetite. (*Note:* In children, consider failure to make expected weight gain.)
 4. Insomnia or hypersomnia.
 5. Psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down).
 6. Fatigue or loss of energy.
 7. Feelings of worthlessness or excessive or inappropriate guilt.
 8. Diminished ability to think or concentrate or indecisiveness.
 9. Recurrent thoughts of death, recurrent suicidal ideation, a suicide attempt, or a specific suicide plan.
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The episode is not due to the direct physiologic effects of a substance (eg, drug of abuse, medication).

Modified from the proposed diagnostic criteria for Major Depression and a Major Depressive Episode, to be published in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on November 11, 2011.

depressed people is high. Unfortunately, depression is underdiagnosed and undertreated: Only 30% of depressed individuals receive treatment. This is especially sad in that treatment can help many people: About 40% of those given antidepressants achieve full remission; another 20% to 30% achieve at least a 50% reduction in symptom severity.

Clinical Features

Diagnostic criteria for a major depression are summarized in Table 32-1. As indicated, the principal symptoms are *depressed mood* and *loss of pleasure or interest in all or nearly all of one's usual activities and pastimes*. Associated symptoms include insomnia (or sometimes hypersomnia); anorexia and weight loss (or sometimes hyperphagia and weight gain); mental slowing and loss of concentration; feelings of guilt, worthlessness, and helplessness; thoughts of death and suicide; and overt suicidal behavior. For a diagnosis to be made, symptoms must be present most of the day, nearly every day, for at least 2 weeks.

It is important to distinguish between major depression and normal grief or sadness. Whereas major depression is an illness, grief or sadness is not. Rather, grief and sadness are appropriate reactions to a major life stressor (eg, death of a loved one, loss of a job). In most cases, grief and sadness resolve spontaneously over several weeks and do not require medical intervention. However, if symptoms are unusually intense, and if they fail to resolve within an appropriate time, a major depressive episode may have been superimposed. If this occurs, treatment is indicated.

Pathogenesis

The etiology of major depression is complex and incompletely understood. For some individuals, depression seems to descend "out of the blue"; otherwise healthy people—unexpectedly and without apparent cause—find themselves feeling profoundly depressed. For many others, depressive episodes are brought on by stressful life events, such as bereavement, loss of a job, or childbirth (Box 32-1). Since depression does not occur in everyone, it would appear that some people are more vulnerable than others. Factors that may contribute to

vulnerability include genetic heritage, a difficult childhood, and chronic low self-esteem.

Clinical observations made in the 1960s led to formulation of the *monoamine-deficiency hypothesis of depression*, which asserts that depression is caused by a functional deficiency of monoamine neurotransmitters (norepinephrine, serotonin, or both). Findings that support the hypothesis include (1) induction of depression with reserpine, a drug that depletes monoamines from the brain; (2) induction of depression with inhibitors of tyrosine hydroxylase, an enzyme needed for monoamine transmitter synthesis; and (3) relief of depression with drugs that intensify monoamine-mediated neurotransmission. Although these observations lend support to the monoamine-deficiency hypothesis, it is clear that the hypothesis is too simplistic. However, despite its shortcomings, the monoamine-deficiency hypothesis does provide a useful conceptual framework for understanding antidepressant drugs.

Treatment Overview

Depression can be treated with three major modalities: (1) pharmacotherapy, (2) depression-specific psychotherapy (eg, cognitive behavioral therapy or interpersonal psychotherapy), and (3) somatic therapies, such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation. For patients with mild to moderate depression, drug therapy and psychotherapy can be equally effective. For those with more severe depression, a combination of drug therapy and psychotherapy is better than either intervention alone. Electroconvulsive therapy can be used when a rapid response is needed, or when drugs and psychotherapy have not worked. For all patients, aerobic exercise and resistance training can improve mood.

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BOX 32-1 ■ SPECIAL INTEREST TOPIC

POSTPARTUM DEPRESSION

The vast majority of women (about 80%) experience depressive symptoms after giving birth. For most, the symptoms are mild and transient, reflecting a condition known as the "baby blues." For others, symptoms are severe and persistent, reflecting true postpartum depression, a condition that merits rapid medical attention.

An estimated 60% to 70% of women get the postpartum blues. Symptoms include tearfulness, sadness, nervousness, irritability, and anxiety, along with difficulty eating and sleeping. The new mom may feel overwhelmed, vulnerable, weak, and alone. She may cry for no clear reason. Her self-esteem and self-confidence may decline, and she may feel unqualified to care for her baby. Fortunately, all of these symptoms pass quickly. As a rule, they develop a few days after delivery and are gone by day 10. Because the baby blues are so common, they're considered a normal postpartum event. Treatment is neither necessary nor recommended.

True postpartum depression is different. The condition is much less common than the baby blues, but much more serious. Left untreated, postpartum depression typically lasts for months, and is likely to become worse as time passes. Not only is the condition detrimental to the mother, it can adversely affect the

child, preventing secure attachment and impairing cognitive, emotional, and behavioral development. Accordingly, immediate intervention is indicated.

Just what is postpartum depression? Simply put, it's an episode of major depression that starts after giving birth. Otherwise, the diagnostic criteria are the same as for all other episodes of major depression (see Table 32-1). According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), for a depressive episode to qualify as having postpartum onset, symptoms must begin within 4 weeks of delivery. However, most clinicians who study the disorder use a different criterion: To them, depression is considered postpartum if it begins within 3 months of delivery—not just within 4 weeks.

Who is likely to suffer postpartum depression? Sometimes the condition occurs in first-time mothers, and sometimes it doesn't strike until a second, third, or fourth child is born. Among first-time mothers, the incidence is between 8% and 15% (about 1 in 8). For women with a history of the disorder, the risk increases to 33% (1 in 3). In addition to a prior history of the disorder, risk factors include a history of depression unrelated to childbirth, a history of premenstrual dysphoric disorder (ie, severe premenstrual syndrome), and major stress re-

Continued

lated to family, work, or residence (eg, death of a loved one, loss of a job, moving away from a familiar town or city).

The underlying cause of postpartum depression is unknown, but several factors are thought to contribute. Heading the list is the sharp drop in estrogen and progesterone levels that occurs after delivery. (Levels of these hormones increase 10-fold during pregnancy, and then return to baseline after the placenta is expelled.) However, since hormone levels fall in all women, but only some get postpartum depression, other factors—physical, emotional, and social—must be involved. The birthing process leaves women feeling weak and fatigued. Caring for a baby, who needs round-the-clock attention and feeding, exacerbates tiredness and exhaustion. Emotional and social factors may also play a role. Feelings of loss are common: Women experience loss of freedom, loss of control, and even loss of identity. In addition, they may feel loss of attractiveness. Stress increases substantially, owing to increased workload and responsibilities, coupled with feelings of self-doubt and inadequacy, and compounded by a self-imposed (albeit highly unrealistic) expectation to be a “perfect” mom. Stress can be made even worse by financial insecurity and inadequate support from one’s partner, family, and friends. Thyroid insufficiency may also contribute: Levels of thyroid hormone often decline after delivery, thereby causing symptoms that can mimic depression. Accordingly, thyroid levels should be checked and, if indicated, replacement therapy should be implemented.

Screening for postpartum depression can be accomplished with a quick test: the Edinburgh Postnatal Depression Scale. The test is administered 6 to 8 weeks after delivery and contains the following short statements:

1. I have been able to laugh and see the funny side of things.
2. I have looked forward with enjoyment to things.
3. I have blamed myself unnecessarily when things went wrong.
4. I have been anxious or worried for no good reason.
5. I have felt scared or panicky for no very good reason.
6. Things have been getting on top of me.
7. I have been so unhappy that I have had difficulty sleeping.
8. I have felt sad or miserable.
9. I have been so unhappy that I have been crying.
10. The thought of harming myself has occurred to me.

Each statement has four possible responses, such as these for statement 10: (1) yes, quite often, (2) sometimes, (3) hardly ever, and (4) never. When taking the test, the mother simply underlines the option that best reflects her feelings during the previous week. If her responses indicate she probably has postpartum depression, she should undergo clinical evaluation to establish a definitive diagnosis.

DRUGS USED FOR DEPRESSION

Drugs are the primary therapy for major depression. However, benefits are limited mainly to patients with *severe* depression. In patients with *mild to moderate* depression, antidepressants have little or no beneficial effect.

Available antidepressants are listed in Table 32-2. As indicated, these drugs fall into five major classes: selective

Treatment of postpartum depression is much like treatment of major depression unrelated to pregnancy. The goal is to normalize mood, and optimize maternal and social functioning. The principal treatment modalities are psychotherapy and antidepressant drugs, both of which can be effective. In addition, the woman should be encouraged to nurture herself as well as her baby: She should:

- Reduce isolation (by going out for at least a short time each day)
- Ensure adequate rest (by doing only what’s really needed and letting the rest go)
- Spend time alone with her partner.

Other beneficial measures include joining a support group for new mothers and recruiting family members and friends to assist with household and baby-related chores.

Although antidepressants are clearly appropriate, there are few published data to guide selection. In one study of women with postpartum depression, fluoxetine [Prozac], a selective serotonin reuptake inhibitor (SSRI), was compared with psychotherapy. Both treatments were equally effective, and both were superior to placebo. Efficacy has also been demonstrated for sertraline [Zoloft], venlafaxine [Effexor], and certain tricyclic antidepressants (TCAs). For initial therapy, an SSRI is an attractive choice. Why? Because these drugs are effective and well tolerated, and present little risk of toxicity if taken in overdose. However, if a woman has responded to an antidepressant from a different class in the past, that drug should be tried first. To minimize side effects, dosage should be low initially (50% of the usual starting dosage) and then gradually increased. To reduce the risk of relapse, treatment should continue for at least 6 months after symptoms have resolved. Unfortunately, even then the relapse rate is high: Between 50% and 85% of patients experience at least one more depressive episode. With each succeeding episode, the risk of another recurrence increases. Accordingly, long-term prophylactic therapy should be considered.

Which antidepressants can be taken safely while breastfeeding? All of these drugs can be detected in breast milk—but levels of some are much lower (safer) than levels of others. Sertraline, for example, appears very safe. Studies show that drug activity in breast-fed infants is extremely low, and no adverse reactions have been observed. The TCAs (eg, nortriptyline, desipramine) also appear safe: Levels are too low for detection in breast-fed infants, and follow-up studies have found no developmental deficits. In contrast to sertraline and the TCAs, fluoxetine appears unsafe: The drug and its metabolites reach therapeutic levels in breast-fed infants; potential consequences include colic and impaired weight gain.

serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants. All of these classes are equally effective, as are the individual drugs within each class. Hence, differences among these drugs relate mainly to side effects and drug interactions.

TABLE 32-2 • Antidepressant Classes and Adult Dosages

Generic Name	Trade Name	Initial Dose ^{*,†} (mg/day)	Maintenance Dose* (mg/day)
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Citalopram	Celexa	20	20–60
Escitalopram	Lexapro, Cipralex [‡]	10	10–20
Fluoxetine	Prozac	20	20–60
Fluvoxamine [‡]	Luvox	50	50–300
Paroxetine	Paxil, Pexeva	12.5–20	20–50
Sertraline	Zoloft	50	50–200
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)			
Desvenlafaxine	Pristiq	50	50
Duloxetine	Cymbalta	60	40–120
Venlafaxine	Effexor XR	37.5	75–375
Tricyclic Antidepressants (TCAs)			
Amitriptyline	generic only	25–50	100–300
Clomipramine [‡]	Anafranil	25	100–250
Desipramine	Norpramin	25–50	100–300
Doxepin	Sinequan [§]	50	75–300
Imipramine	Tofranil	25–50	100–300
Maprotiline	generic only	75	100–225
Nortriptyline	Aventyl, Pamelor	25	50–200
Protriptyline	Vivactil	10–20	20–60
Trimipramine	Surmontil	25–50	75–300
Monoamine Oxidase Inhibitors (MAOIs)			
Isocarboxazid	Marplan	10–20	30–60
Phenelzine	Nardil	15	45–90
Selegiline (transdermal)	Emsam	6	6–12
Tranylcypromine	Parnate	10	30–60
Atypical Antidepressants			
Amoxapine	generic only	50	200–400
Bupropion	Wellbutrin, others	150	300–450
Mirtazapine	Remeron	15	15–45
Nefazodone	generic only	50	150–300
Trazodone	generic only	150	150–600
Vilazodone	Viibryd	10	40

*Doses listed are *total daily doses*. Depending on the drug and the patient, the total dose may be given in a single dose or in divided doses.

†Initial doses are employed for 4 to 8 weeks, the time required for most symptoms to respond. Dosage is gradually increased as required.

‡Fluvoxamine and clomipramine are not approved for major depression.

§Doxepin is also available in a low-dose formulation, sold as *Silenor*, for treating insomnia.

BASIC CONSIDERATIONS

In this section we consider basic issues that apply to all antidepressant drugs. The information on suicide risk is especially important.

Time Course of Response

With all antidepressants, symptoms resolve slowly. Initial responses develop in 1 to 3 weeks. Maximal responses may not be seen until 12 weeks. Because therapeutic effects are delayed, antidepressants cannot be used PRN. Furthermore, a therapeutic trial should not be considered a failure until a drug has been taken for at least 1 month without success.

Drug Selection

Since all antidepressants have nearly equal efficacy, selection among them is based largely on tolerability and safety. Additional considerations are drug interactions, patient preference,

and cost. The usual drugs of first choice are the SSRIs, SNRIs, bupropion, and mirtazapine. Older antidepressants—TCAs and MAOIs—are more dangerous and less well tolerated than the first-line agents, and hence are generally reserved for patients who have not responded to the first-line drugs.

In some cases, the side effects of a drug, when matched to the right patient, can actually be beneficial. Here are some examples:

- For a patient with fatigue, choose a drug that causes CNS stimulation (eg, fluoxetine, bupropion).
- For a patient with insomnia, choose a drug that causes substantial sedation (eg, mirtazapine).
- For a patient with sexual dysfunction, choose bupropion, a drug that enhances libido.
- For a patient with chronic pain, choose duloxetine or a TCA, drugs that can relieve chronic pain.

Managing Treatment

Once a drug has been selected for initial treatment, it should be used for 4 to 8 weeks to assess efficacy. As a rule, dosage should be low initially (to reduce side effects), and then gradually increased (see Table 32-2). If the initial drug is not effective, we have four major options. Specifically, we can:

- Increase the dosage
- Switch to another drug in the same class
- Switch to another drug in a different class
- Add a second drug, such as lithium, thyroid hormone, or an atypical antidepressant

After symptoms are in remission, treatment should continue for at least 4 to 9 months to prevent relapse. To this end, patients should be encouraged to take their drugs even if they are symptom free, and hence feel that continued dosing is unnecessary. When antidepressant therapy is discontinued, dosage should be gradually tapered over several weeks. Why? Because abrupt withdrawal can trigger withdrawal symptoms.

Suicide Risk with Antidepressant Drugs

Patients with depression often think about or attempt suicide. During treatment with antidepressants, especially early on, the risk of suicide may actually *increase*. Which antidepressants increase the risk of suicide? All of them: According to two recent reports, risk appears equal for all antidepressant groups, and for all individual drugs within those groups. In recognition of this risk, all antidepressants now carry a black box warning about a possible increase in suicidal thoughts or behavior. Concerns about antidepressant-induced suicide apply mainly to children, adolescents, and adults under the age of 25.

To reduce the risk of suicide, patients taking antidepressant drugs should be observed closely for suicidality, worsening mood, and unusual changes in behavior. Close observation is especially important during the first few months of therapy and whenever antidepressant dosage is changed (either increased or decreased). Ideally, the patient or caregiver should meet with the prescriber at least weekly during the first 4 weeks of treatment, then biweekly for the next 4 weeks, then once 1 month later, and periodically thereafter. Phone contact may be appropriate between visits. In addition, family members or caregivers should monitor the patient *daily*, being alert for symptoms of decline (eg, anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, hypomania, and, of course, emergence of suicidality). If these symptoms are severe or develop abruptly, the patient should see his or her prescriber immediately.

Because antidepressant drugs can be used to *commit* suicide, two precautions should be observed. First, prescriptions should be written for the smallest number of doses consistent with good patient management. Second, dosing of inpatients should be directly observed to ensure that each dose is swallowed and not "cheeked," thereby preventing the patient from accumulating multiple doses that might be taken with suicidal intent.

What should be done if suicidal thoughts emerge during drug therapy, or if depression is persistently worse while taking drugs? One option is to switch to another antidepressant. However, as noted, the risk of suicidality appears equal with

all antidepressants. Another option is to stop antidepressants entirely. However, this option is probably unwise. Why? Because the long-term risk of suicide from untreated depression is much greater than the long-term risk associated with antidepressant drugs. If the risk of suicide appears high, temporary hospitalization may be the best protection.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

The SSRIs were introduced in 1987 and have since become our most commonly prescribed antidepressants, accounting for over \$3 billion in annual sales. These drugs are indicated for major depression as well as several other psychological disorders (Table 32-3). Characteristic side effects are nausea, agitation/insomnia, and sexual dysfunction (especially anorgasmia). The SSRIs can interact adversely with MAOIs and other serotonergic drugs, and hence these combinations must be avoided. In addition, when used late in pregnancy, SSRIs can lead to a withdrawal syndrome and persistent pulmonary hypertension in the infant. Like all other antidepressants, SSRIs may increase the risk of suicide. Compared with the TCAs and MAOIs, SSRIs are equally effective, better tolerated, and much safer. Death by overdose is extremely rare.

Fluoxetine

Fluoxetine [Prozac, Prozac Weekly, Sarafem, Selfemra], the first SSRI available, will serve as our prototype for the group. At one time, this drug was the most widely prescribed antidepressant in the world, and its commercial success led *Fortune* magazine to call it one of the "Products of the Century."

Mechanism of Action

The mechanism of action of fluoxetine and the other SSRIs is depicted in Figure 32-1. As shown, SSRIs selectively block neuronal reuptake of serotonin (5-hydroxytryptamine, or 5-HT), a monoamine neurotransmitter. As a result of reuptake blockade, the concentration of 5-HT in the synapse increases, causing increased activation of postsynaptic 5-HT receptors. This mechanism is consistent with the theory that depression stems from a *deficiency* in monoamine-mediated transmission—and hence should be relieved by drugs that can intensify monoamine effects.

It is important to appreciate that blockade of 5-HT reuptake, by itself, cannot fully account for therapeutic effects. Why? Because clinical responses to SSRIs (relief of depressive symptoms) and the biochemical effect of the SSRIs (blockade of 5-HT reuptake) do not occur in the same time frame. That is, whereas SSRIs block 5-HT reuptake within hours of dosing, relief of depression takes several weeks to fully develop. This delay suggests that therapeutic effects are the result of adaptive cellular changes that take place in response to prolonged reuptake blockade. Fluoxetine and the other SSRIs do not block reuptake of dopamine or norepinephrine (NE). In contrast to the TCAs (see below), fluoxetine does not block cholinergic, histaminergic, or α -adrenergic receptors. Furthermore, fluoxetine produces CNS excitation rather than sedation.

TABLE 32-3 ■ Therapeutic Uses of Selective Serotonin Reuptake Inhibitors

Drug	Therapeutic Use*†							
	Major Depression	OCD	Panic Disorder	Social Phobia	GAD	PTSD	PMDD	Bulimia Nervosa
Citalopram [Celexa]	A	U	U	U	U	U	U	
Escitalopram [Lexapro]	A	A	U		A	U		
Fluoxetine [Prozac]	A	A	A	U	U	U	A	A
Fluvoxamine [Luvox]	U	A	U	A	U	U	U	U
Paroxetine [Paxil]	A	A	A	A	A	A	A	
Sertraline [Zoloft]	A	A	A	A	U	A	A	

*A = approved use, U = unlabeled use.

†GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, PMDD = premenstrual dysphoric disorder, PTSD = post-traumatic stress disorder.

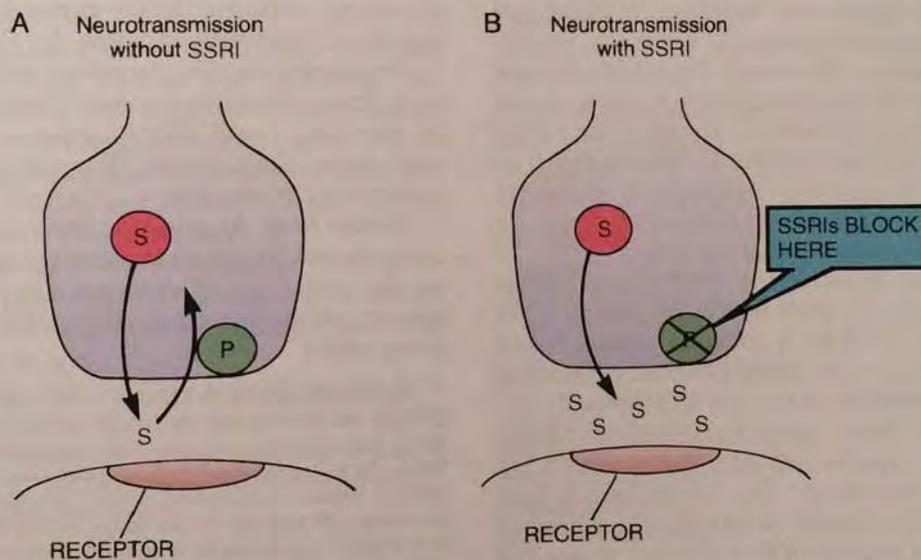


Figure 32-1 ■ Mechanism of action of selective serotonin reuptake inhibitors.

A, Under drug-free conditions, the actions of serotonin are terminated by active uptake of the transmitter back into the nerve terminals from which it was released. B, By inhibiting the reuptake pump for serotonin, the SSRIs cause the transmitter to accumulate in the synaptic space, thereby intensifying transmission. (P = uptake pump, S = serotonin, SSRI = selective serotonin reuptake inhibitor.)

Therapeutic Uses

Fluoxetine is used primarily for major depression. In addition, the drug is approved for bipolar disorder (see Chapter 33), obsessive-compulsive disorder (see Chapter 35), panic disorder (see Chapter 35), bulimia nervosa, and premenstrual dysphoric disorder (see Chapter 61). Unlabeled uses include post-traumatic stress disorder, social phobia, alcoholism, attention-deficit/hyperactivity disorder, migraine, Tourette's syndrome, and obesity.

Pharmacokinetics

Fluoxetine is well absorbed following oral administration, even in the presence of food. The drug is widely distributed and highly bound to plasma proteins. Fluoxetine undergoes extensive hepatic metabolism, primarily by CYP2D6 (the 2D6 isozyme of cytochrome P450). The major metabolite—norfluoxetine—is active, and later undergoes metabolic inactivation, followed by excretion in the urine. The half-life of fluoxetine is 2 days and the half-life of norfluoxetine is 7 days.

Because the effective half-life is prolonged, about 4 weeks are required to produce steady-state plasma drug levels—and about 4 weeks are required for washout after dosing stops.

Adverse Effects

Fluoxetine is safer and better tolerated than TCAs and MAOIs. Death from overdose with fluoxetine alone has not been reported. In contrast to TCAs, fluoxetine does not block receptors for histamine, NE, or acetylcholine, and hence does not cause sedation, orthostatic hypotension, anticholinergic effects, or cardiotoxicity. The most common side effects are sexual dysfunction (70%), nausea (21%), headache (20%), and manifestations of CNS stimulation, including nervousness (15%), insomnia (14%), and anxiety (10%). Weight gain can also occur. Fluoxetine and most other SSRIs appear safe for use during pregnancy. Paroxetine is the principal exception (see below).

Sexual Dysfunction. Fluoxetine causes sexual problems (impotence, delayed or absent orgasm, delayed or absent ejaculation, decreased sexual interest) in nearly 70% of men and women. The underlying mechanism is unknown.

Sexual dysfunction can be managed in several ways. In some cases, reducing the dosage or taking “drug holidays” (eg, discontinuing medication on Fridays and Saturdays) can help. Another solution is to add a drug that can overcome the problem. Among these are yohimbine, buspirone [BuSpar], and three atypical antidepressants: bupropion [Wellbutrin, others], nefazodone, and mirtazapine [Remeron]. Drugs like sildenafil [Viagra] can also help: In *men*, these drugs improve erectile dysfunction, as well as arousal, ejaculation, orgasm, and overall satisfaction; in *women*, they can improve delayed orgasm. If all of these measures fail, the patient can try a different antidepressant. Agents that cause the least sexual dysfunction are the same three atypical antidepressants just mentioned.

Sexual problems often go unreported, either because patients are uncomfortable discussing them or because patients don't realize their medicine is the cause. Accordingly, patients should be informed about the high probability of sexual dysfunction and told to report any problems so they can be addressed.

Weight Gain. Like many other antidepressants, fluoxetine and other SSRIs cause weight gain. When these drugs were first introduced, we thought they caused weight loss. Why? Because during the first few weeks of therapy patients do lose weight, perhaps because of drug-induced nausea and vomiting. However, with long-term treatment, the lost weight is regained. Furthermore, about one-third of patients continue putting on weight—up to 20 pounds or more. Although the reason for weight gain is unknown, a good possibility is decreased sensitivity of 5-HT receptors that regulate appetite.

Serotonin Syndrome. By increasing serotonergic transmission in the brainstem and spinal cord, fluoxetine and other SSRIs can cause serotonin syndrome. This syndrome usually begins 2 to 72 hours after treatment onset. Signs and symptoms include altered mental status (agitation, confusion, disorientation, anxiety, hallucinations, poor concentration) as well as incoordination, myoclonus, hyperreflexia, excessive sweating, tremor, and fever. Deaths have occurred. The syndrome resolves spontaneously after discontinuing the drug. The risk of serotonin syndrome is increased by concurrent use of MAOIs and other drugs (see below under Drug Interactions).

Withdrawal Syndrome. Abrupt discontinuation of SSRIs can cause a withdrawal syndrome. Symptoms include dizziness, headache, nausea, sensory disturbances, tremor, anxiety,

and dysphoria. These begin within days to weeks of the last dose, and then persist for 1 to 3 weeks. Resumption of drug use will make symptoms subside. The withdrawal syndrome can be minimized by tapering the dosage slowly. Of the SSRIs in use today, fluoxetine is least likely to cause a withdrawal reaction. Why? Because fluoxetine has a prolonged half-life. Hence, when dosing is stopped, plasma levels decline slowly. When SSRIs are discontinued, it is important to distinguish between symptoms of withdrawal and return of depression.

Neonatal Effects from Use in Pregnancy. Use of fluoxetine and other SSRIs late in pregnancy poses a small risk of two adverse effects in the newborn: (1) *neonatal abstinence syndrome* (NAS) and (2) *persistent pulmonary hypertension of the newborn* (PPHN). NAS is characterized by irritability, abnormal crying, tremor, respiratory distress, and possibly seizures. The syndrome can be managed with supportive care and generally abates within a few days. PPHN, which compromises tissue oxygenation, carries a significant risk of death, and, among survivors, a risk of cognitive delay, hearing loss, and neurologic abnormalities. Treatment measures include providing ventilatory support, giving oxygen and nitric oxide (to dilate pulmonary blood vessels), and giving IV sodium bicarbonate (to maintain alkalosis) and dopamine or dobutamine (to increase cardiac output, and thereby maintain pulmonary perfusion). Infants exposed to SSRIs late in gestation should be monitored closely for NAS and PPHN.

Teratogenesis. Do fluoxetine and other SSRIs cause birth defects? Probably not. And if they do, the risk appears to be very low. Two SSRIs—*paroxetine* and *fluoxetine*—may cause septal heart defects. But even with these agents, the absolute risk is very low.

Suicide Risk. As discussed above, antidepressants may increase the risk of suicide in depressed patients, especially during the early phase of treatment. The risk of antidepressant-induced suicide is greatest among children, adolescents, and young adults.

Extrapyramidal Side Effects. SSRIs cause extrapyramidal symptoms (EPS) in about 0.1% of patients. This is much less frequent than among patients taking antipsychotic medications (see Chapter 31). Among patients taking SSRIs, the most common EPS is akathisia, characterized by restlessness and agitation. However, parkinsonism, dystonic reactions, and tardive dyskinesia can also occur. EPS typically develop during the first month of treatment. The risk is increased by concurrent use of an antipsychotic drug. The underlying cause of SSRI-induced EPS may be alteration of serotonergic transmission within the extrapyramidal system. For a detailed discussion of EPS, refer to Chapter 31.

Bruxism. SSRIs may cause bruxism (clenching and grinding of teeth). However, since bruxism usually occurs during sleep, the condition often goes unrecognized. Sequelae of bruxism include headache, jaw pain, and dental problems (eg, cracked fillings).

How do SSRIs cause bruxism? One theory is that they inhibit release of dopamine, a neurotransmitter that suppresses activity in certain muscles, including those of the jaw. By decreasing dopamine availability, SSRIs could release these muscles from inhibition, and excessive activity could result. This same mechanism may be responsible for SSRI-induced EPS.

How can bruxism be managed? One option is to reduce the SSRI dosage. However, this may cause depression to return. Other options include switching to a different class of antidepressant, use of a mouth guard, and treatment with low-dose buspirone (5 to 10 mg 1 to 3 times a day).

Bleeding Disorders. Fluoxetine and other SSRIs can increase the risk of bleeding in the GI tract and at other sites. How? By impeding platelet aggregation: Platelets require 5-HT for aggregation, but can't make it themselves, and hence must take 5-HT up from the blood; by blocking 5-HT uptake, SSRIs suppress aggregation. The SSRIs cause a threefold increase in the risk of GI bleeding. However, the absolute risk is still low (about 1 case for every 8000 prescriptions). Caution is advised in patients with ulcers or a history of GI bleeding, in patients older than 60, and in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulants.

Fluoxetine and other SSRIs have been associated with an increased risk of hemorrhagic stroke. However, a causal relationship has not been established.

Hyponatremia. Fluoxetine can cause hyponatremia (serum sodium below 135 mEq/L), probably by increasing secretion of antidiuretic hormone. Most cases involve older patients taking thiazide diuretics. Accordingly, when fluoxetine is used in older patients, sodium should be measured at baseline and periodically thereafter.

Other Adverse Effects. Fluoxetine may cause *dizziness* and *fatigue*; patients who experience intense dizziness and fatigue should be warned against driving and other hazardous activities. *Skin rash*, which can be severe, has occurred in 4% of patients; in most cases, rashes readily respond to drug therapy (antihistamines, glucocorticoids) or to withdrawal of fluoxetine. Other common reactions include *diarrhea* (12%) and *excessive sweating* (8%).

Drug Interactions

MAOIs and Other Drugs That Increase the Risk of Serotonin Syndrome. MAOIs increase 5-HT availability, and hence greatly increase the risk of serotonin syndrome. Accordingly, use of MAOIs with SSRIs is *contraindicated*. Because MAOIs cause *irreversible* inhibition of monoamine oxidase (MAO; see below), their effects persist long after dosing stops. Therefore, MAOIs should be withdrawn at least 14 days before starting an SSRI. Because fluoxetine and its active metabolite have long half-lives, at least 5 weeks should elapse between stopping fluoxetine and starting an MAOI. For other SSRIs, at least 2 weeks should elapse between treatment cessation and starting an MAOI.

Other drugs that increase the risk of serotonin syndrome include the serotonergic drugs listed in Table 32-4, drugs that inhibit CYP2D6 (and thereby raise fluoxetine levels), tramadol (an analgesic), and linezolid (an antibiotic that inhibits MAO).

Tricyclic Antidepressants and Lithium. Fluoxetine can elevate plasma levels of TCAs and lithium. Exercise caution if fluoxetine is combined with these agents.

Antiplatelet Drugs and Anticoagulants. Antiplatelet drugs (eg, aspirin, NSAIDs) and anticoagulants (eg, warfarin) increase the risk of GI bleeding. Exercise caution if fluoxetine is combined with these drugs.

The risk of bleeding with *warfarin* is compounded by a pharmacokinetic interaction. Because fluoxetine is highly bound to plasma proteins, it can displace other highly bound drugs. Displacement of *warfarin* is of particular concern. Monitor responses to *warfarin* closely.

Drugs That Are Substrates for or Inhibitors of CYP2D6. Fluoxetine and most other SSRIs are inactivated by CYP2D6. Accordingly, drugs that inhibit this enzyme can raise SSRI levels, thereby posing a risk of toxicity.

In addition to being a substrate for CYP2D6, fluoxetine itself can *inhibit* CYP2D6. As a result, fluoxetine can raise levels of other drugs that are CYP2D6 substrates. Among these are TCAs, several antipsychotics, and two antiarrhythmics: propafenone and flecainide. Combined use of fluoxetine with these drugs should be done with caution.

Preparations, Dosage, and Administration

Preparations. Fluoxetine is available in several oral formulations and is sold under four trade names: Prozac, Prozac Weekly, Sarafem, and Selfemra. Products available under each trade name are as follows:

- Prozac—oral solution (20 mg/5 mL)
- Prozac Pulvules—capsules (10, 20, and 40 mg)
- Prozac Weekly—delayed-release, enteric-coated capsules (90 mg)
- Sarafem—tablets (10, 15, and 20 mg)
- Sarafem Pulvules—capsules (10 and 20 mg)
- Selfemra—capsules (10 and 20 mg)

In addition to these single-ingredient products, fluoxetine is available in a fixed-dose combination with olanzapine (an antipsychotic), sold as *Symbyax*, for treating bipolar disorder (see Chapter 33) and treatment-resistant major depression.

TABLE 32-4 ■ Drugs That Promote Activation of Serotonin Receptors

Drug	Mechanism
Selective Serotonin Reuptake Inhibitors (SSRIs)	
Citalopram [Celexa]	Block 5-HT reuptake and thereby increase 5-HT in the synapse
Escitalopram [Lexapro, Cipralex ♣]	
Fluoxetine [Prozac]	
Fluvoxamine [Luvox]	
Paroxetine [Paxil]	
Sertraline [Zoloft]	
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)	
Desvenlafaxine [Pristiq]	Same as SSRIs
Duloxetine [Cymbalta]	
Venlafaxine [Effexor]	
Tricyclic Antidepressants (TCAs)	
Amitriptyline	Same as SSRIs
Clomipramine [Anafranil]	
Doxepin [Sinequan]	
Imipramine [Tofranil]	
Trimipramine [Surmontil]	
Monoamine Oxidase Inhibitors (MAOIs)	
Desipramine [Norpramin]	Inhibit neuronal breakdown of 5-HT by MAO, and thereby increase stores of 5-HT available for release
Isocarboxazid [Marplan]	
Phenelzine [Nardil]	
Selegiline [Emsam]	
Atypical Antidepressants	
Mirtazapine [Remeron]	Promotes release of 5-HT
Nefazodone	Same as SSRIs
Trazodone [Oleptro]	Same as SSRIs
Analgesics	
Meperidine [Demerol]	Same as SSRIs and MAOIs
Methadone [Dolophine]	Same as MAOIs?
Tramadol [Ultram]	Same as SSRIs
Triptan Antimigraine Drugs	
Almotriptan [Axert]	Cause direct activation of serotonin receptors
Eletriptan [Relpax]	
Frovatriptan [Frova]	
Rizatriptan [Maxalt]	
Sumatriptan [Imitrex]	
Zolmitriptan [Zomig]	
Others	
St. John's wort	Same as SSRIs and MAOIs
Linezolid [Zyvox]	Same as MAOIs

5-HT = serotonin, MAO = monoamine oxidase.

Dosage for Depression. Daily Dosing. The recommended initial dosage is 20 mg/day, taken with or without food. If needed, dosage may be increased gradually to a maximum of 80 mg/day. However, doses greater than 20 mg/day may increase adverse effects without increasing benefits. If daily doses above 20 mg are used, they should be divided. For elderly patients and patients with impaired liver function, the dosage should be low initially and then cautiously increased if needed. Since fluoxetine often impairs sleep, evening dosing should generally be avoided.

Weekly Dosing. Patients who have been treated successfully with 20 mg of fluoxetine daily for at least 13 weeks can be switched to once-weekly dosing (using 90-mg delayed-release capsules) for maintenance. Weekly dosing is initiated 7 days after the last 20-mg dose of daily fluoxetine.

Withdrawal. When discontinuing the drug, dosage should be reduced gradually.

Other SSRIs

In addition to fluoxetine, five other SSRIs are available: citalopram [Celexa], escitalopram [Lexapro, Cipralex[®]], fluvoxamine [Luvox], paroxetine [Paxil, Pexeva], and sertraline [Zoloft]. All five are similar to fluoxetine. Antidepressant effects equal those of TCAs. Characteristic side effects are nausea, insomnia, headache, nervousness, weight gain, sexual dysfunction, hyponatremia, GI bleeding, and NAS and PPHN (in infants who were exposed to these drugs late in gestation). Serotonin syndrome is a potential complication with all SSRIs, especially if these agents are combined with MAOIs or other serotonergic drugs. The principal differences among the SSRIs relate to duration of action. Patients who experience intolerable adverse effects with one SSRI may find a different SSRI more acceptable. As with fluoxetine, withdrawal should be done slowly. In contrast to the TCAs, the SSRIs do not cause hypotension or anticholinergic effects, and, with the exception of fluvoxamine, do not cause sedation. When taken in overdose, these drugs do not cause cardiotoxicity. Therapeutic uses for individual SSRIs are summarized in Table 32-3.

Sertraline

Sertraline [Zoloft] is much like fluoxetine: both drugs block reuptake of 5-HT, both relieve symptoms of major depression, both cause CNS stimulation rather than sedation, and both have minimal effects on seizure threshold and the electrocardiogram (ECG). Sertraline is indicated for major depression, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder (social phobia). The drug is used off-label to treat generalized anxiety disorder.

Sertraline is slowly absorbed following oral administration. Food increases the extent of absorption. In the blood, the drug is highly bound (99%) to plasma proteins. Sertraline undergoes extensive hepatic metabolism followed by elimination in the urine and feces. The plasma half-life is approximately 1 day.

Common side effects include headache, tremor, insomnia, agitation, nervousness, nausea, diarrhea, weight gain, and sexual dysfunction. Treatment may also increase the risk of suicide. Because of the risk of serotonin syndrome, sertraline must not be combined with MAOIs and other serotonergic drugs (see Table 32-4). MAOIs should be withdrawn at least 14 days before starting sertraline, and sertraline should be withdrawn at least 14 days before starting an MAOI. Because of a risk of pimozide-induced dysrhythmias, sertraline (which raises pimozide levels) and pimozide should not be combined. Like fluoxetine and other SSRIs, sertraline poses a risk of hyponatremia, GI bleeding, and NAS and PPHN when used late in pregnancy.

Sertraline is available in tablets (25, 50, and 100 mg) and a concentrated oral solution (20 mg/mL). For treatment of depression, the initial adult daily dosage is 50 mg, administered in the morning or evening. After 4 to 8 weeks, the dosage may be increased by 50-mg increments to a maximum of 200 mg/day. When discontinuing the drug, dosage should be reduced gradually.

Fluvoxamine

Like other SSRIs, fluvoxamine [Luvox] produces powerful and selective inhibition of 5-HT reuptake. The drug is approved for obsessive-compulsive disorder and social anxiety disorder. Unlabeled uses include major depression, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and bulimia nervosa.

Fluvoxamine is rapidly absorbed from the GI tract, both in the presence and absence of food. The drug undergoes extensive hepatic metabolism followed by excretion in the urine. The half-life is about 15 hours.

Common side effects include nausea, vomiting, dry mouth, headache, constipation, weight gain, and sexual dysfunction. In contrast to other SSRIs, fluvoxamine has moderate sedative effects, although it nonetheless can cause insomnia. Some patients have developed abnormal liver function tests. Accordingly, liver function should be assessed prior to treatment and weekly during the first month of therapy. Like other SSRIs, fluvoxamine interacts adversely with MAOIs and other serotonergic drugs, and hence these combinations must be avoided. As with other SSRIs, fluvoxamine poses a risk of hyponatremia, GI bleeding, and NAS and PPHN in infants exposed to the drug *in utero*.

Fluvoxamine is available in immediate-release tablets (25-, 50-, and 100-mg), sold as *Luvox*, and controlled-release capsules (100 and 150 mg), sold as *Luvox CR*. With the immediate-release formulation, dosing begins at 50

mg once a day at bedtime, and can be gradually increased to a maximum of 300 mg/day, given in two divided doses when the daily total exceeds 100 mg. With the controlled-release capsules, dosing begins at 100 mg once daily, and can be gradually increased to 300 mg once daily. With either formulation, drug withdrawal should be done gradually.

Paroxetine

Like other SSRIs, paroxetine [Paxil, Paxil CR, Pexeva] produces powerful and selective inhibition of 5-HT reuptake. The drug is indicated for major depression, obsessive-compulsive disorder, social anxiety disorder, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, and premenstrual dysphoric disorder. Paroxetine is used off-label to treat bipolar disorder and postmenopausal hot flashes.

Paroxetine is well absorbed following oral administration, even in the presence of food. The drug is widely distributed and highly bound (95%) to plasma proteins. Concentrations in breast milk equal those in plasma. The drug undergoes hepatic metabolism followed by renal excretion. The half-life is about 20 hours.

Side effects are dose-dependent and generally mild. Early reactions include nausea, somnolence, sweating, tremor, and fatigue. These tend to diminish over time. After 5 to 6 weeks, the major complaints are headache, weight gain, and sexual dysfunction. Like fluoxetine, paroxetine causes signs of CNS stimulation (increased awakenings, reduced time in rapid-eye-movement sleep, insomnia). In contrast to TCAs, paroxetine has no effect on heart rate, blood pressure, or the ECG—but does have some antimuscarinic effects. Like other SSRIs, paroxetine interacts adversely with MAOIs and other serotonergic drugs, and hence these combinations must be avoided. Also, like other SSRIs, paroxetine can increase the risk of GI bleeding, and can cause hyponatremia (especially in elderly patients taking thiazide diuretics). As with other SSRIs, use late in pregnancy can result in NAS and PPHN. In addition, paroxetine, but not other SSRIs (except possibly fluoxetine), poses a small risk of cardiovascular birth defects, primarily ventricular septal defects. Because of this risk, the drug is classified in FDA Pregnancy Risk Category D. Like all other antidepressants, paroxetine may increase the risk of suicide, especially in children and young adults.

Paroxetine is available as two salts: paroxetine *hydrochloride* and paroxetine *mesylate*. Although the two preparations have not been compared directly, effects are likely to be identical. The hydrochloride salt is available in immediate-release (IR) tablets (10, 20, 30, and 40 mg) and an oral suspension (2 mg/mL) as *Paxil*, and controlled-release (CR) tablets (12.5, 25, and 37.5 mg) as *Paxil CR*. Please note that the CR tablets are *not* longer acting than the IR tablets. Rather, the CR tablets are designed to dissolve in the lower intestine, and hence may cause less GI disturbance than the IR tablets. The mesylate salt [Pexeva] is available only in tablets (10, 20, 30, and 40 mg).

The initial dosage for depression is 12.5 to 20 mg/day. The entire daily dose is administered in the morning (to minimize sleep disturbance) and with food (to minimize GI upset). Dosage may be increased gradually (every 2 to 4 weeks) to a maximum of 50 mg/day. When discontinuing the drug, dosage should be reduced gradually.

Citalopram

Citalopram [Celexa] is very similar to fluoxetine and the other SSRIs. Benefits derive from selective blockade of 5-HT reuptake. The drug does not block receptors for 5-HT, acetylcholine, NE, or histamine. Its only approved indication is major depression. Unlabeled uses include panic disorder, social anxiety disorder, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and premenstrual dysphoric disorder.

Citalopram is rapidly absorbed from the GI tract, both in the presence and absence of food. Plasma levels peak about 4 hours after dosing. The drug undergoes hepatic metabolism followed by excretion in the urine and feces. The half-life is about 35 hours.

The most common adverse effects are nausea, somnolence, dry mouth, and sexual dysfunction. Additional side effects include weight gain, edema, postural hypotension, headache, paresthesias, hyponatremia, and increased risk of GI bleeding. Large doses are teratogenic in animals. Citalopram enters breast milk in amounts sufficient to cause somnolence, reduced feeding, and weight loss in the infant. Use late in pregnancy can result in NAS and PPHN in the infant. Like all other antidepressants, citalopram may increase the risk of suicide, especially in children and young adults.

Citalopram prolongs the QT interval, and hence may pose a risk of fatal dysrhythmias, especially when the dosage exceeds 40 mg/day. Risk is increased in patients with heart disease, long QT syndrome, and low blood levels of potassium and magnesium. Because of the risk of serotonin syndrome, citalopram should not be combined with MAOIs or other serotonergic drugs. Allow at least 14 days to pass between stopping an MAOI and starting citalopram, or vice versa.

Citalopram [Celexa] is available in tablets (10, 20, and 40 mg) and an oral solution (2 mg/mL). The drug may be taken in the morning or evening, with or without food. The initial dosage for depression is 20 mg once a day. Dosage may be increased slowly to a maximum of 40 mg/day. Doses above 40 mg/day offer no increase in benefits, but do increase the risk of dysrhythmias and other adverse effects. Dosage should remain low in elderly patients and those with liver impairment. When discontinuing citalopram, dosage should be reduced gradually.

Escitalopram

Escitalopram [Lexapro, Cipralex[®]] is the *S*-isomer of citalopram [Celexa], which is a 50:50 mixture of *S*- and *R*-isomers. The *S*-isomer (escitalopram) is responsible for antidepressant effects. The *R*-isomer has no antidepressant actions, but does contribute to side effects. Accordingly, escitalopram retains the therapeutic benefits of citalopram, but may be better tolerated. Otherwise, the pharmacology of the two drugs is largely the same. Escitalopram is approved for major depression, obsessive-compulsive disorder, and generalized anxiety disorder, and has been used off-label for panic disorder. The drug can also reduce hot flashes in some menopausal women.

Like citalopram and other SSRIs, escitalopram is generally well tolerated. In clinical trials, the most common side effects were nausea (15%), insomnia (9%), somnolence (6%), sweating (5%), and fatigue (5%). In addition, 9% of males reported ejaculatory disorders. However, the true incidence of sexual dysfunction may be higher. Why? Because the incidence of sexual problems reported during clinical trials is usually considerably lower than the incidence seen in actual practice. As with other SSRIs, combined use with MAOIs and other serotonergic drugs increases the risk of serotonin syndrome. At least 14 days should separate use of MAOIs and escitalopram. Like citalopram and other SSRIs, escitalopram increases the risk of hyponatremia and GI bleeding, and, when used late in pregnancy, may cause NAS or PPHN in the newborn. Like all other antidepressants, this drug can increase the risk of suicide, especially in children and young adults.

Escitalopram [Lexapro, Cipralex[®]] is available in tablets (5, 10, and 20 mg) and an oral solution (1 mg/mL). The recommended initial dosage is 10 mg/day, taken in the morning or evening, with or without food. In clinical trials, dosages above 10 mg/day did not increase antidepressant effects, but did intensify side effects. There is no need to reduce the dosage in elderly patients or in patients with either hepatic impairment or mild to moderate renal impairment. However, in patients with severe renal impairment, a dosage reduction may be required. When discontinuing the drug, dosage should be reduced gradually.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

Three drugs—venlafaxine, desvenlafaxine, and duloxetine—block neuronal reuptake of serotonin and norepinephrine, with minimal effects on other transmitters or receptors. Pharmacologic effects are similar to those of the SSRIs, although the SSRIs may be better tolerated.

Venlafaxine

Venlafaxine [Effexor XR], the first SNRI available, is approved for major depression, generalized anxiety disorder, social anxiety disorder (social phobia), and panic disorder. The drug produces powerful blockade of NE and 5-HT reuptake and weak blockade of dopamine reuptake. The relationship of these actions to therapeutic effects is uncertain. Venlafaxine does not block cholinergic, histaminergic, or alpha₁-adrenergic receptors. Despite impressions that venlafaxine may be superior to SSRIs, when compared directly in clinical trials, the drugs were about equally effective—and SSRIs are probably safer.

Venlafaxine is well absorbed following oral administration, both in the presence and absence of food. In the liver, much of each dose is converted to desvenlafaxine, an active metabolite. The half-life is 5 hours for the parent drug and 11 hours for the active metabolite.

Venlafaxine can cause a variety of adverse effects. The most common is nausea (37% to 58%), followed by headache, anorexia, nervousness, sweating, somnolence, and insomnia. Dose-dependent weight loss may occur secondary to anorexia. Venlafaxine can also cause dose-related sustained diastolic hypertension; blood pressure should be monitored. Sexual dysfunction (eg, impotence, anorgasmia) may occur too. Some patients experience sustained mydriasis (dilation of the pupil), which can increase the risk of eye injury in those with elevated intraocular pressure or glaucoma. Like the SSRIs, venlafaxine can cause hyponatremia, especially in elderly patients taking diuretics. Like all other antidepressants, venlafaxine may increase the risk of suicide, especially in children and young adults.

Combined use of venlafaxine with MAOIs and other serotonergic drugs (see Table 32-4) increases the risk of serotonin syndrome, a potentially fatal reaction. If the clinical situation demands, venlafaxine may be cautiously combined with an SSRI or another SNRI. However, combined use with an MAOI is *contraindicated*. Accordingly, MAOIs should be withdrawn at least 14 days before starting venlafaxine. When switching from venlafaxine to an MAOI, venlafaxine should be discontinued 7 days before starting the MAOI.

As with the SSRIs, use of venlafaxine late in pregnancy can result in a neonatal withdrawal syndrome, characterized by irritability, abnormal crying, tremor, respiratory distress, and possibly seizures. Symptoms, which can be managed with supportive care, generally abate within a few days.

Abrupt discontinuation can cause an intense withdrawal syndrome. Symptoms include anxiety, agitation, tremors, headache, vertigo, nausea, tachycardia, and tinnitus. Worsening of pretreatment symptoms may also occur. Withdrawal symptoms can be minimized by tapering the dosage over 2 to 4 weeks. Warn patients not to stop venlafaxine abruptly.

Venlafaxine is available in three formulations: immediate-release (IR) tablets (25, 37.5, 50, 75, and 100 mg) sold generically, extended-release (ER) tablets (37.5, 75, 150, and 225 mg) sold generically, and ER capsules (37.5, 75, and 150 mg) sold as Effexor XR. The ER capsules and ER tablets are bioequivalent. All doses should be taken with food. Inform patients that the ER tablets should be swallowed intact, but the ER capsules can be opened and sprinkled on applesauce. For treatment of depression, the recommended initial dosage is 75 mg/day (taken in two or three divided doses using IR tablets, or in a single dose using ER tablets or ER capsules). If needed, the dosage may be gradually increased. The usual maximum dosage is 225 mg/day. However, dosages as large as 375 mg/day have been used for severely depressed patients. Dosage should be reduced in patients with liver disease, and possibly in those with kidney disease. As with all other antidepressants, dosage should be tapered slowly when treatment is stopped.

Desvenlafaxine

Desvenlafaxine [Pristiq], approved in 2008, is the major active metabolite of venlafaxine. Accordingly, the actions and adverse effects of both drugs are similar. Like venlafaxine, desvenlafaxine is a strong inhibitor of 5-HT and NE reuptake, and does not block cholinergic, histaminergic, or alpha₁-adrenergic receptors. At this time, desvenlafaxine is approved only for major depression, in contrast to venlafaxine, which is approved for major depression, generalized anxiety disorder, panic disorder, and social phobia.

Desvenlafaxine is well absorbed following oral administration, both in the presence and absence of food. Plasma levels peak about 7.5 hours after dosing. The drug undergoes some hepatic metabolism, and is excreted in the urine as metabolites and parent drug. The elimination half-life is 1 hour.

Adverse effects are like those of venlafaxine. The most common are nausea (22%), headache (20%), dizziness (13%), insomnia (9%), diarrhea (11%), dry mouth (11%), sweating (10%), and constipation (9%). Sexual effects include erectile dysfunction (3%) and decreased libido (4%). Like all other antidepressants, desvenlafaxine may increase the risk of suicide in children and young adults. Some neonates exposed to the drug *in utero* have required prolonged hospitalization, respiratory support, and tube feeding. Additional concerns include hyponatremia, sustained hypertension, serotonin syndrome, bleeding, seizures, and withdrawal symptoms if the drug is discontinued abruptly.

As with venlafaxine, combining desvenlafaxine with another serotonergic drug increases the risk of serotonin syndrome. Combined use with an SSRI or another SNRI may be done cautiously. In contrast, combined use with an MAOI is *contraindicated*. Accordingly, MAOIs should be withdrawn at least 14 days before starting desvenlafaxine, and desvenlafaxine should be withdrawn at least 7 days before starting an MAOI.

Desvenlafaxine [Pristiq] is available in 50- and 100-mg ER tablets, which should be swallowed whole with fluid, and not crushed, chewed, or dissolved. The recommended dosage is 50 mg once daily, taken with or without food, about the same time each day. Increasing the dose to 100 mg/day offers no therapeutic benefit, but does increase the risk of side effects. In patients with severe renal impairment (creatinine clearance less than 30 mL/min), the dosage should be reduced to 50 mg every other day. There is no need to reduce the dosage in patients with moderate renal impairment or in those with liver impairment of any degree. To minimize withdrawal reactions, the drug should be discontinued slowly (by gradually increasing the dosing interval).

Duloxetine

Mechanism of Action and Therapeutic Uses. Duloxetine [Cymbalta] was the second SNRI approved for major depression. The drug is a powerful inhibitor of 5-HT and NE reuptake, and a much weaker inhibitor of

dopamine reuptake. Duloxetine does not bind with receptors for NE, serotonin, dopamine, acetylcholine, or histamine, and does not inhibit MAO.

Data on the antidepressant effects of duloxetine are limited. Clinical trials have shown that duloxetine is clearly superior to placebo. Treatment reduces depressive symptoms and may also reduce physical pain associated with depression (eg, backache). Furthermore, benefits may develop quickly, in some cases within 2 weeks of starting treatment. Unfortunately, there have been no trials comparing duloxetine directly with other antidepressants, such as venlafaxine or the SSRIs. Also, there is little information on the drug's long-term efficacy or safety. As a result, there is no basis for choosing this newer drug over older ones.

In addition to its use in depression, duloxetine is approved for *fibromyalgia*, *generalized anxiety disorder*, *pain of diabetic peripheral neuropathy*, and *chronic musculoskeletal pain*, including low back pain and pain from osteoarthritis. The drug is used off-label for *stress urinary incontinence* (in contrast to *urge urinary incontinence*).

Pharmacokinetics. Duloxetine is well absorbed following oral dosing. Food reduces the rate of absorption but not the extent. In the blood, duloxetine is highly (90%) bound to albumin. The drug undergoes extensive hepatic metabolism, primarily by the CYP2D6 and CYP1A2 isozymes of cytochrome P450. Metabolites are excreted in the urine (70%) and feces (20%). The elimination half-life is 12 hours. In patients with severe renal impairment, levels of duloxetine and its metabolites are greatly increased, and in those with severe hepatic impairment, the half-life is greatly prolonged. Accordingly, duloxetine is not recommended for patients with severe renal or hepatic dysfunction.

Adverse Effects. Duloxetine is generally well tolerated. In clinical trials, the most common adverse effects were nausea (20% vs. 7% with placebo), dry mouth (15% vs. 6%), insomnia (11% vs. 6%), somnolence (7% vs. 3%), constipation (11% vs. 4%), reduced appetite (8% vs. 2%), fatigue (8% vs. 4%), increased sweating (6% vs. 2%), and blurred vision (4% vs. 1%). Duloxetine can cause a small increase in blood pressure, and hence blood pressure should be measured at baseline and periodically thereafter. Some males experience sexual dysfunction (loss of libido, impotence). Duloxetine promotes mydriasis, and hence should not be used by patients with uncontrolled narrow-angle glaucoma. Weight gain has not been observed.

Liver toxicity is a concern. Elevation of serum transaminases, indicating liver damage, occurs in about 1% of patients. There have been reports of hepatitis, hepatomegaly, cholestatic jaundice, and elevation of transaminases to more than 20 times the upper limit of normal. To reduce risk, duloxetine should not be given to patients with pre-existing liver disease or to those who drink alcohol heavily.

As with venlafaxine, abrupt cessation of treatment can cause a withdrawal syndrome. Symptoms include nausea, vomiting, dizziness, headache, nightmares, and paresthesias. To minimize risk, duloxetine should be withdrawn slowly. Use of duloxetine late in pregnancy can lead to a withdrawal syndrome in the infant.

Like all other antidepressants, duloxetine may increase the risk of suicide, especially in children and young adults.

Effects in Pregnancy and Lactation. Animal studies indicate that duloxetine interferes with fetal and postnatal development, causing reduced fetal weight, decreased postnatal survival, and neurologic disturbances. The drug is excreted in the milk of lactating rats. Studies in pregnant or lactating women have not been conducted. Until human data are available, use of duloxetine during pregnancy and lactation is not recommended.

Drug Interactions. The combination of duloxetine with heavy alcohol consumption greatly increases the risk of liver damage. Accordingly, duloxetine should not be prescribed to heavy drinkers.

Like venlafaxine and other drugs that block 5-HT reuptake, duloxetine can cause serotonin syndrome if combined with an MAOI or any other serotonergic drug. MAOIs should be withdrawn at least 14 days before starting duloxetine, and duloxetine should be withdrawn at least 5 days before starting an MAOI.

Drugs that inhibit CYP1A2 or CYP2D6 can increase duloxetine levels, and may thereby cause toxicity. Inhibitors of CYP1A2 include cimetidine [Tagamet], fluvoxamine [Luvox], and ciprofloxacin [Cipro]. Inhibitors of CYP2D6 include fluoxetine [Prozac], paroxetine [Paxil], and quinidine [Quinidex].

Duloxetine is a moderate inhibitor of CYP2D6, and hence may raise levels of drugs that are extensively metabolized by this enzyme. Among these are certain TCAs (eg, amitriptyline, nortriptyline), type IC antiarrhythmics (propafenone [Rythmol] and flecainide [Tambocor]), and phenothiazines, including thioridazine [Mellaril]. Interaction with thioridazine is of special concern owing to the risk of serious ventricular dysrhythmias. Accordingly, the two drugs should not be combined.

Preparations, Dosage, and Administration. Duloxetine is available in delayed-release capsules (20, 30, and 60 mg) that should be swallowed

whole, with or without food. The usual dosage for depression is 60 mg/day initially, followed by 40 to 100 mg/day for maintenance. For all other indications—depression, generalized anxiety disorder, pain of diabetic neuropathy, and chronic musculoskeletal pain—the dosage is 30 mg once daily for 1 week, followed by 60 mg once daily for maintenance. When treatment is discontinued, dosage should be tapered slowly.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

The first tricyclic agent—*imipramine*—was introduced to psychiatry in the late 1950s. Since then, the ability of TCAs to relieve depressive symptoms has been firmly established. For decades, TCAs were drugs of first choice for depression. However, owing to the development of safer alternatives, especially the SSRIs, use of TCAs has greatly declined. The most common adverse effects are sedation, orthostatic hypotension, and anticholinergic effects. The most dangerous effect is cardiac toxicity. When taken in overdose, TCAs can readily prove lethal. Like all other antidepressants, TCAs may increase the risk of suicide. Because all of the TCAs have similar properties, we will discuss these drugs as a group, rather than focusing on a representative prototype.

Chemistry

The structure of imipramine, a representative TCA, is shown in Figure 32-2. As you can see, the nucleus of this drug has three rings, hence the classification *tricyclic* antidepressant.

As indicated in Figure 32-2, the three-ringed nucleus of the TCAs is very similar to the three-ringed nucleus of the phenothiazine antipsychotics. Because of this structural similarity, TCAs and phenothiazines have several actions in common. Specifically, both groups produce varying degrees of *sedation*, *orthostatic hypotension*, and *anticholinergic effects*.

Mechanism of Action

The TCAs block neuronal reuptake of two monoamine transmitters: NE and 5-HT. As a result, TCAs increase the concentration of these transmitters at CNS synapses, and thereby intensify their effects. As indicated in Table 32-5, some TCAs block reuptake of NE and 5-HT, whereas others only block reuptake of NE. As with the SSRIs, biochemical effects (blockade of transmitter reuptake) occur within hours, whereas therapeutic effects (relief of depression) develop over several weeks. This delay suggests that antidepressant effects are due



Figure 32-2 • Structural similarities between tricyclic antidepressants and phenothiazine antipsychotics. Except for the areas highlighted, the phenothiazine nucleus is nearly identical to that of TCAs. Because of their structural similarities, TCAs and phenothiazines have several pharmacologic properties in common.

TABLE 32-5 • Antidepressants: Adverse Effects and Impact on Neurotransmitters

Transmitters Affected ^a	Agitation/Insomnia	Anticholinergic Activity	Sedation	Hypotension	Seizure Risk	Cardiac Toxicity	Weight Gain	Sexual Dysfunction	Other Side Effects
Selective Serotonin Reuptake Inhibitors (SSRIs)									
Citalopram	+	0/+	0/+	0	0/+	0	+	++	GI bleeding,
Escitalopram	+	0/+	0/+	0	0/+	0	+	++	hyponatremia, NAS
Fluoxetine	+	0	b	0	0/+	0/+	+	++	and PPHN in
Fluvoxamine	+	0/+	0/+	0	0/+	0	+	++	newborns, Citalopram
Paroxetine	+	0/+	b	0	0/+	0	+	++	may cause
Sertraline	+	0	b	0	0/+	0	+	++	dysrhythmias. ^c
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)									
Desvenlafaxine	+	0	0	0	0/+	0/+	0	++	
Duloxetine	+	0	0	0/+	0/+	0/+	0/+	++	Hepatotoxicity
Venlafaxine	+	0	0	0	0/+	0/+	0	++	
Tricyclic Antidepressants (TCAs)									
Amitriptyline	0/+	+	+	+	+	+	+	+	
Clomipramine	+	+	+	+	+	+	+	+	
Doxepin	0/+	+	+	+	+	+	+	+	
Imipramine	+	+	+	+	+	+	+	+	
Trimipramine	0/+	+	+	+	+	+	+	+	
Desipramine	+	+	b	+	+	+	+	+	
Maprotiline	+	+	+	+	+	+	+	+	
Nortriptyline	+	+	+	+	+	+	+	+	
Protriptyline	+	+	b	+	+	+	+	+	
Monoamine Oxidase Inhibitors (MAOIs)									
Isocarboxazid	+	0	+	+	0	0	+	++	Hypertensive crisis from tyramine in food ^d
Phenelzine	+	0	+	+	0	0	+	++	
Selegiline	+	0	0	0	0	0	0	++	
Tranylcypromine	+	0	b	+	0	0	+	++	
Atypical Antidepressants									
Amoxapine	0/+	+	+	+	+	+	+	+	Parkinsonism
Bupropion	+	0/+	b	0	+	0	0	+	Seizures
Mirtazapine	0/+	0/+	+	0/+	0	0	+	0	
Nefazodone	0/+	0/+	+	0	0	0/+	0/+	0/+	
Trazodone	0/+	0/+	+	+	0	0/+	+	+	Priapism ^g
Vilazodone	+	0	+	0	0	0	0	+	Bleeding, hyponatremia

^aDA = dopamine, 5-HT = serotonin, NE = norepinephrine. All of the antidepressants increase synaptic activity of the transmitters indicated—with the exception of amoxapine, which increases activity of NE, but blocks receptors for DA. The TCAs, SSRIs, SNRIs, amoxapine, bupropion, nefazodone, and trazodone decrease transmitter reuptake; vilazodone blocks transmitter reuptake and directly activates 5-HT receptors; MAOIs block transmitter breakdown; and mirtazapine promotes transmitter release.

^bProduces moderate stimulation, not sedation.

^cNAS = neonatal abstinence syndrome, PPHN = persistent pulmonary hypertension of the newborn.

^dHypertensive crisis is not a risk with low-dose (6 mg/day) transdermal selegiline, and possibly not with higher doses.

^eAmoxapine blocks reuptake of NE and blocks receptors for DA.

^fBupropion may increase sexual desire.

^gTrazodone can cause priapism (persistent painful erection).

to adaptive changes brought on by prolonged reuptake blockade, and not to reuptake blockade directly.

Pharmacokinetics

The half-lives of TCAs are long and variable. Because their half-lives are long, TCAs can usually be administered in a single daily dose. Because their half-lives are variable, TCAs require individualization of dosage.

Therapeutic Uses

Depression. TCAs are effective agents for major depression. These drugs can elevate mood, increase activity and alertness, decrease morbid preoccupation, improve appetite, and normalize sleep patterns. Despite their efficacy, TCAs are generally considered second-line drugs, owing to the development of safer and better tolerated alternatives.

Bipolar Disorder. Bipolar disorder (manic-depressive illness) is characterized by alternating episodes of mania and depression (see Chapter 33). TCAs can help during depressive episodes.

Fibromyalgia Syndrome. Fibromyalgia syndrome is a chronic disorder characterized by diffuse musculoskeletal pain, profound fatigue, disturbed sleep, and cognitive dysfunction. As discussed in Chapter 107, TCAs are the most effective drugs we have for reducing symptoms.

Other Uses. TCAs can benefit patients with neuropathic pain (see Chapter 29), chronic insomnia (see Chapter 34), attention-deficit/hyperactivity disorder (see Chapter 36), and panic disorder or obsessive-compulsive disorder (see Chapter 35).

Adverse Effects

The most common adverse effects are orthostatic hypotension, sedation, and anticholinergic effects. The most serious adverse effect is cardiotoxicity. These effects occur because, in addition to blocking reuptake of NE and 5-HT, TCAs cause direct blockade of receptors for histamine, acetylcholine, and NE. Adverse effects of individual agents are summarized in Table 32-5.

Orthostatic Hypotension. Orthostatic hypotension is the most serious of the common adverse responses to TCAs. Hypotension is due in large part to blockade of α_1 -adrenergic receptors on blood vessels. Patients should be informed that they can minimize orthostatic hypotension by moving slowly when assuming an upright posture. In addition, patients should be instructed to sit or lie down if symptoms (dizziness, lightheadedness) occur. For hospitalized patients, blood pressure and pulse rate should be monitored on a regular schedule (eg, 4 times a day). These measurements should be taken while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes. If blood pressure is low or pulse rate is high, medication should be withheld and the prescriber notified.

Anticholinergic Effects. The TCAs block muscarinic cholinergic receptors, and can thereby cause an array of anticholinergic effects (dry mouth, blurred vision, photophobia, constipation, urinary hesitancy, and tachycardia). Patients should be informed about possible anticholinergic responses and instructed in ways to minimize discomfort. A detailed discussion of anticholinergic effects and their management is presented in Chapter 14.

Diaphoresis. Despite their anticholinergic properties, TCAs often cause diaphoresis (sweating). The mechanism of this paradoxical effect is unknown.

Sedation. Sedation is a common response to TCAs. The cause is blockade of histamine receptors in the CNS. Patients should be advised to avoid hazardous activities if sedation is prominent.

Cardiac Toxicity. Tricyclics can adversely affect cardiac function. However, in the absence of an overdose or pre-existing cardiac impairment, serious effects are rare. The TCAs affect the heart by (1) decreasing vagal influence on the heart (secondary to muscarinic blockade) and (2) acting directly on the bundle of His to slow conduction. Both effects increase the risk of dysrhythmias. To minimize risk, all patients should undergo ECG evaluation prior to treatment and periodically thereafter. Risk of cardiac toxicity may be higher with desipramine than with other TCAs.

Seizures. TCAs lower seizure threshold, and thereby seizure risk. Exercise caution in patients with epilepsy and other seizure disorders.

Hypomania. On occasion, TCAs produce too much of a good thing, elevating mood from depression all the way to hypomania (mild mania). If hypomania develops, the patient should be evaluated to determine whether elation is drug induced or the result of bipolar disorder.

Suicide Risk. As discussed above, TCAs and all other antidepressants may increase the risk of suicide in depressed patients, especially during the early phase of treatment. The risk of antidepressant-induced suicide is greatest among children, adolescents, and young adults.

Yawngasm. Rarely, patients taking *clomipramine* [Anafranil] experience yawngasm. Experience *what?* A spontaneous orgasm while yawning. Honest. This unusual side effect, which affects both males and females, may be considered adverse or beneficial, depending on one's view of such things. In at least one documented case, yawngasms strongly influenced adherence, as evidenced by the patient asking how long she would be "allowed" to continue treatment. Although data are scarce, one might guess that the occasional yawngasm would help relieve depression. *Note:* Clomipramine is used off-label for major depression; it is not approved for this disorder.

Drug Interactions

Monoamine Oxidase Inhibitors. The combination of a TCA with an MAOI can lead to *severe hypertension*, owing to excessive adrenergic stimulation of the heart and blood vessels. Excessive adrenergic stimulation occurs because (1) inhibition of MAO causes accumulation of NE in adrenergic neurons and (2) blockade of NE reuptake by the tricyclics decreases NE inactivation. Because of the potential for hypertensive crisis, combined therapy with TCAs and MAOIs is generally avoided.

Direct-Acting Sympathomimetic Drugs. Tricyclics potentiate responses to direct-acting sympathomimetics (ie, drugs such as epinephrine and dopamine that produce their effects by direct interaction with adrenergic receptors). Why are responses increased? Because TCAs block uptake of these agents into adrenergic nerve terminals, and thereby prolong their presence in the synaptic space.

Indirect-Acting Sympathomimetic Drugs. TCAs decrease responses to indirect-acting sympathomimetics (ie, drugs such as ephedrine and amphetamine that promote release of transmitter from adrenergic nerves). Why? Because TCAs block uptake of these agents into adrenergic nerves.

thereby preventing them from reaching their site of action within the nerve terminal.

Anticholinergic Agents. Since TCAs have anticholinergic actions of their own, they will intensify the effects of other anticholinergic medications. Consequently, patients receiving TCAs should be advised to avoid all other drugs with anticholinergic properties, including antihistamines and certain over-the-counter sleep aids.

CNS Depressants. CNS depression caused by TCAs will add with CNS depression caused by other drugs. Accordingly, patients should be warned against taking all other CNS depressants, including alcohol, antihistamines, opioids, and barbiturates.

Toxicity

Overdose with a TCA can be life threatening. The lethal dose is only 8 times the average therapeutic dose. To minimize the risk of death by suicide, acutely depressed patients should be given no more than a 1-week supply of their TCA at a time.

Clinical Manifestations. Symptoms result primarily from anticholinergic and cardiotoxic actions. The combination of cholinergic blockade and direct cardiotoxicity can produce *dysrhythmias*, including tachycardia, intraventricular blocks, complete atrioventricular block, ventricular tachycardia, and ventricular fibrillation. Responses to peripheral muscarinic blockade include hyperthermia, flushing, dry mouth, and dilation of the pupils. CNS symptoms are prominent. Early responses are confusion, agitation, and hallucinations. Seizures and coma may follow.

Treatment. Absorption of ingested drug can be reduced with gastric lavage followed by ingestion of activated charcoal. Physostigmine (a cholinesterase inhibitor) is given to counteract anticholinergic actions. Propranolol, lidocaine, or phenytoin can control dysrhythmias. Dysrhythmias should not be treated with procainamide or quinidine, because these drugs cause cardiac depression.

Dosage and Routes of Administration

Dosage. Dosages for individual TCAs are summarized in Table 32-2. General guidelines for dosing are discussed below.

Initial doses of TCAs should be low (eg, 50 mg of imipramine a day for adult outpatients). Low initial doses minimize adverse reactions and thereby help promote adherence. High initial doses are both undesirable and unnecessary. High doses are undesirable in that they pose an increased risk of adverse reactions. They are unnecessary in that onset of therapeutic effects is delayed regardless of dosage, and hence aggressive initial dosing offers no benefit.

Because of interpatient variability in TCA metabolism, dosing is highly individualized. As a rule, dosage is adjusted on the basis of clinical response. However, if there is no observable response, plasma drug levels can be used as a guide. For example, levels of imipramine must be above 225 ng/mL to be effective. If a patient has not responded to imipramine, measurements should be made to ensure that the plasma level is adequate. If the level is below 225 ng/mL, dosage should be increased.

Once an effective dosage has been established, most patients can take their entire daily dose at bedtime; the long half-lives of the TCAs make divided daily doses unnecessary. Once-a-day dosing at bedtime has three advantages: (1) it's

easy, and hence facilitates adherence; (2) it promotes sleep by causing maximal sedation at night; and (3) it reduces the intensity of side effects during the day. If bedtime dosing causes residual sedation in the morning, dosing earlier in the evening can help. Although once-a-day dosing is generally desirable, not all patients can use this schedule. The elderly, for example, can be especially sensitive to the cardiotoxic actions of the tricyclics. As a result, if the entire daily dose were taken at one time, effects on the heart might be intolerable.

Preparations and Drug Selection

Preparations. In the United States, nine TCAs are available (see Tables 32-2 and 32-5). All nine are equally effective. Principal differences among these drugs concern side effects (see Table 32-5).

Drug Selection. Selection among TCAs is based on side effects. For example, if the patient is experiencing insomnia, a drug with prominent sedative properties (eg, doxepin) might be selected. Conversely, if daytime sedation is undesirable, a less sedating agent (eg, desipramine) might be preferred. Elderly patients with glaucoma or constipation and males with prostatic hypertrophy can be especially sensitive to anticholinergic effects. Hence, for these patients, a drug with weak anticholinergic properties (eg, nortriptyline) would be appropriate.

MONOAMINE OXIDASE INHIBITORS (MAOIs)

The MAOIs are second- or third-choice antidepressants for most patients. Although these drugs are as effective as the SSRIs and TCAs, they are more dangerous. The greatest concern is hypertensive crisis, which can be triggered by eating foods rich in tyramine. At this time, MAOIs are drugs of choice only for atypical depression. Three MAOIs—*isocarboxazid* [Marplan], *phenelzine* [Nardil], and *tranylcypromine* [Parnate]—are administered orally, and one—*selegiline* [Emsam]—is administered by transdermal patch.

Oral MAOIs

Mechanism of Action

Before discussing the MAOIs, we need to discuss MAO itself. MAO is an enzyme found in the liver, the intestinal wall, and terminals of monoamine-containing neurons. The function of MAO in neurons is to convert monoamine neurotransmitters—NE, 5-HT, and dopamine—into inactive products. In the liver and intestine, MAO serves to inactivate tyramine and other biogenic amines in food. In addition, these enzymes inactivate biogenic amines administered as drugs.

The body has two forms of MAO, named MAO-A and MAO-B. In the brain, MAO-A inactivates NE and 5-HT, whereas MAO-B inactivates dopamine. In the intestine and liver, MAO-A acts on dietary tyramine and other compounds. All of the MAOIs used for depression are *nonselective*. That is, at *therapeutic* doses, they inhibit both MAO-A and MAO-B. One agent—*selegiline* (used for depression and Parkinson's disease)—is selective for MAO-B at the low doses used for Parkinson's disease, but is nonselective at the higher doses used for depression.

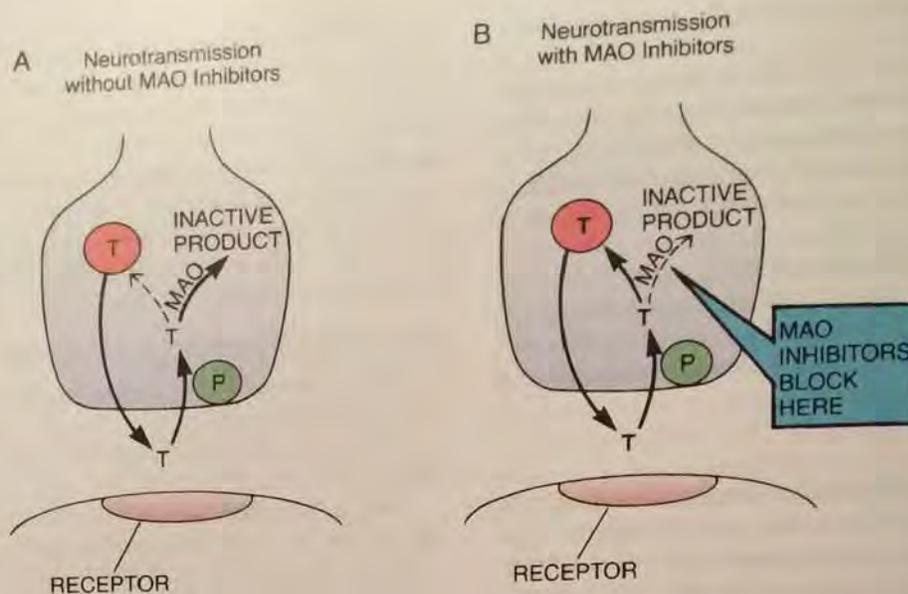


Figure 32-3 • Mechanism of action of monoamine oxidase inhibitors.

A, Under drug-free conditions, much of the norepinephrine or serotonin that undergoes reuptake into nerve terminals becomes inactivated by MAO. Inactivation helps maintain an appropriate concentration of transmitter within the terminal. **B**, MAO inhibitors prevent inactivation of norepinephrine and serotonin, thereby increasing the amount of transmitter available for release. Release of supranormal amounts of transmitter intensifies transmission. (MAO = monoamine oxidase, P = uptake pump, T = transmitter [norepinephrine or serotonin].)

Antidepressant effects of the MAOIs result from inhibiting MAO-A in nerve terminals (Fig. 32-3). By inhibiting intraneuronal MAO-A, these drugs increase the amount of NE and 5-HT available for release, and thereby intensify transmission at noradrenergic and serotonergic junctions.

Please note that antidepressant effects of the MAOIs cannot be fully explained by MAO inhibition alone. Why? Because the biochemical action of MAOIs (inhibition of MAO) takes place rapidly, whereas the clinical response to MAOIs (relief of depression) develops slowly. In the interval between initial inhibition of MAO and relief of depression, secondary neurochemical events must be taking place. These secondary events, which have not been identified, are ultimately responsible for the beneficial response to treatment.

The MAOIs can act on MAO in two ways: reversibly and irreversibly. All of the MAOIs in current use cause *irreversible* inhibition. Since recovery from irreversible inhibition requires synthesis of new MAO molecules, effects of the irreversible inhibitors persist for about 2 weeks after drug withdrawal. In contrast, recovery from reversible inhibition is more rapid, occurring in 3 to 5 days.

Therapeutic Uses

Depression. MAOIs are equal to SSRIs and TCAs for relieving depression. However, because MAOIs can be hazardous, they are generally reserved for patients who have not responded to SSRIs, TCAs, and other safer drugs. Nonetheless, there is one group of patients—those with *atypical depression*—for whom MAOIs are the treatment of choice. As with other antidepressants, beneficial effects do not reach their peak for several weeks.

Other Psychiatric Uses. MAOIs have been used with some success to treat *bulimia nervosa* and *obsessive-compulsive disorder*. Like SSRIs and TCAs, MAOIs can reduce *panic attacks* in patients with panic disorder.

Adverse Effects

CNS Stimulation. MAOIs cause direct CNS stimulation (in addition to exerting antidepressant effects). Excessive stimulation can produce anxiety, insomnia, agitation, hypomania, and even mania.

Orthostatic Hypotension. Despite their ability to increase the NE content of peripheral sympathetic neurons, the MAOIs *reduce blood pressure* when administered in usual therapeutic doses. Patients should be informed about signs of hypotension (dizziness, lightheadedness) and advised to sit or lie down if these occur. Also, they should be informed that hypotension can be minimized by moving slowly when assuming an erect posture. For the hospitalized patient, blood pressure and pulse rate should be monitored on a regular schedule (eg, 4 times daily). These measurements should be taken while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes.

How do MAOIs reduce blood pressure? Through actions in the CNS. The following sequence has been proposed: (1) Inhibition of MAO increases the NE content of neurons within the vasomotor center. (2) When NE is released, it binds to postsynaptic alpha receptors on neurons within the vasomotor center, thereby *decreasing* the firing rate of sympathetic nerves that control vascular tone. (3) This reduction in sympathetic activity results in vasodilation, causing blood pressure to fall.

Hypertensive Crisis from Dietary Tyramine. Although the MAOIs normally produce *hypotension*, they can be the cause of severe *hypertension* if the patient eats food that is rich in *tyramine*, a substance that promotes the release of NE from sympathetic neurons. Hypertensive crisis is characterized by severe headache, tachycardia, hypertension, nausea, vomiting, confusion, and profuse sweating—possibly leading to stroke and death.

Before considering the mechanism by which hypertensive crisis is produced, let's consider the effect of dietary tyramine

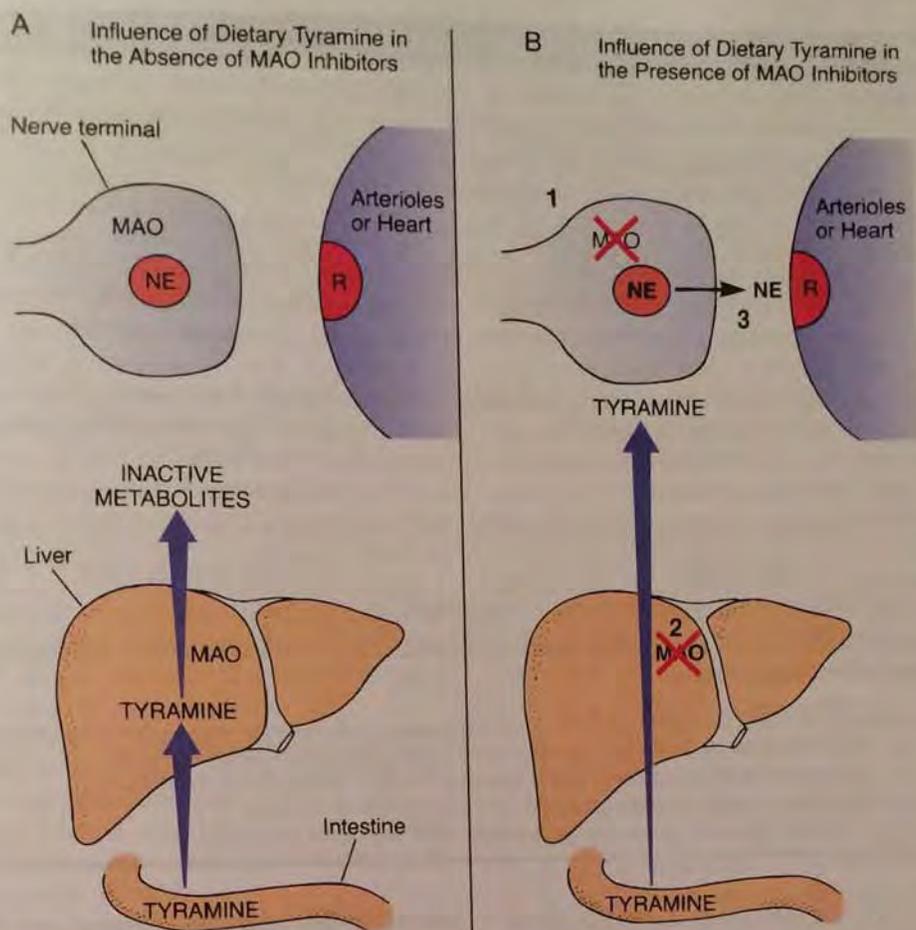


Figure 32-4 • Interaction between dietary tyramine and MAOIs.

A, In the absence of MAOIs, much of ingested tyramine is inactivated by MAO in the intestinal wall (not shown in the figure). Any dietary tyramine that is not metabolized in the intestinal wall is transported directly to the liver, where it undergoes immediate inactivation by hepatic MAO. No tyramine reaches the general circulation. **B**, Three events occur in the presence of MAOIs: (1) Inhibition of neuronal MAO raises levels of norepinephrine in sympathetic nerve terminals. (2) Inhibition of intestinal and hepatic MAO allows dietary tyramine to pass through the intestinal wall and liver to enter the systemic circulation intact. (3) Upon reaching peripheral sympathetic nerve terminals, tyramine promotes the release of accumulated norepinephrine stores, thereby causing massive vasoconstriction and excessive stimulation of the heart. (MAO = monoamine oxidase, NE = norepinephrine, R = receptor for norepinephrine.)

under drug-free conditions. In the absence of MAO inhibition, dietary tyramine is not a threat. Much of the tyramine in food is metabolized by MAO in the intestinal wall. Furthermore, as shown in Figure 32-4A, any dietary tyramine that gets through the intestinal wall intact will then pass directly to the liver via the hepatic portal circulation. Once in the liver, tyramine is immediately inactivated by MAO there. Hence, as long as intestinal and hepatic MAO are functioning, dietary tyramine is prevented from reaching the general circulation, and therefore is devoid of adverse effects.

In the presence of MAOIs, the picture is very different: dietary tyramine can produce a life-threatening hypertensive crisis. Three steps are involved (Fig. 32-4B). First, inhibition of neuronal MAO augments NE levels within the terminals of sympathetic neurons that regulate cardiac function and vascular tone. Second, inhibition of intestinal and hepatic MAO allows dietary tyramine to pass directly through the intestinal wall and liver, and then enter the systemic circulation intact. Third, upon reaching peripheral sympathetic nerves, tyramine stimulates

the release of the accumulated NE, thereby causing massive vasoconstriction and intense stimulation of the heart. Hypertensive crisis results. To reduce the risk of tyramine-induced hypertensive crisis, the following precautions must be taken:

- MAOIs must not be dispensed to patients considered incapable of rigid adherence to dietary restrictions.
- Before an MAOI is dispensed, the patient must be fully informed about the hazard of ingesting tyramine-rich foods.
- The patient must be given a detailed list of foods and beverages to avoid. These foods—which include yeast extracts, most cheeses, fermented sausages (eg, salami, pepperoni, bologna), and aged fish or meat—are listed in Table 32-6.
- The patient should be instructed to avoid all drugs not specifically approved by the prescriber.

Patients should be informed about the symptoms of hypertensive crisis (headache, tachycardia, palpitations, nausea, vomiting, sweating) and instructed to seek immediate medical atten-

TABLE 32-6 • Foods That Can Interact with MAO Inhibitors

Foods That Contain Tyramine		Safe Foods (Little or No Tyramine)
Category	Unsafe Foods (High Tyramine Content)	
Vegetables	Avocados, especially if overripe; fermented bean curd; fermented soybean; soybean paste	Most vegetables
Fruits	Figs, especially if overripe; bananas, in large amounts	Most fruits
Meats	Meats that are fermented, smoked, or otherwise aged; spoiled meats; liver, unless <i>very</i> fresh	Meats that are known to be fresh (exercise caution in restaurants; meat may not be fresh)
Sausages	Fermented varieties: bologna, pepperoni, salami, others	Nonfermented varieties
Fish	Dried or cured fish; fish that is fermented, smoked, or otherwise aged; spoiled fish	Fish that is known to be fresh; vacuum-packed fish, if eaten promptly or refrigerated only briefly after opening
Milk, milk products	Practically all cheeses	Milk, yogurt, cottage cheese, cream cheese
Foods with yeast	Yeast extract (eg, Marmite, Bovril)	Baked goods that contain yeast
Beer, wine	Some imported beers, Chianti wine	Major domestic brands of beer, most wines
Other foods	Protein dietary supplements; soups (may contain protein extract), shrimp paste; soy sauce	

Foods That Contain Nontyramine Vasopressors	
Food	Comments
Chocolate	Contains phenylethylamine, a pressor agent; large amounts can cause a reaction.
Fava beans	Contain dopamine, a pressor agent; reactions are most likely with overripe beans.
Ginseng	Headache, tremulousness, and manic-like reactions have occurred.
Caffeinated beverages	Caffeine is a weak pressor agent; large amounts may cause a reaction.

tion if these develop. In the event of hypertensive crisis, blood pressure can be lowered with an IV vasodilator. Options include *sodium nitroprusside* (a nitric oxide donor), *phentolamine* (an alpha-adrenergic antagonist), and *labetalol* (an alpha/beta-adrenergic antagonist). Sublingual *nifedipine*, a calcium channel blocker, is an alternative. Like the IV agents, sublingual *nifedipine* acts rapidly to promote vasodilation. Some authorities recommend that patients carry a 10-mg *nifedipine* capsule for emergency use. However, an IV vasodilator, administered in an emergency department, is preferred.

In addition to tyramine, several other dietary constituents (eg, caffeine, phenylethylamine) can precipitate hypertension in patients taking MAOIs. Foods that contain these compounds are listed in Table 32-6. Patients should be instructed to avoid them.

Drug Interactions

The MAOIs can interact with many drugs to cause potentially disastrous results. Accordingly, patients should be instructed to avoid all medications—prescription drugs and over-the-counter drugs—that have not been specifically approved by the prescriber.

Indirect-Acting Sympathomimetic Agents. Indirect-acting sympathomimetics (eg, ephedrine, amphetamine) are drugs that promote the release of NE from sympathetic nerves. In patients taking MAOIs, these drugs can produce *hypertensive crisis*. The mechanism is the same as that described for tyramine. Patients should be instructed to avoid all sympathomimetic drugs, including ephedrine, methylphenidate, amphetamines, and cocaine. Sympathomimetic agents may be present in cold remedies, nasal decongestants, and asthma medications; all of these should be avoided unless approved by the prescriber.

Interactions Secondary to Inhibition of Hepatic MAO. Inhibition of MAO in the liver can decrease the metabolism of

several drugs, including epinephrine, NE, and dopamine. These drugs must be used with caution because their effects will be more intense and prolonged.

Tricyclic Antidepressants. The combination of a TCA with an MAOI may produce hypertensive episodes or hypertensive crisis. As a result, this combination of antidepressants is not employed routinely. However, although potentially dangerous, the combination can benefit certain patients. If this combination is employed, caution must be exercised.

Serotonergic Drugs. Combining MAOIs with SSRIs and other serotonergic drugs (see Table 32-4) poses a risk of serotonin syndrome. Accordingly, these combinations should be avoided.

Antihypertensive Drugs. Combined use of MAOIs and antihypertensive agents may result in excessive lowering of blood pressure. This response should be no surprise considering that MAOIs, by themselves, can cause hypotension.

Meperidine. Meperidine [Demerol], a strong analgesic, can cause hyperpyrexia (excessive elevation of temperature) in patients receiving MAOIs. Accordingly, if a strong analgesic is required, an agent other than meperidine should be chosen. Furthermore, the analgesic should be administered in its lowest effective dosage.

Preparations, Dosage, and Administration

Three oral MAOIs are available: isocarboxazid [Marplan], 10-mg tablets; phenelzine [Nardil], 15-mg tablets; and tranlycypromine [Parnate], 10-mg tablets. Dosages are presented in Table 32-2.

Transdermal MAOI: Selegiline

Transdermal selegiline [Emsam], approved in 2006, is the first and only transdermal treatment for major depression. Oral formulations, available for decades, are approved for Parkinson's

disease (see Chapter 21). At the blood levels achieved during oral therapy of Parkinson's disease, selegiline produces selective inhibition of MAO-B. However, at the blood levels achieved with transdermal therapy of depression, selectivity is lost, and hence the drug inhibits MAO-A as well as MAO-B. Like other MAOIs, selegiline should be reserved for patients who have not responded to preferred antidepressant drugs.

The pharmacology of transdermal selegiline is much like that of the oral MAOIs, but with one important difference: The risk of hypertensive crisis from dietary tyramine is much lower than with oral dosing. Why? Because with transdermal dosing, selegiline enters the systemic circulation without first passing through the GI tract. As a result, it can achieve therapeutic levels in the CNS while preserving activity of MAO-A in the intestinal wall and liver. Therefore, dietary tyramine will be destroyed before it can promote NE release in the periphery. Clinical trials have shown that restricting dietary tyramine is unnecessary with low-dose selegiline (24 mg/24 hr). However, owing to a lack of data, tyramine restriction is recommended at higher selegiline doses. Furthermore, with all doses of selegiline, sympathomimetic drugs (eg, phenylephrine, ephedrine, pseudoephedrine, amphetamines) are still able to promote NE release, and hence must be avoided, just as with oral MAOIs.

Two drugs—carbamazepine [Tegretol] and oxcarbazepine [Trileptal]—can significantly raise levels of selegiline. Accordingly, these drugs are contraindicated.

The most common adverse reaction is localized rash, which develops in about one-third of patients. Rash can be managed with topical glucocorticoids.

Selegiline transdermal patches are available in three strengths, delivering 6, 9, and 12 mg over 24 hours. Application is done every 24 hours to intact, dry skin of the upper torso, upper thigh, or outer surface of the upper arm. The recommended starting dose is 6 mg/24 hr. If necessary, dosage may be increased to 9 mg/24 hr, and then to 12 mg/24 hr after a minimum of 2 weeks at the lower dose.

ATYPICAL ANTIDEPRESSANTS

Bupropion

Actions and Uses. Bupropion [Wellbutrin, Aplenzin, Budeprion] is a unique antidepressant similar in structure to amphetamine. Like amphetamine, bupropion has stimulant actions and suppresses appetite. Antidepressant effects begin in 1 to 3 weeks. The mechanism by which depression is relieved is unclear, but may be related to blockade of dopamine and/or NE reuptake. The drug does not affect serotonergic, cholinergic, or histaminergic transmission, and does not inhibit MAO. In contrast to SSRIs, bupropion does not cause weight gain or sexual dysfunction. In fact, it appears to increase sexual desire and pleasure—hence bupropion has been used to (1) counteract sexual dysfunction in patients taking SSRIs, and (2) heighten sexual interest in women with hypoactive sexual desire disorder. Because of its efficacy and side effect profile, bupropion is a good alternative to SSRIs for patients who cannot tolerate SSRIs. Bupropion has two antidepressant indications: (1) major depressive disorder and (2) prevention of seasonal affective disorder (SAD). In addition to its use in depression, bupropion, marketed as Zyban and Buproban, is approved as an aid to quit smoking (see Chapter 39). Unlabeled uses include relief of neuropathic pain and management of attention-deficit/hyperactivity disorder.

Pharmacokinetics. Bupropion is administered orally. With the immediate-release tablets, plasma levels peak about 2 hours after dosing. Bioavailability is low: In animals, only 5% to 20% of each dose reaches the systemic circulation. Bupropion undergoes extensive hepatic metabolism, primarily by CYP2B6 (the 2B6 isozyme of cytochrome P450). The elimination half-life ranges from 8 to 24 hours.

Adverse Effects. Bupropion is generally well tolerated, but can cause seizures. The most common adverse effects are agitation (31%), headache (27%), dry mouth (27%), constipation (26%), weight loss (23%), GI upset (22%), dizziness (21%), tremor (21%), insomnia (19%), blurred vision (15%), and tachycardia (11%). In addition, bupropion carries a small risk of causing psychotic symptoms, including hallucinations and delusions. Accordingly, the drug should not be used in patients with psychotic disorders. Like other antidepressants, bupropion may increase the risk of suicide in children, adolescents, and young adults. In contrast to many other antidepressants, bupropion does not cause adverse sexual effects.

Seizures are the side effect of greatest concern. At doses greater than 450 mg/day, bupropion produces seizures in about 0.4% of patients. Seizure risk can be reduced by:

- Avoiding doses above 450 mg/day.
- Avoiding rapid dosage titration (see below).
- Avoiding bupropion in patients with seizure risk factors, such as head trauma, pre-existing seizure disorder, CNS tumor, and use of other drugs that lower seizure threshold.
- Avoiding bupropion in patients with anorexia nervosa or bulimia, which seem to increase seizure risk.
- Avoiding drugs that inhibit CYP2B6, which can elevate bupropion levels.

Drug Interactions. As noted, drugs that inhibit CYP2B6 (eg, sertraline, fluoxetine, paroxetine) can elevate bupropion levels, thereby increasing the risk of seizures. Combined use with these drugs should be avoided.

MAOIs can increase the risk of bupropion toxicity. Accordingly, patients should discontinue MAOIs at least 2 weeks before starting bupropion.

Preparations, Dosage, and Administration. Preparations for Depression. For treatment of depression, bupropion is available as two salts: bupropion hydrochloride and bupropion hydrobromide. Bupropion hydrochloride is available in immediate-release tablets (75 and 100 mg) as Wellbutrin, sustained-release tablets (100, 150, and 200 mg) as Wellbutrin SR and Budeprion SR, and extended-release tablets (150 and 300 mg) as Wellbutrin XL and Budeprion XL.* Bupropion hydrobromide is available in extended-release, alcohol-resistant tablets (174, 348, and 522 mg) as Aplenzin.

Dosage for Major Depression. Dosing must be done carefully to minimize the risk of seizures. Dosage escalation should be done slowly. The dosing schedule depends on the formulation being used. With the immediate-release tablets, the initial dosage is 75 mg twice a day. After 4 days, the dosage can be increased to 100 mg 3 times a day. If necessary, the dosage can be increased to a maximum of 150 mg 3 times a day. For maintenance therapy, once-daily dosing with Wellbutrin XL, Budeprion XL, or Aplenzin are attractive options.

Dosage for Seasonal Affective Disorder. To prevent SAD, dosing should begin in the fall—using Wellbutrin XL—and taper off in the spring. The dosage is 150 mg/day initially, and can later increase to 300 mg/day, if needed.

Preparations for Smoking Cessation. Bupropion hydrochloride marketed for smoking cessation is available in 150-mg sustained-release tablets sold as Zyban and Buproban. Dosages are presented in Chapter 39.

*Some patients who have switched from Wellbutrin XL to the generic Budeprion XL have reported worsening of side effects and relapse of previously controlled depressive symptoms. Whether these experiences are due to differences in the formulations or are just a coincidence has not been established.

Mirtazapine

Mirtazapine [Remeron] is the first representative of a new class of antidepressants. Benefits appear to result from increased release of 5-HT and NE. The mechanism is blockade of presynaptic α_2 -adrenergic receptors that serve to inhibit release. In addition to promoting transmitter release, mirtazapine is a powerful blocker of two serotonin receptor subtypes: 5-HT₂ and 5-HT₃. The contribution of this effect is unclear. Mirtazapine blocks histamine receptors, and thereby promotes sedation and weight gain. Antidepressant effects equal those of SSRIs and may develop faster.

Mirtazapine is well absorbed following oral dosing and reaches peak plasma levels in 2 hours. The drug undergoes extensive hepatic metabolism followed by excretion in the urine (75%) and feces (25%). The elimination half-life is 20 to 40 hours.

Mirtazapine is generally well tolerated. Somnolence is the most prominent adverse effect, occurring in 54% of patients. Weight gain, increased appetite, and elevated cholesterol are also common. Sexual dysfunction is minimal. Reversible agranulocytosis was reported in early trials, but was not confirmed in later clinical experience. Blockade of muscarinic receptors is moderate, and hence anticholinergic effects are mild. Mirtazapine-induced somnolence can be exacerbated by alcohol, benzodiazepines, and other CNS depressants. Accordingly, these agents should be avoided. Mirtazapine should not be combined with MAOIs.

Mirtazapine is available in standard tablets (7.5, 15, 30, and 45 mg) under the trade name *Remeron*, and in orally disintegrating tablets (15, 30, and 45 mg) under the trade name *Remeron SolTab*. The initial dosage is 15 mg once a day at bedtime. Dosage may be gradually increased to a maximum of 45 mg/day.

Other Atypical Antidepressants

Nefazodone

Nefazodone, formerly available as *Serzone*, is a novel drug indicated only for depression. Neuropharmacologic actions include blockade of 5-HT₂ receptors and α_1 -adrenergic receptors, and weak inhibition of NE and 5-HT reuptake. The contribution of these actions to therapeutic effects is unknown. Life-threatening liver failure is the adverse effect of greatest concern.

Nefazodone is rapidly and completely absorbed following oral administration. Food delays absorption and decreases bioavailability by 20%. Plasma drug levels peak about 1 hour after oral dosing. In the liver, nefazodone undergoes conversion to three active metabolites. The effective half-life of the parent drug and metabolites is 11 to 24 hours.

Nefazodone is generally well tolerated. The most common side effects are sedation, headache, somnolence, dry mouth, nausea, constipation, dizziness, blurred vision, and other visual disturbances. Weight gain and sexual dysfunction are minimal.

Nefazodone can cause life-threatening liver failure. However, the incidence is extremely low: only 1 case leading to death or liver transplantation for every 250,000 to 300,000 patient-years. As a rule, nefazodone should not be given to patients with pre-existing liver disease. Patients who develop signs of liver injury (eg, nausea, anorexia, abdominal pain, malaise, jaundice) should seek immediate medical attention. If laboratory tests confirm hepatocellular injury, nefazodone should be withdrawn.

Drugs that block reuptake of 5-HT, NE, or both can cause serious reactions if combined with an MAOI. Accordingly, nefazodone and MAOIs must not be combined. If the patient has been taking an MAOI, it should be discontinued at least 2 weeks before starting nefazodone. Conversely, when switching from nefazodone to an MAOI, nefazodone should be discontinued at least 7 days before starting the MAOI.

Nefazodone inhibits hepatic drug-metabolizing enzymes, and can thereby raise levels of other drugs, including certain antihistamines, benzodiazepines, and digoxin.

Nefazodone is available in tablets (50, 100, 150, 200, and 250 mg) for oral use. The initial dosage is 50 mg/day. If needed, the dosage can be gradually increased to between 150 and 300 mg/day. For elderly patients, the usual effective range is 50 to 200 mg twice daily.

Trazodone

Trazodone [Oleptro] is a second-line agent for depression. The drug is not very effective when used alone, but, because of its pronounced sedative effects, can be a helpful adjunct for patients with antidepressant-induced insomnia. Trazodone produces selective (but moderate) blockade of 5-HT reuptake. Antidepressant effects take several weeks to develop.

Common side effects are sedation, orthostatic hypotension, and nausea. In contrast to the tricyclic agents, trazodone has minimal anticholinergic actions. Accordingly, trazodone may be useful for elderly patients and other individuals for whom the anticholinergic effects of the TCAs may be intolerable.

Trazodone prolongs the QT interval, and hence poses a risk of dysrhythmias. In postmarketing reports, the drug has been associated with tachycardia, premature ventricular contractions, and potentially fatal torsades de pointes. Fortunately, these reports have been rare. To reduce the risk of dysrhythmias, trazodone should be used with caution in patients with hypokalemia, hypomagnesemia, congenital long QT syndrome, and other cardiac disorders.

Trazodone can cause priapism (prolonged, painful erection). In some cases, surgical intervention has been required. Priapism itself or the procedures required for relief can result in permanent impotence. Patients should be instructed to notify their prescriber or to go to an emergency department if persistent erection occurs. Prolonged clitoral erection can also occur, but the incidence is extremely low (0.016%).

Overdose with trazodone is considered safer than with TCAs or MAOIs. Death from overdose with trazodone alone has not been reported (although death has occurred following overdose with trazodone in combination with another CNS depressant).

Drugs that inhibit CYP3A4 (the 3A4 isozyme of cytochrome P450) can decrease metabolism of trazodone, and thereby increase its concentration. Toxicity may result. Accordingly, if trazodone is combined with a strong CYP3A4 inhibitor (eg, ketoconazole, ritonavir), dosage of trazodone should be reduced.

Trazodone is available in immediate-release (IR) tablets (50, 100, 150, and 300 mg) sold generically, and extended-release (ER) tablets (150 and 300 mg) sold as *Oleptro*. The ER tablets can be cut in half, but should not be crushed or chewed. Dosage depends on the formulation employed. With the IR tablets, dosage is 150 mg/day (in divided doses) initially, and then gradually increased to a maximum of 400 mg/day (for outpatients) and 600 mg/day (for hospitalized patients). With the ER tablets, dosage is 150 mg once a day initially, and then increased by 75 mg/day every 3 days up to a maximum of 375 mg once daily. All doses of the ER tablets should be taken on an empty stomach at the same time every day, preferably in the evening.

Vilazodone

Vilazodone [Viibryd] was approved for major depression in 2011. The drug works by two mechanisms. First, like the SSRIs, vilazodone selectively blocks serotonin reuptake. Second, vilazodone causes direct activation of serotonin receptors (by acting as a partial agonist). No other antidepressant combines both actions. The drug is more effective than a placebo, but is not more effective than fluoxetine or citalopram—and causes more GI side effects.

Vilazodone is administered by mouth, and food greatly enhances absorption. Plasma levels peak 4 to 5 hours after dosing. In the blood, the drug is highly (96% to 99%) protein bound. Vilazodone undergoes extensive hepatic metabolism—mainly by CYP3A4—followed by excretion in the urine.

The most common adverse effects are diarrhea (28%), nausea (23%), dizziness (9%), and insomnia (6%). Sexual dysfunction is also relatively common: Vilazodone reduces libido in males (5%) and females (3%); causes abnormal orgasms in males (4%) and females (2%); and also causes delayed ejaculation (2%) and erectile dysfunction (2%). Like the SSRIs, vilazodone poses a risk of serotonin syndrome, hyponatremia, and abnormal bleeding. Like all other antidepressants, vilazodone may increase suicidality. On the positive side, vilazodone appears to carry little or no risk of seizures, hypotension, weight gain, cardiotoxicity, hepatotoxicity, or anticholinergic effects.

Drug interactions are a concern. The risk of serotonin syndrome is increased by MAOIs and other serotonergic drugs (see Table 32-4). Use of MAOIs with vilazodone is contraindicated, and other serotonergic drugs should be used with caution, if at all. Vilazodone levels can be raised by drugs that inhibit CYP3A4 (eg, ketoconazole, ritonavir) and lowered by drugs that induce CYP3A4 (eg, rifampin, isoniazid, barbiturates). A dosage adjustment may be needed. The risk of bleeding is increased by anticoagulants (eg, warfarin) and by drugs that impede platelet function (eg, aspirin, NSAIDs).

Vilazodone [Viibryd] is supplied in 10-, 20-, and 40-mg tablets. Dosage should be done with food to enhance absorption. Dosage is titrated as follows:

low: 10 mg once daily for 7 days, then 20 mg once daily for 7 days, then 40 mg once daily for maintenance. MAOIs should be discontinued at least 14 days before starting vilazodone, and vilazodone should be discontinued at least 14 days before starting an MAOI. As with other antidepressants, dosage should be tapered slowly when ending treatment.

Amoxapine

Amoxapine, formerly available as *Asendin*, is chemically related to the antipsychotic agent loxapine, and has both antidepressant and neuroleptic properties. Antidepressant effects are equivalent to those of the TCAs. Because it can cause serious side effects, amoxapine should be reserved for patients with psychotic depression.

Amoxapine is generally well tolerated. Anticholinergic and sedative effects are moderate. Following overdose, the risk of seizures is greater than with TCAs. Exercise caution in patients with epilepsy.

Like loxapine and the other antipsychotics, amoxapine can block receptors for dopamine. As a result, the drug can cause extrapyramidal side effects (eg, parkinsonism, akathisia). Because of the risk of tardive dyskinesia (an extrapyramidal effect that develops with prolonged use of dopamine antagonists), long-term use of amoxapine should generally be avoided.

Amoxapine is available in tablets (25, 50, 100, and 200 mg). The usual dosage for depression is 200 to 300 mg/day.

Reboxetine

Reboxetine [Vestra] is the first representative of a new class of antidepressants: the *selective norepinephrine reuptake inhibitors*. The drug is not related chemically to TCAs, MAOIs, SSRIs, or SNRIs. Biochemical effects are limited almost entirely to enhancing transmission at receptors for NE. The drug has little or no impact on receptors for 5-HT, dopamine, acetylcholine, or histamine. Reboxetine is available in 50 countries, but not in the United States.

In clinical trials, antidepressant effects were comparable to those of TCAs and fluoxetine [Prozac], an SSRI. With short-term use, reboxetine induced remission and, with long-term use, prevented relapse. Because reboxetine is a new drug, its therapeutic niche has not been established. However, available data suggest that it may be especially good for patients with severe depression and for those in whom social functioning is severely impaired.

Reboxetine is rapidly absorbed following oral dosing. Plasma levels peak within 2 hours. High-fat meals reduce the rate of absorption, but not the extent. Reboxetine undergoes extensive hepatic metabolism followed by excretion in the urine. The drug's half-life is 12 to 16 hours, but may be prolonged in patients with liver dysfunction.

Reboxetine is generally well tolerated. The most common side effects are dry mouth, hypotension, constipation, urinary hesitancy or retention, and decreased libido. Other effects include dizziness, headache, nausea, insomnia, tremor, diaphoresis, and tachycardia. Reboxetine does not cause sedation or weight gain, and has minimal effects on psychomotor or cognitive function.

Combining reboxetine with an MAOI may pose a risk of hypertensive crisis. Accordingly, MAOIs should be withdrawn at least 14 days before giving reboxetine.

The recommended starting dosage is 4 mg twice daily. In patients with liver dysfunction, the initial dosage should be reduced to 2 mg twice daily. In clinical trials, dosages ranged between 4 and 12 mg/day.

NONCONVENTIONAL DRUGS FOR DEPRESSION

Ketamine

As discussed in Chapter 27, ketamine is a short-acting, IV drug used to produce dissociative anesthesia, primarily in children. Remarkably, when given to acutely depressed suicidal adults, low-dose ketamine can alleviate depressive symptoms and suicidal thoughts with stunning speed: A single bolus dose (0.2 mg/kg over 1 to 2 minutes) can produce marked improvement in just 40 minutes. Furthermore, the improvement is durable for at least 10 days. The major side effects are psychotic-like symptoms, which resolve in 40 minutes.

How does ketamine relieve depression? Recent data indicate that ketamine activates the brain's mTOR (mammalian target of rapamycin) signaling pathway—a pathway that regulates the synthesis of proteins needed to make new synaptic connections. Unfortunately, this same pathway is implicated in causing certain cancers (see Chapter 103), and hence prolonged use of a drug that works like ketamine could be dangerous. Nonetheless, the ability of ketamine to relieve depression rapidly is unprecedented, and suggests we may be able to develop other drugs that work rapidly too, hopefully without posing a risk of cancer.

St. John's Wort

St. John's wort (*Hypericum perforatum*) is an herbal product used for oral therapy of depression. For patients with *mild to moderate major depression*, the product is superior to placebo, and may equal the TCAs. However, for patients with *severe depression*, there is no convincing proof of efficacy. Adverse effects are generally mild. But interactions with conventional drugs are a concern. St. John's wort can decrease the effects of many drugs by (1) inducing cytochrome P450 drug-metabolizing enzymes and (2) inducing P-glycoprotein, a transport protein that exports drugs into the intestinal lumen and urine. In addition, the herb has can intensify serotonergic neurotransmission, and hence poses a risk of serotonin syndrome if combined with other serotonergic drugs. The pharmacology of St. John's wort is discussed further in Chapter 108 (Dietary Supplements).

S-Adenosylmethionine

S-adenosylmethionine (SAME) is a naturally occurring compound present in high concentration in the brain, liver, adrenal glands, and pineal gland. In the brain, SAME serves as a methyl donor for the synthesis of neurotransmitters (NE, 5-HT, dopamine) and cell membranes. In patients with severe depression, levels of SAME in the cerebrospinal fluid (CSF) are reduced. When these patients are given oral or parenteral SAME, there is a rise in CSF levels of SAME, and a corresponding improvement in depressive symptoms. When compared directly with TCAs, SAME was more effective and better tolerated. In treatment-resistant patients receiving SSRIs, adding SAME to the regimen was associated with moderate symptomatic improvement, and did not increase the risk of serotonin syndrome. Although studies to date are encouraging, experience with SAME is limited, and hence there are insufficient data to recommend SAME for routine use. In the United States, SAME is available without prescription as an enteric-coated dietary supplement.

SOMATIC (NONDRUG) THERAPIES FOR DEPRESSION

Nondrug therapies are reserved for patients with severe depression that has not responded to drugs or psychotherapy. Of the four treatments discussed below, ECT appears most effective.

Electroconvulsive Therapy

Electroconvulsive therapy is a valuable tool for treating depression. This procedure is safe and effective, and benefits develop more rapidly than with drugs or psychotherapy. Accordingly, ECT is especially appropriate when speed is critical. Candidates for ECT include (1) severely depressed, suicidal patients; (2) elderly patients at risk of starving to death because of depression-induced lack of appetite; and (3) patients who have not responded to antidepressant drugs (50% to 60% will respond to ECT). Since ECT as practiced today does not cause convulsions (see below), a more appropriate name might be *electroshock therapy*.

A single treatment consists of delivering an electrical shock to the scalp that is sufficient to induce a generalized seizure lasting 20 to 30 seconds. Success requires a series of these treatments, typically 2 to 3 per week for a total of 6 to 12 treatments.

Thanks to the adjunctive use of drugs, ECT is much less dramatic and traumatic than in the past. Prior to the delivery of electroshock, patients are treated with two drugs: a *short-acting neuromuscular blocker* (succinylcholine) and a *short-acting intravenous anesthetic* (eg, propofol, etomidate, methohexital). The neuromuscular blocker prevents shock-induced convulsive movements, which are both hazardous and unnecessary for a therapeutic response. The IV anesthetic

prevents conscious awareness of the ECT procedure (without interfering with beneficial actions). Patients may also receive an anticholinergic drug (eg, glycopyrrolate) to minimize bradycardia and salivation.

ECT can terminate an ongoing depression episode, but a single series of treatments cannot prevent recurrence. Accordingly, some patients are now given “maintenance” treatments, at weekly or monthly intervals. In one study, the relapse rate at 6 months in the absence of maintenance was 73%, compared with only 8% when maintenance ECT was used. Maintenance with antidepressant drugs (eg, lithium plus amitriptyline) is another option, but appears significantly less effective than maintenance with ECT.

Electroconvulsive therapy is very safe. There are no absolute contraindications to its use. The principal adverse effect is amnesia, primarily for events immediately surrounding treatment. However, patients may also experience some loss of older memories, but these usually return within 6 months. There is also transient impairment of cognitive function. Minor adverse effects, which occur immediately after treatment, include nausea, headache, confusion, and muscle discomfort.

Transcranial Magnetic Stimulation

Like ECT, transcranial magnetic stimulation (TMS) is reserved for patients with major depression that has not responded to antidepressant drugs. Magnetic stimulation is accomplished using the *NeuroStar TMS System*, a device that employs an insulated magnetic coil, placed against the scalp, to deliver pulsed magnetic fields to the left dorsolateral prefrontal cortex. The magnetic fields induce electrical currents in the brain, which in turn cause neuronal depolarization and other changes in brain activity. A full course of treatment consists of daily 40-minute sessions for 6 weeks or so. How effective is TMS? Trial results have been inconsistent. In some trials, TMS was just as effective as ECT, but in other trials, TMS was less effective. How safe is TMS? The procedure is generally well tolerated. Principal adverse effects are transient headaches and scalp discomfort. Patients may also experience eye pain, toothache, muscle

twitching, and seizures. Cognitive changes have not been reported.

Vagus Nerve Stimulation

In 2005, the Food and Drug Administration (FDA) approved the Vagus Nerve Stimulation (VNS) Therapy System for adjunctive, long-term therapy of patients with “treatment-resistant depression” (TRD), which the manufacturer defines as major depression that has not responded to at least four different antidepressant drugs. The VNS Therapy System—an implanted device that delivers electrical pulses to the vagus nerve—was first developed to treat drug-resistant epilepsy. In the course of that research, mood elevation was observed in some patients. A trial was then conducted in patients with TRD. However, the results were equivocal, and led the FDA review team to request more data. The data never came, but the device was approved anyway—thanks to the intervention of Daniel Schultz, director of the FDA’s Center for Devices and Radiological Health, who overruled his own team of reviewers. So, depending on who you believe, the device works, or it doesn’t. Nonetheless, it’s still available for use. The mechanism by which VNS alleviates depression (if it really does) is unknown. The principal side effects of VNS are hoarseness, voice alteration, cough, and dyspnea, all of which tend to diminish over time. The cost of the VNS system along with surgical implantation and calibration is about \$25,000. The VNS Therapy System and its use in epilepsy are discussed further in Box 24-1 (Nondrug Therapies for Epilepsy).

Light Therapy

Exposure to bright light is an effective treatment of seasonal affective disorder (SAD) and for nonseasonal major depression. The more intense the light, the greater the response. Light can be beneficial alone, and can enhance the response to antidepressant drugs. How does light relieve depression? Possibly by enhancing serotonergic neurotransmission. Light therapy is attractive owing to low cost and low risk.

KEY POINTS

- The principal symptoms of major depression are depressed mood and loss of pleasure or interest in one’s usual activities and pastimes.
- Patients with mild depression can be treated equally well with antidepressant drugs or psychotherapy. Patients with severe depression respond better to a combination of drugs plus psychotherapy than to either intervention alone.
- Patients with depression often think about or attempt suicide. During treatment with antidepressants, especially initially, the risk of suicide may *increase*. To reduce the risk of suicide, patients should be followed closely by family members, caregivers, and the prescriber. Suicide risk is greatest in children and young adults.
- All antidepressants appear equally effective. Differences relate primarily side effects, drug interactions, and cost.
- Therapeutic responses to antidepressants develop slowly. Initial responses develop in 1 to 3 weeks. Maximal responses may not be seen until 12 weeks.
- Antidepressant therapy should continue for 4 to 9 months after symptoms resolve.
- SSRIs block reuptake of serotonin, and thereby intensify transmission at serotonergic synapses. Over time, this

induces adaptive cellular responses that are ultimately responsible for relieving depression.

- SSRIs have two major advantages over TCAs: they cause fewer side effects and are safer when taken in overdose.
- Most SSRIs have stimulant properties, and hence can cause insomnia and agitation. This contrasts with TCAs, which cause sedation.
- Like most other antidepressants, SSRIs can cause weight gain.
- Sexual dysfunction (eg, impotence, anorgasmia) is more common with SSRIs than with most other antidepressants.
- SSRIs can cause serotonin syndrome, especially when combined with MAOIs. Symptoms include agitation, confusion, hallucinations, hyperreflexia, tremor, and fever. Combined use of SSRIs and MAOIs is contraindicated, and combined use with other serotonergic drugs (see Table 32-4) should be done with extreme caution, if at all.
- TCAs block reuptake of NE and 5-HT, and thereby intensify transmission at noradrenergic and serotonergic synapses. Over time, this induces adaptive cellular responses that are ultimately responsible for relieving depression.
- The most common adverse effects of TCAs are sedation, orthostatic hypotension, and anticholinergic effects (eg, dry mouth, constipation).
- The most serious adverse effect of TCAs is cardiotoxicity, which can be lethal if an overdose is taken.
- TCAs can cause a hypertensive crisis if combined with an MAOI. Accordingly, the combination is generally avoided.
- TCAs intensify responses to direct-acting sympathomimetics (eg, epinephrine) and diminish responses to indirect-acting sympathomimetics (eg, amphetamine).
- MAOIs increase neuronal stores of NE and 5-HT, and thereby intensify transmission at noradrenergic and sero-

tonergic synapses. Over time, this induces adaptive cellular responses that are ultimately responsible for relieving depression.

- MAOIs are as effective as SSRIs and TCAs, but are much more dangerous.
- MAOIs are first-choice drugs only for patients with atypical depression.
- Like SSRIs (and unlike TCAs), MAOIs cause direct CNS stimulation.
- Like TCAs (and unlike SSRIs), MAOIs cause orthostatic hypotension.
- Patients taking MAOIs must not eat tyramine-rich foods because hypertensive crisis can result.
- Hypertensive crisis can be treated with an IV vasodilator (eg, sodium nitroprusside, labetalol, phentolamine). Sublingual nifedipine is an alternative.
- MAOIs must not be combined with indirect-acting sympathomimetics (eg, amphetamine, cocaine) because hypertensive crisis can result.
- MAOIs must not be combined with SSRIs and other serotonergic drugs because serotonin syndrome could result.
- ECT relieves depression faster than antidepressant drugs, and often helps when antidepressants have failed.
- ECT as practiced today is safer and less traumatic than in the past, owing to adjunctive use of (1) a short-acting IV anesthetic (eg, propofol, etomidate) to produce unconsciousness, and (2) a short-acting muscle relaxant (succinylcholine) to prevent convulsions.

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Summary of Major Nursing Implications*

IMPLICATIONS THAT APPLY TO ALL ANTIDEPRESSANTS

Psychologic Assessment

Observe and record the patient's behavior. Factors to assess include affect, thought content, interest in the environment, appetite, sleep patterns, and appearance.

Reducing the Risk of Suicide

Depression carries a risk of suicide, which may increase during the initial phase of antidepressant therapy or when antidepressant dosage is changed. The risk is greatest among children and young adults. Advise family members and caregivers to monitor for symptoms of clinical decline (eg, anxiety, agitation, panic attacks, insomnia, irritability, hostility,

impulsivity, hypomania, and emergence of suicidal thoughts), and to immediately report symptoms that are severe or develop abruptly. Arrange for the patient or caregiver to meet with the prescriber at least weekly during the first 4 weeks of treatment, then biweekly for the next 4 weeks, then once 1 month later, and periodically thereafter.

Patients who are so depressed that they are a risk to themselves and others should be hospitalized until symptoms are under control. Suicide potential should be evaluated carefully. To prevent patients from accumulating a potentially lethal supply of medication, ensure that each dose is swallowed and not cheeked. Provide outpatients with no more than a 1-week supply of medication at a time. For patients considered at high risk of suicide, TCAs and MAOIs should be avoided; SSRIs are much safer.

*Patient education information is highlighted as blue text.

Continued

Promoting Adherence

Inform the patient that antidepressant effects usually develop slowly, over 1 to 3 weeks. This knowledge will make expectations more realistic, which should help promote adherence.

Premature discontinuation of therapy can result in relapse. Educate patients about the importance of taking their medication as prescribed, even though they may be symptom free and therefore feel "cured." In general, treatment should continue for 4 to 9 months after symptoms resolve.

Nondrug Therapy

For patients with severe depression, treatment with drugs alone is not optimal. Emotional support and psychotherapy can complement and reinforce responses to antidepressants. ECT may be indicated for suicidal patients and for patients who fail to respond to antidepressant drugs and psychotherapy. Other options include low-dose intravenous ketamine, transcranial magnetic stimulation, and vagus nerve stimulation.

Evaluating Therapeutic Effects

Assess patients for improvement in symptoms, especially depressed mood and loss of interest or pleasure in usual activities.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

- Citalopram
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline

In addition to the implications summarized below, see *Implications That Apply to All Antidepressants* above.

Preadministration Assessment

Therapeutic Goal

Alleviation of Symptoms of Major Depression. All SSRIs except fluvoxamine are approved for treating depression.

Other Goals. SSRIs are used to relieve symptoms of many psychologic disorders, including obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and bulimia nervosa (see Table 32-3).

Identifying High-Risk Patients

SSRIs are *contraindicated* for patients taking MAOIs, and should be used with *caution* in patients taking other serotonergic drugs. Use with *caution* in patients with liver disease and in the elderly and in women who are pregnant or breastfeeding.

Implementation: Administration

Route
Oral.

Administration

All SSRIs may be administered with food. Dosing in the morning minimizes sleep disruption.

Warn patients not to discontinue treatment once mood has improved, since doing so could lead to relapse.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Suicide Risk. See *Implications That Apply to All Antidepressants*.

CNS Stimulation. *Citalopram*, *escitalopram*, *fluoxetine*, *paroxetine*, and *sertraline* can cause nervousness, insomnia, and anxiety. These reactions may respond to a decrease in dosage. (Fluvoxamine causes mild sedation.)

Serotonin Syndrome. Symptoms of this potentially fatal syndrome include agitation, confusion, disorientation, anxiety, hallucinations, poor concentration, incoordination, myoclonus, hyperreflexia, excessive sweating, tremor, and fever. The risk is reduced by avoiding concurrent use of MAOIs and certain other drugs (see below under *Minimizing Adverse Interactions*). Serotonin syndrome resolves spontaneously after discontinuing the SSRI.

Sexual Dysfunction. Inform patients about possible sexual dysfunction (anorgasmia, impotence, decreased libido), and encourage them to report problems. Management strategies include dosage reduction, drug holidays, adding a drug to counteract sexual dysfunction (eg, sildenafil, bupropion), and switching to an antidepressant that causes less sexual dysfunction (eg, bupropion, nefazodone, mirtazapine).

Dizziness and Fatigue. Inform patients about possible dizziness and fatigue, and advise them to exercise caution while performing hazardous tasks (eg, driving).

Rash. *Fluoxetine* may cause rash. Inform patients about the risk of rash and instruct them to notify the prescriber if one develops. Treatment consists of drug therapy (antihistamines, glucocorticoids) or withdrawal of fluoxetine.

Weight Gain. Long-term therapy can result in significant weight gain. Advise patients to restrict caloric intake and to get appropriate exercise.

Neonatal Abstinence Syndrome (NAH) and Persistent Pulmonary Hypertension of the Newborn (PPHN). Use of SSRIs late in pregnancy poses a small risk of NAH and PPHN. Newborns exposed to SSRIs *in utero* should be monitored for both disorders. If NAH occurs, it can be managed with supportive care, and generally abates within a few days. Treatment measures for PPHN include providing mechanical ventilatory support, giving inhaled nitric oxide and oxygen, and giving IV sodium bicarbonate and dopamine.

Teratogenesis. Two SSRIs—*fluoxetine* and *paroxetine*—pose a small risk of birth defects, especially ventricular septal defects and other cardiovascular anomalies. Other SSRIs are preferred during pregnancy.

Dysrhythmias. *Citalopram* may cause severe dysrhythmias, especially when doses are too high. Warn patients not to exceed 40 mg/day. Use with caution in patients with dysrhythmia risk factors, including heart disease, long QT syndrome, and low blood levels of potassium or magnesium.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

GI Bleeding. SSRIs impair platelet aggregation, and can thereby increase the risk of GI bleeding. Exercise caution in elderly patients, patients with ulcers or a history of GI bleeding, and patients taking antiplatelet drugs or anticoagulants.

Hyponatremia. SSRIs can cause hyponatremia, primarily in older patients taking diuretics. When SSRIs and diuretics are used in older patients, serum sodium should be measured at baseline and periodically thereafter.

Bruxism. SSRIs can cause bruxism (clenching and grinding of teeth), usually during sleep. **Alert patients to the sequelae of bruxism (headache, jaw pain, and dental problems, such as cracked fillings).** If these develop, investigate whether an SSRI is the cause. Bruxism can be managed by (1) reducing the SSRI dosage (but then depression may return), (2) switching to a different class of antidepressants, (3) using a mouth guard, and (4) treating with low-dose buspirone.

Minimizing Adverse Interactions

MAOIs and Other Drugs That Increase the Risk of Serotonin Syndrome. MAOIs greatly increase the risk of serotonin syndrome, and hence should be withdrawn at least 14 days before starting an SSRI. The risk of serotonin syndrome can also be increased by other serotonergic drugs (see Table 32-4), and by tramadol (an analgesic) and linezolid (an antibiotic that inhibits MAO). Withdraw fluoxetine at least 5 weeks before starting an MAOI, and withdraw other SSRIs at least 2 weeks before starting an MAOI.

TCA's and Lithium. Fluoxetine can increase levels of these drugs. Exercise caution.

Antiplatelet Drugs and Anticoagulants. Antiplatelet drugs (eg, aspirin, NSAIDs) and anticoagulants (eg, warfarin) increase the risk of GI bleeding. Exercise caution.

The risk of bleeding with *warfarin* is compounded by a pharmacokinetic interaction with *fluoxetine*, which can displace warfarin from binding sites on plasma proteins, causing levels of free warfarin to rise. Monitor responses to warfarin closely.

Drugs That Are Substrates for or Inhibitors of CYP2D6. Drugs that inhibit CYP2D6 can raise levels of SSRIs, and can thereby pose a risk of toxicity. In addition to being substrates for CYP2D6, two SSRIs—*fluoxetine* and *paroxetine*—can inhibit CYP2D6, and can thereby raise levels of other drugs that are CYP2D6 substrates, including TCAs, some antipsychotics, and two antidysrhythmic drugs: propafenone and flecainide. Exercise caution.

TRICYCLIC ANTIDEPRESSANTS

Amitriptyline
Clomipramine
Desipramine
Doxepin
Imipramine
Maprotiline
Nortriptyline
Protriptyline
Trimipramine

In addition to the implications summarized below, see *Implications That Apply to All Antidepressants* above.

*Patient education information is highlighted as blue text.

Preadministration Assessment

Therapeutic Goal

Alleviation of symptoms of major depression.

Baseline Data

Assess psychologic status. Arrange for an ECG, especially for patients with cardiac disease and those over age 40.

Identifying High-Risk Patients

TCAs are generally *contraindicated* for patients taking MAOIs.

Use TCAs with *caution* in patients with cardiac disorders (eg, coronary heart disease, progressive heart failure, paroxysmal tachycardia), elevated intraocular pressure, urinary retention, hyperthyroidism, seizure disorders, and liver or kidney dysfunction.

Doxepin is *contraindicated* for patients with glaucoma or a tendency to urinary retention.

Maprotiline is *contraindicated* for patients with seizure disorders.

Implementation: Administration

Routes

Oral.

Administration

Instruct patients to take medication daily as prescribed and not PRN. Warn patients not to discontinue treatment once mood has improved, since doing so may result in relapse. Once an effective dosage has been established, the entire daily dose can usually be taken at bedtime.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Suicide Risk. See *Implications That Apply to All Antidepressants*.

Orthostatic Hypotension. Inform patients about symptoms of hypotension (dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when assuming an erect posture. For hospitalized patients, monitor blood pressure and pulse rate on a regular schedule; take measurements while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes. If blood pressure is low or pulse rate is high, withhold medication and inform the prescriber.

Anticholinergic Effects. Inform patients about possible anticholinergic effects (dry mouth, blurred vision, photophobia, urinary hesitancy, constipation, tachycardia), and advise them to notify the prescriber if these are troublesome. A detailed summary of nursing implications for anticholinergic drugs is presented in Chapter 14.

Diaphoresis. TCAs promote sweating (despite their anticholinergic properties). Excessive sweating may necessitate frequent changes of bedding and clothing.

Sedation. Sedation is most intense during the first weeks of therapy and declines with continued drug use. Advise pa-

Summary of Major Nursing Implications*—cont'd

tients to avoid hazardous activities (eg, driving, operating dangerous machinery) if sedation is significant. Giving TCAs at bedtime minimizes daytime sedation and promotes sleep.

Cardiotoxicity. TCAs can disrupt cardiac function, but usually only when taken in excessive doses or by patients with heart disease. All patients should receive an ECG prior to treatment and periodically thereafter. Risk of cardiac toxicity may be higher with *desipramine* than with other TCAs.

Seizures. TCAs decrease seizure threshold. Exercise caution in patients with seizure disorders.

Hypomania. TCAs may shift mood from depression up to hypomania. If hypomania develops, the patient must be evaluated to determine if elation is drug induced or indicates bipolar disorder.

Minimizing Adverse Interactions

MAO Inhibitors. Rarely, the combination of a TCA and an MAOI has produced hypertensive episodes and hypertensive crisis. Exercise caution if this combination is employed.

Sympathomimetic Agents. TCAs decrease the effects of indirect-acting sympathomimetics (eg, ephedrine, amphetamine), but potentiate the actions of direct-acting sympathomimetics (eg, epinephrine, dopamine). If sympathomimetics are to be used, these effects must be accounted for.

Anticholinergic Agents. Drugs capable of blocking muscarinic receptors will enhance the anticholinergic effects of TCAs. **Warn patients against concurrent use of other anticholinergic drugs (eg, scopolamine, antihistamines, phenothiazines).**

CNS Depressants. These will enhance the depressant effects of TCAs. **Warn patients against using alcohol and all other drugs with CNS-depressant properties (eg, opioids, antihistamines, barbiturates, benzodiazepines).**

MONOAMINE OXIDASE INHIBITORS

Isocarboxazid
Phenelzine
Selegiline
Tranlycypromine

In addition to the implications summarized below, see *Implications That Apply to All Antidepressants* above.

Preadministration Assessment

Therapeutic Goal

Alleviation of symptoms of major depression, especially atypical depression.

Identifying High-Risk Patients

MAOIs are *contraindicated* for patients taking SSRIs; for patients with pheochromocytoma, heart failure, liver disease, severe renal impairment, cerebrovascular defect (known or suspected), cardiovascular disease, and hypertension; and for patients over the age of 60 (because of possible cerebral sclerosis associated with vessel damage).

Use with *caution* in patients taking serotonergic drugs.

Implementation: Administration

Routes

Oral. Isocarboxazid, phenelzine, tranlycypromine.
Transdermal. Selegiline.

Administration

All MAOIs. Instruct patients to take MAOIs every day as prescribed—not PRN. Warn patients not to discontinue treatment once mood has improved, since doing so may result in relapse.

Transdermal Selegiline. Instruct patients to apply the Emsam patch to intact, dry skin of the upper torso, upper thigh, or outer surface of the upper arm once every 24 hours.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Suicide Risk. See *Implications That Apply to All Antidepressants*.

Hypertensive Crisis. Dietary tyramine, certain other dietary constituents (see Table 32-6), and indirect-acting sympathomimetics (eg, amphetamine, methylphenidate, ephedrine, cocaine) can precipitate a hypertensive crisis in patients taking MAOIs.

Inform patients about symptoms of hypertensive crisis—severe headache, tachycardia, hypertension, nausea, vomiting, confusion, and profuse sweating—and instruct them to seek immediate medical attention if these develop.

To reduce the risk of hypertensive crisis, the following precautions must be observed:

- Do not give MAOIs to patients who are suicidal or who are considered incapable of rigid adherence to dietary constraints.
- Forewarn patients about the hazard of hypertensive crisis and the need to avoid tyramine-rich foods and sympathomimetic drugs. (Patients on low-dose transdermal selegiline needn't avoid tyramine-containing foods, but do need to avoid sympathomimetic drugs.)
- Provide patients with a list of specific foods to avoid (see Table 32-6).
- Instruct them to avoid all drugs not approved by the prescriber.

If hypertensive crisis develops, blood pressure can be lowered with an IV vasodilator, such as sodium nitropruside, labetalol, or phentolamine. If IV therapy is not available, sublingual nifedipine is an alternative.

Orthostatic Hypotension. Inform patients about signs of hypotension (dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when assuming an erect posture. For the hospitalized patient, monitor blood pressure and pulse rate on a regular schedule. Take these measurements while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes. If blood pressure is low, withhold medication and inform the prescriber.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Skin Rash. Application-site rash is common with transdermal selegiline, and can be managed with a topical glucocorticoid.

Minimizing Adverse Interactions

All Drugs. MAOIs can interact adversely with many other drugs. **Instruct the patient to avoid all medications—prescription and nonprescription—that have not been specifically approved by the prescriber.**

Indirect-Acting Sympathomimetics. Concurrent use with MAOIs can precipitate a hypertensive crisis. **Warn patients against use of any indirect-acting sympathomimetics (eg, ephedrine, methylphenidate, amphetamines, cocaine).**

Tricyclic Antidepressants. Concurrent use with MAOIs can produce hypertensive episodes and hypertensive crisis. Use this combination with caution.

Serotonergic Drugs. Combining MAOIs with other serotonergic drugs (see Table 32-4) poses a risk of serotonin syndrome. Accordingly, these combinations should generally be avoided.

Antihypertensive Drugs. These drugs will potentiate the hypotensive effects of MAOIs. If these agents are combined, monitor blood pressure periodically.

Meperidine. Meperidine can produce hyperthermia in patients taking MAOIs and hence should be avoided.

*Patient education information is highlighted as **blue text**.

Characteristics of Bipolar Disorder

Types of Mood Episodes Seen in BPD
Patterns of Mood Episodes

Etiology

Treatment of Bipolar Disorder

Drug Therapy

Nondrug Therapy

Mood-Stabilizing Drugs

Lithium

Antiepileptic Drugs

Antipsychotic Drugs



Box-1. Omega-3 Fatty Acids for Bipolar Disorder: A Fish Story with a Happy Ending

Our topic for this chapter is *bipolar disorder* (BPD), formerly known as *manic-depressive illness*. The disease afflicts an estimated 3.7% of the adult population—more than 6.7 million Americans. The mainstays of therapy are lithium and divalproex sodium (valproate), drugs that can stabilize mood. Many patients also receive an antipsychotic agent, and some may require an antidepressant. Bipolar disorder is a chronic condition that requires treatment lifelong.

CHARACTERISTICS OF BIPOLAR DISORDER

Bipolar disorder is a severe biologic illness characterized by recurrent fluctuations in mood. Typically, patients experience alternating episodes in which mood is abnormally elevated or abnormally depressed—separated by periods in which mood is relatively normal. Symptoms usually begin in adolescence or early adulthood, but can occur before adolescence or as late as the fifth decade of life. In the absence of treatment, episodes of mania or depression generally persist for several months. As time passes, manic and depressive episodes tend to recur more frequently. Although the precise etiology of BPD is unknown, it is clear that symptoms are caused by altered brain physiology—not by a character flaw or an unstable personality.

Types of Mood Episodes Seen in BPD

Patients with BPD may experience four types of mood episodes. These are described below.

Pure Manic Episode (Euphoric Mania). Manic episodes are characterized by persistently heightened, expansive, or ir-

ritable mood—typically associated with hyperactivity, excessive enthusiasm, and flight of ideas. Manic individuals display overactivity at work and at play and have a reduced need for sleep. Mania produces excessive sociability and talkativeness. Extreme self-confidence, grandiose ideas, and delusions of self-importance are common. Manic individuals often indulge in high-risk activities (eg, questionable business deals, reckless driving, gambling, sexual indiscretions), giving no forethought to the consequences. In severe cases, symptoms may resemble those of paranoid schizophrenia (hallucinations, delusions, bizarre behavior).

Detailed criteria for a manic episode are set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The criteria now in use, published in the fourth edition of the DSM (DSM-IV), were released in 1994. Revised criteria will appear in fifth edition of the DSM (DSM-5), scheduled for release in 2013. The proposed DSM-5 criteria, which are nearly identical to those in DSM-IV, are summarized in Table 33-1.

Hypomanic Episode (Hypomania). Hypomania can be viewed as a mild form of mania. As in mania, mood is persistently elevated, expansive, or irritable. However, symptoms are not severe enough to cause marked impairment in social or occupational functioning, or to require hospitalization. Psychotic symptoms are absent.

Major Depressive Episode (Depression). A major depressive episode is characterized by depressed mood and loss of pleasure or interest in all or nearly all of one's usual activities and pastimes. Associated symptoms include disruption of sleeping and eating patterns; difficulty concentrating; feelings of guilt, worthlessness, and helplessness; and thoughts of death and suicide. The characteristics of major depression are discussed further in Chapter 32.

Mixed Episode. In a true mixed episode, patients experience symptoms of mania and depression simultaneously. Patients may be agitated and irritable (as in mania), but may also feel worthless and depressed. The combination of high energy and depression puts them at significant risk of suicide.

Patterns of Mood Episodes

Among people with BPD, mood episodes can occur in a variety of patterns. Contrary to popular belief, not all patients alternate repeatedly between mania and depression. Some experience repeated episodes of mania, and some experience repeated episodes of depression (with an occasional episode of mania). Mood may be normal between episodes of mania and depression, or it may be slightly elevated (hypomania) or slightly depressed (dysphoria).

Mood episodes can vary greatly with respect to how often they occur and how long they last. A single episode may last

TABLE 33-1 ■ Proposed DSM-5 Criteria for a Manic Episode

- A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
- B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree, and represent a noticeable change from usual behavior:
1. Inflated self-esteem or grandiosity
 2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
 3. More talkative than usual or pressure to keep talking
 4. Flight of ideas or subjective experience that thoughts are racing
 5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
 7. Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- C. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- D. The episode is not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication, or other treatment).

Note: A full manic episode emerging during antidepressant treatment (medication, ECT, etc.) and persisting beyond the physiologic effect of that treatment is sufficient evidence for a manic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a manic episode.

Modified from the proposed criteria for a manic episode, to be published in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on November 20, 2010.

for days, weeks, months, or more than a year. In the absence of treatment, episodes of mania or hypomania typically last a few months, whereas episodes of major depression typically last at least 6 months. On average, people with BPD experience only 4 episodes during the first 10 years of their illness. However, some people cycle much more rapidly, experiencing many episodes every year.

On the basis of mood episode type and frequency, BPD can be subdivided into two major categories:

- *Bipolar I Disorder*—Patients experience manic or mixed episodes, and usually depressive episodes too.
- *Bipolar II Disorder*—Patients experience hypomanic or depressive episodes, but not manic or mixed episodes.

Etiology

Theories regarding the etiology of BPD continue to evolve. In the past, there was general agreement that BPD was due primarily to an imbalance in neurotransmitters. Today, researchers suspect the real cause may be disruption of neuronal growth and survival. Why? First, neuroimaging studies have shown an association between prolonged mood disorders and atrophy of specific brain regions—especially the subgenual prefrontal cortex, an area involved in emotionality. Second, mood-stabilizing drugs can prevent or reverse neuronal atrophy in patients with BPD, apparently by influencing signaling pathways that regulate neuronal growth and survival.

TREATMENT OF BIPOLAR DISORDER

Drug Therapy

Types of Drugs Employed

Bipolar disorder is treated with three major groups of drugs: mood stabilizers, antipsychotics, and antidepressants. In addition, benzodiazepines are frequently used for sedation.

Mood Stabilizers. Mood stabilizers are drugs that (1) relieve symptoms during manic and depressive episodes, (2) prevent recurrence of manic and depressive episodes, and (3) do not worsen symptoms of mania or depression, or accelerate the rate of cycling. The principal mood stabilizers are *lithium* and two drugs originally developed for epilepsy: *divalproex sodium* (valproate) and *carbamazepine*. These drugs are the mainstays of treatment. The pharmacology of lithium and the antiepileptic drugs is discussed below.

Antipsychotics. In patients with BPD, antipsychotic drugs are given to help control symptoms during severe manic episodes, even if psychotic symptoms are absent. Although antipsychotics can be used alone, they are usually employed in combination with a mood stabilizer. For reasons discussed below, the second-generation antipsychotics (eg, olanzapine, risperidone) are generally preferred to the first-generation agents (eg, haloperidol).

Antidepressants. Antidepressants may be needed during a depressive episode. However, in patients with BPD, antidepressants are *always* combined with a mood stabilizer. Why? Because of the long-held belief that, when used alone, antide-

TABLE 33-2 • Initial Treatment of First Manic Episode

Clinical Presentation	Preferred Strategy	Preferred Drugs*	
		Mood Stabilizers	Antipsychotics
Euphoric mania	Mood stabilizer alone	Valproate or lithium	
Dysphoric mania or true mixed mania	Mood stabilizer alone	Valproate or lithium	
Mania with psychosis	Mood stabilizer plus an antipsychotic	Valproate or lithium	Olanzapine or risperidone
Rapid cycling (currently manic)	Mood stabilizer alone	Valproate	

Valproate = divalproex sodium.

*Drugs of choice, if established, are presented in **bold type**.

pressants may elevate mood so much that a hypomanic or manic episode will result. However, data published in 2007 indicate that the risk of inducing mania may be much lower than previously thought. Nonetheless, until the issue is fully resolved, it would seem prudent to continue the traditional practice of using an antidepressant only if a mood stabilizer is being used as well.

Although antidepressants have been studied extensively in patients with major depression, very little research has been done in patients with BPD. As a result, we lack reliable information on which to base drug selection. Even so, experts do have their preferences. Among clinicians with extensive experience in BPD, the following are considered antidepressants of choice: *bupropion* [Wellbutrin], *venlafaxine* [Effexor XR], and the *selective serotonin reuptake inhibitors* (SSRIs), such as fluoxetine [Prozac] and sertraline [Zoloft]. The pharmacology of these drugs is discussed in Chapter 32.

Drug Selection

Acute Therapy: Manic Episodes. Two mood stabilizers—lithium and valproate—are preferred drugs for acute management of manic episodes. The choice between them is based on clinical presentation (eg, euphoric mania, mania with psychosis, rapid-cycling BPD). As shown in Table 33-2, valproate is preferred to lithium in most cases. In fact, the only exception is euphoric mania, for which lithium is the drug of choice. If the patient does not respond adequately to lithium or valproate alone, the drugs may be used together. Responses to mood stabilizers develop slowly, taking 2 or more weeks to become maximal.

If needed, an antipsychotic agent or a benzodiazepine may be added to the regimen. These adjuvants can help relieve symptoms (eg, insomnia, anxiety, agitation) until the mood stabilizer takes full effect. For patients with mild mania, a benzodiazepine (eg, lorazepam [Ativan]) may be adequate. For patients with severe mania or with symptoms of psychosis, an antipsychotic is preferred; olanzapine or risperidone would be a good choice.

Acute Therapy: Depressive Episodes. Depressive episodes may be treated with a mood stabilizer alone, or with a mood stabilizer *plus* an antidepressant—but *never* with an antidepressant alone (because hypomania or mania might result). If depression is mild, monotherapy with a mood stabilizer (lithium or valproate) may be sufficient. If the mood stabilizer is inadequate, an antidepressant can be added, although benefits may be limited. Preferred antidepressants are bupropion, venlafaxine, or an SSRI.

Long-Term Preventive Treatment. The purpose of long-term therapy is to prevent recurrence of both mania and depression. As a rule, one or more mood stabilizers are employed. Drug selection is based on what worked acutely. For example, if the patient responded to acute therapy with lithium alone, then lithium alone should be tried long term. Other long-term options include valproate alone, and valproate plus lithium. More recently, antipsychotic agents have been employed for long-term maintenance, either as monotherapy or in combination with a mood stabilizer.

Promoting Adherence

Poor patient adherence can frustrate attempts to treat a manic episode. Patients may resist treatment because they fail to see anything wrong with their thinking or behavior. Furthermore, the experience is not necessarily unpleasant. In fact, individuals going through a manic episode may well enjoy it. As a result, in order to ensure adherence, short-term hospitalization may be required. To achieve this, collaboration with the patient's family may be needed. Since hospitalization per se won't guarantee success, lithium administration should be directly observed to ensure that each dose is actually taken.

After an acute manic episode has been controlled, long-term prophylactic therapy is indicated, making adherence an ongoing issue. To promote adherence, the patient and family should be educated about the nature of BPD and the importance of taking medication as prescribed. Family members can help ensure adherence by overseeing medication use, and by urging the patient to visit his or her prescriber or a psychiatric clinic if a pattern of nonadherence develops.

Nondrug Therapy

Education and Psychotherapy

Ideally, BPD should be treated with a combination of drugs and adjunctive psychotherapy (individual, group, or family); drug therapy alone is not optimal. Bipolar disorder is a chronic illness that requires supportive therapy and education for the patient and family. Counseling can help patients cope with the sequelae of manic episodes, such as strained relationships, reduced self-confidence, and a sense of shame regarding uncontrolled behavior. Certain life stresses (eg, moving, job loss, bereavement, childbirth) can precipitate a mood change. Therapy can help reduce the destabilizing impact of these events. Patients should be taught to recognize early symptoms of mood change, and encouraged to contact their

primary clinician immediately if these develop. Additional measures by which patients can help themselves include

- Maintaining a stable sleep pattern
- Maintaining a regular pattern of activity
- Avoiding alcohol and psychoactive street drugs
- Enlisting the support of family and friends
- Taking steps to reduce stress at work
- Keeping a mood chart to monitor progress

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is an effective intervention that can be lifesaving in patients with severe mania or severe depression. However, ECT is not a treatment of first choice. Rather, it should be reserved for patients who have not responded adequately to drugs. Candidates for ECT include patients with psychotic depression, severe nonpsychotic depression, severe mania, and rapid-cycling BPD. Details of ECT are discussed in Chapter 32.

MOOD-STABILIZING DRUGS

As noted, mood stabilizers are drugs that can relieve an acute manic or depressive episode, and can prevent symptoms from recurring—all without aggravating mania or depression, and without accelerating cycling. The agents used most often are lithium, valproate, and carbamazepine.

Lithium

Lithium [Lithobid, Lithonate, Lithotabs, Carbolith[®]] can stabilize mood in patients with BPD. Beneficial effects were first described in 1949 by John Cade, an Australian psychiatrist. Because of concerns about toxicity, lithium was not ap-

proved for use in the United States until 1970. Lithium has a low therapeutic index. As a result, toxicity can occur at blood levels only slightly greater than therapeutic levels. Accordingly, monitoring lithium levels is mandatory.

Chemistry

Lithium is a simple inorganic ion that carries a single positive charge. In the periodic table of elements, lithium is in the same group as potassium and sodium. Not surprisingly, lithium has properties in common with both elements. Lithium is found naturally in animal tissues but has no known physiologic function.

Therapeutic Uses

Bipolar Disorder. Lithium is a drug of choice for controlling acute manic episodes in patients with BPD and for long-term prophylaxis against recurrence of mania or depression. In manic patients, lithium reduces euphoria, hyperactivity, and other symptoms but does not cause sedation. Antimanic effects begin 5 to 7 days after treatment onset, but full benefits may not develop for 2 to 3 weeks. In the past, lithium was considered the drug of choice for all patients experiencing an acute manic episode, regardless of clinical presentation. Today, however, lithium is reserved primarily for patients with classic (euphoric) mania. Valproate is generally preferred for all other patients (see Table 33–2). However, recent data show that lithium is superior to valproate at preventing suicide in patients with BPD, and hence use of lithium is likely to increase.

Other Uses. Although approved only for treatment of BPD, lithium has been used with varying degrees of success in other psychiatric disorders, including *alcoholism*, *bulimia*, *schizophrenia*, and *glucocorticoid-induced psychosis*. Nonpsychiatric uses include *hyperthyroidism*, *cluster headache*, *migraine*, and *syndrome of inappropriate secretion of antidiuretic hormone*. In addition, lithium can *raise neutrophil counts* in children with chronic neutropenia and in patients receiving anticancer drugs or zidovudine (AZT).

BOX 33–1 ■ SPECIAL INTEREST TOPIC

OMEGA-3 FATTY ACIDS FOR BIPOLAR DISORDER: A FISH STORY WITH A HAPPY ENDING

In 1999, researchers from Harvard University made an exciting discovery: Fish oil can stabilize mood in people with bipolar disorder. Their results were so striking, in fact, that the experiment was stopped after 4 months so that control patients could switch to the fish-oil regimen. All subjects in the study had diagnosed bipolar disorder. Some took 9.6 gm of fish oil daily, and some took olive oil as a control. All continued on their usual medications. Among the group that ate fish oil, 11 of 15 improved after 4 months—and only 2 suffered eventual relapse. Among the group that ate olive oil, only 6 of 20 improved after 4 months—and 11 experienced relapse. Patients taking the fish oil had longer periods of remission, and, when symptoms did appear, they were less severe. Several patients were able to discontinue their medications and remain symptom free on fish oil alone. Side effects of the fish oil were minor—nausea, belching, fishy taste, loose stools—and easily controlled. At

this time, the long-term benefits or detriments of fish oil are unknown. This study is of special interest in that it suggests that dietary therapy for a major illness can be as effective as drugs.

How does fish oil work? No one knows. Fish oil is composed of omega-3 fatty acids*—specifically, eicosapentaenoic acid and docosahexaenoic acid. In humans, the highest concentrations of omega-3s are found in the eyes and brain, where they are present in cell membranes. It may be that eating fish oil increases the concentration of omega-3s in neuronal membranes, and thereby slows nerve signaling, which in turn may stabilize mood. There is some evidence that omega-6 fatty acids—the kind found in vegetable oils, margarine, and mayonnaise—may negate the beneficial effects of omega-3s. Accordingly, patients taking fish oil for bipolar disorder should probably decrease intake of omega-6s.

*Omega-3 fatty acids are long-chain polyunsaturated fats that have a double bond located three carbons from the methyl terminus of the chain.

Mechanism of Action

Although lithium has been studied extensively, the precise mechanism by which it stabilizes mood is unknown. In the past, research focused on three aspects of brain neurochemistry: (1) altered distribution of certain ions (calcium, sodium, magnesium) that are critical to neuronal function; (2) altered synthesis and release of norepinephrine, serotonin, and dopamine; and (3) effects on second messengers (eg, cyclic AMP, phosphatidyl inositol), which mediate intracellular responses to neurotransmitters. Unfortunately, this research has failed to provide a definitive explanation of how lithium works. Current neurochemical research suggests that lithium may work by (1) altering glutamate uptake and release, (2) blocking the binding of serotonin to its receptors, and/or (3) inhibiting glycogen synthase kinase-3 beta.

Recently, there has been growing interest in the neurotrophic and neuroprotective actions of lithium. As noted above, there is evidence that symptoms of BPD may result from neuronal atrophy in certain brain areas. In animal studies, "therapeutic" doses of lithium doubled the level of neurotrophic Bcl-2 proteins. In addition, lithium has been shown to facilitate regeneration of damaged optic nerves. In patients with BPD taking lithium long term, volume of the subgenual prefrontal cortex is greater than in untreated patients. Furthermore, lithium can increase total gray matter in regions known to atrophy in BPD, including the prefrontal cortex, hippocampus, and caudate nucleus. All of these studies suggest that the benefits of lithium may result at least in part from an ability to protect against neuronal atrophy and/or promote neuronal growth.

Pharmacokinetics

Absorption and Distribution. Lithium is well absorbed following oral administration. The drug distributes evenly to all tissues and body fluids.

Excretion. Lithium has a short half-life owing to rapid renal excretion. Because of its short half-life (and high toxicity), the drug must be administered in divided daily doses. Large, single daily doses cannot be used, even when a slow-release preparation is prescribed. Because lithium is excreted by the kidneys, it must be employed with great care in patients with renal impairment.

Renal excretion of lithium is affected by blood levels of sodium. Specifically, lithium excretion is *reduced* when levels of sodium are *low*. Why? Because the kidney processes lithium and sodium in the same way. Hence, when the kidney senses that sodium levels are inadequate, it retains lithium in an attempt to compensate. Because of this relationship, in the presence of low sodium, lithium can accumulate to toxic levels. Accordingly, it is important that sodium levels remain normal. Patients should be instructed to maintain normal sodium intake. Obviously, a sodium-free diet cannot be used. Since diuretics promote sodium loss, these agents must be employed with caution. Also, sodium loss secondary to diarrhea can be sufficient to cause lithium accumulation. The patient should be told about this possibility.

Dehydration will cause lithium retention by the kidneys, posing the risk of accumulation to dangerous levels. Potential causes of dehydration include hot weather and diarrhea. Counsel patients to maintain adequate hydration.

Monitoring Plasma Lithium Levels. Measurement of plasma lithium levels is an essential component of treatment.

TABLE 33-3 ■ Toxicities Associated with Excessive Plasma Level of Lithium

Plasma Lithium Level (mEq/L)	Signs of Toxicity
Below 1.5	Nausea, vomiting, diarrhea, thirst, polyuria, lethargy, slurred speech, muscle weakness, fine hand tremor
1.5-2	Persistent GI upset, coarse hand tremor, confusion, hyperirritability of muscles, ECG changes, sedation, incoordination
2-2.5	Ataxia, giddiness, high output of dilute urine, serious ECG changes, fasciculations, tinnitus, blurred vision, clonic movements, seizures, stupor, severe hypotension, coma, death (usually secondary to pulmonary complications)
Above 2.5	Symptoms may progress rapidly to generalized convulsions, oliguria, and death

ECG = electrocardiogram.

Lithium levels must be kept below 1.5 mEq/L; levels greater than this can produce significant toxicity. For initial therapy of a manic episode, lithium levels should range from 0.8 to 1.4 mEq/L. Once the desired therapeutic effect has been achieved, the dosage should be reduced to produce *maintenance* levels of 0.4 to 1 mEq/L. Blood for lithium determinations should be drawn in the morning, 12 hours after the evening dose. During maintenance therapy, lithium levels should be measured every 3 to 6 months.

Adverse Effects

The adverse effects of lithium can be divided into two categories: (1) effects that occur at excessive lithium levels and (2) effects that occur at therapeutic lithium levels. In the discussion below, adverse effects produced at excessive lithium levels are considered as a group. Effects produced at therapeutic levels are considered individually.

Adverse Effects That Occur When Lithium Levels Are Excessive. Certain toxicities are closely correlated with the concentration of lithium in blood. As indicated in Table 33-3, mild responses (eg, fine hand tremor, GI upset, thirst, muscle weakness) can develop at lithium levels that are still within the therapeutic range (ie, below 1.5 mEq/L). When plasma levels exceed 1.5 mEq/L, more serious toxicities appear. At drug levels above 2.5 mEq/L, death can occur. Patients should be informed about early signs of toxicity and instructed to interrupt lithium dosing if these appear. In adherent patients, the most common cause of lithium accumulation is sodium depletion. To keep lithium levels within the therapeutic range, plasma drug levels should be monitored routinely. Levels should be measured every 2 to 3 days at the beginning of treatment and every 3 to 6 months during maintenance therapy.

Treatment of acute overdose is primarily supportive; there is no specific antidote. The severely intoxicated patient should be hospitalized. Hemodialysis is an effective means of lithium removal and should be considered whenever drug levels exceed 2.5 mEq/L.

Adverse Effects That Occur at Therapeutic Levels of Lithium. **Early Adverse Effects.** Several responses occur early in treatment and then usually subside. *Gastrointestinal effects* (eg, nausea, diarrhea, abdominal bloating, anorexia) are common but transient. About 30% of patients experience *transient fatigue, muscle weakness, headache, confusion, and memory impairment.* *Polyuria* and *thirst* occur in 30% to 50% of patients and may persist.

Tremor. Patients may develop a fine hand tremor, especially in the fingers, that can interfere with writing and other motor skills. Lithium-induced tremor can be augmented by stress, fatigue, and certain drugs (antidepressants, antipsychotics, caffeine). Tremor can be reduced with a beta blocker (eg, propranolol) and by measures that reduce peak levels of lithium (ie, dosage reduction, use of divided doses, or use of a sustained-release formulation).

Polyuria. Polyuria occurs in 50% to 70% of patients taking lithium chronically. In some patients, daily urine output may exceed 3 L. Lithium promotes polyuria by antagonizing the effects of antidiuretic hormone. To maintain adequate hydration, patients should be instructed to drink 8 to 12 glasses of fluids daily. Polyuria, nocturia, and excessive thirst can discourage patients from adhering to the regimen.

Lithium-induced polyuria can be reduced with *amiloride* [Midamor], a potassium-sparing diuretic. Amiloride appears to help by reducing the entry of lithium into epithelial cells of the renal tubule. Polyuria can also be reduced with a thiazide diuretic. However, because thiazides can lower levels of sodium (see Chapter 41), and would thereby increase lithium retention, amiloride is preferred.

Renal Toxicity. Chronic lithium use has been associated with degenerative changes in the kidney. The risk of renal injury can be reduced by keeping the dosage low and, when possible, avoiding long-term lithium therapy. Kidney function should be assessed prior to treatment and once a year thereafter.

Goiter and Hypothyroidism. Lithium can reduce incorporation of iodine into thyroid hormone, and can inhibit thyroid hormone secretion. With long-term use, the drug can cause *goiter* (enlargement of the thyroid gland). Although usually benign, lithium-induced goiter is sometimes associated with *hypothyroidism*. Treatment with thyroid hormone (levothyroxine) or withdrawal of lithium will reverse both goiter and hypothyroidism. Levels of thyroid hormones—triiodothyronine (T_3) and thyroxine (T_4)—and levels of thyroid-stimulating hormone (TSH) should be measured prior to giving lithium and annually thereafter.

Teratogenesis. Lithium may—or may not—be a teratogen. In older studies, lithium appeared to have significant teratogenic effects: drug use during the first trimester of preg-

nancy was associated with an 11% incidence of birth defects (usually malformations of the heart). However, in more recent studies, lithium showed little or no teratogenic potential. Nonetheless, lithium is still classified in Food and Drug Administration (FDA) Pregnancy Risk Category D. To minimize any potential fetal risk, *lithium should be avoided during the first trimester of pregnancy* and, unless the benefits of therapy clearly outweigh the risks, it should be avoided during the remainder of pregnancy as well. Women of child-bearing age should be counseled to avoid pregnancy while taking lithium. Also, pregnancy should be ruled out before initiating lithium therapy.

Use in Lactation. Lithium readily enters breast milk and can achieve concentrations that might harm the nursing infant. Consequently, breast-feeding during lithium therapy should be discouraged.

Other Side Effects. Lithium can cause mild, reversible *leukocytosis* (10,000 to 18,000 white blood cells/mm³); complete blood counts with a differential should be obtained prior to treatment and annually thereafter. Possible *dermatologic reactions* include psoriasis, acne, folliculitis, and alopecia.

Drug Interactions

Diuretics. Diuretics promote sodium loss, and can thereby increase the risk of lithium toxicity. Toxicity can occur because, in the presence of low sodium, renal excretion of lithium is reduced, causing lithium levels to rise.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs). NSAIDs can increase lithium levels by as much as 60%. How? NSAIDs suppress prostaglandin synthesis in the kidney, and can thereby disrupt (increase) renal reabsorption of lithium (and also sodium), causing lithium levels to rise. NSAIDs known to increase lithium levels include ibuprofen [Motrin, others], naproxen [Naprosyn], piroxicam [Feldene], indomethacin [Indocin], and celecoxib [Celebrex]. Interestingly, aspirin (the prototype NSAID) and sulindac [Clinoril] do *not* increase lithium levels. Accordingly, if a mild analgesic is needed, aspirin or sulindac would be a good choice.

Anticholinergic Drugs. Anticholinergics can cause urinary hesitancy. Coupled with lithium-induced polyuria, this can result in considerable discomfort. Accordingly, patients should avoid drugs with prominent anticholinergic actions (eg, antihistamines, phenothiazine antipsychotics, tricyclic antidepressants).

Preparations, Dosage, and Administration

Preparations and Administration. *Lithium carbonate* is supplied in capsules, standard tablets, and slow-release tablets (Table 33-4). *Lithium citrate* syrup is no longer available. Gastric upset can be reduced by administering lithium with meals or milk.

TABLE 33-4 • Lithium Carbonate Preparations

Formulation	Lithium Content*	Trade Name
Capsules	4.06 mEq lithium (150 mg Li ₂ CO ₃)	generic only
	8.12 mEq lithium (300 mg Li ₂ CO ₃)	Lithonate, Carbolith♦
	16.24 mEq lithium (600 mg Li ₂ CO ₃)	generic only
Tablets: immediate-release	8.12 mEq lithium (300 mg Li ₂ CO ₃)	Lithotabs
Tablets: slow-release	8.12 mEq lithium (300 mg Li ₂ CO ₃)	Lithobid

*Lithium content is expressed in two ways: milliequivalents (mEq) of lithium ion, and milligrams (mg) of lithium carbonate.

Dosing. Lithium dosing is highly individualized. Dosage adjustments are based on plasma drug levels and clinical response.

Plasma levels should be kept within the therapeutic range. Levels between 0.8 and 1.4 mEq/L are generally appropriate for *acute therapy* of manic episodes. For *maintenance therapy*, lithium levels should range from 0.4 to 1 mEq/L. (Levels of 0.6 to 0.8 mEq/L are effective for most patients.) To avoid serious toxicity, *lithium levels should not exceed 1.5 mEq/L.*

Knowledge of plasma drug levels is not the only guide to lithium dosing; the clinical response is at least as important. Accordingly, when evaluating lithium dosage, we must not forget to look at the patient. Laboratory tests are all well and good, but they are not a substitute for clinical assessment. For example, if blood levels of lithium appear proper but clinical evaluation indicates toxicity, there is no question as to what should be done: Reduce the dosage—despite the apparent acceptability of the dosage as reflected by plasma lithium levels.

Because of its short half-life and low therapeutic index, *lithium cannot be administered in a single daily dose:* With once-a-day dosing, peak levels would be excessive. Hence, a typical dosage is 300 mg taken 3 or 4 times a day. A dosage of 600 mg twice a day is acceptable, provided a slow-release formulation is employed. However, even these preparations cannot be given once daily.

Antiepileptic Drugs

Three antiepileptic drugs—divalproex sodium, carbamazepine, and lamotrigine—can suppress mania and/or depression and stabilize mood in patients with BPD. The efficacy of these agents is firmly established. In fact, one drug—divalproex sodium—is so effective that it has replaced lithium as the drug of choice for many patients. The basic pharmacology of the antiepileptic drugs and their use in seizure disorders is discussed in Chapter 24. Discussion here focuses on their use in BPD.

Divalproex Sodium (Valproate)

Divalproex sodium* [Depakote, Epival \clubsuit], or simply valproate, was the first antiseizure agent approved for BPD. Valproate can control symptoms in acute manic episodes and can help prevent relapse into mania. However, the drug is less effective at treatment and prevention of depressive episodes. As with lithium, benefits appear to result at least in part from neurotrophic and neuroprotective effects. In patients with BPD, valproate compares favorably with lithium: both drugs are highly effective, and valproate works faster and has a higher therapeutic index and a more desirable side effect profile. However, lithium is superior in two important respects. First, lithium is better at reducing the risk of suicide. And second, lithium is more effective at preventing relapses. Nonetheless, because of its rapid onset, safety, and overall efficacy, valproate has become a first-line treatment for BPD. The starting dosage for acute mania in adults is 250 mg 3 times a day or 500 mg once daily at bedtime. Typical main-

TABLE 33-5 ■ Adult Oral Dosages for Atypical Antipsychotics Used in Bipolar Disorder

Drug	Dosage
Aripiprazole [Abilify]	<i>Acute Mania:</i> Start with 30 mg once daily and do not exceed this dose. Decrease to 15 mg once daily if needed.
Olanzapine [Zyprexa]	<i>Acute Mania:</i> Start with 10–15 mg once daily. Increase or decrease, in 5-mg/day increments, as indicated. The effective range is 5–20 mg once daily. <i>Maintenance Therapy:</i> The effective range is 5–20 mg once daily.
Olanzapine/ Fluoxetine [Symbax]	<i>Depressive Episodes:</i> Start with 6 mg olanzapine/25 mg fluoxetine once daily in the evening. The effective range for antidepressant effects is olanzapine 6–12 mg and fluoxetine 25–50 mg.
Quetiapine [Seroquel]	<i>Acute Mania (with normal liver function):</i> Give 100 mg (in two divided doses) on day 1, 200 mg on day 2, 300 mg on day 3, and 400 mg on day 4. If needed, increase to 600 mg on day 5 and 800 mg on day 6. <i>Acute Mania (with liver impairment):</i> Give 25 mg on day 1, then increase by 25–50 mg/day until symptoms are controlled or side effects are intolerable, whichever comes first. <i>Depressive Episodes:</i> Give once-daily doses at bedtime as follows: 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, and 300 mg on day 4; if needed, increase to 400 mg on day 5, and 600 mg on day 8.
Risperidone, short-acting [Risperdal]	<i>Acute Mania:</i> Start with 2–3 mg once daily; increase to a maximum of 6 mg once daily; if needed.
Risperidone, long-acting [Risperdal Consta]	<i>Maintenance Therapy:</i> Start with 25 mg IM every 2 weeks. After at least 4 weeks, dosage may be increased to 37.5 mg IM every 2 weeks, and after at least 4 more weeks, increased again to 50 mg IM every 2 weeks.
Ziprasidone [Geodon]	<i>Acute Mania:</i> On day 1, give 80 mg (in two divided doses with food). On day 2, increase to 60 or 80 mg twice daily. Based on tolerability and efficacy, adjust dosage within the range of 40–80 mg twice daily. <i>Maintenance Therapy:</i> The effective range is 15–30 mg daily.

tenance dosages range from 1000 to 2500 mg/day. The target trough plasma level is 50 to 120 mcg/mL.

Although valproate has a higher therapeutic index than lithium and is generally better tolerated, it *can* cause serious toxicity. Of greatest concern are rare cases of thrombocytopenia, pancreatitis, and liver failure—all of which require immediate drug withdrawal. In addition, valproate is a teratogen, and hence should not be used during pregnancy. Gastrointestinal disturbances (nausea, vomiting, diarrhea, dyspepsia, indigestion) are common. Despite causing GI distress, valproate frequently causes weight gain, a serious and chronic complication of treatment.

*As discussed in Chapter 24, divalproex sodium [Depakote] is a mixture of valproic acid [Depakene, Depacon, Stavzor] and its sodium salt [Depakene]. Only divalproex sodium is approved for BPD, although all three preparations have identical actions.

Carbamazepine

Carbamazepine [Tegretol, Equetro, others] is approved for treatment and prevention of manic episodes in patients with BPD. Like valproate, carbamazepine appears less effective at treatment and prevention of depression. For treatment of acute manic episodes, the dosage should be low initially (100 or 200 mg twice daily) and then gradually increased. The maximum dosage is 1600 mg/day. The target trough plasma level is 4 to 12 mcg/mL. Neurologic side effects (visual disturbances, ataxia, vertigo, unsteadiness, headache) are common early in treatment, but generally resolve despite continued drug use. Hematologic effects (leukopenia, anemia, thrombocytopenia, aplastic anemia) are relatively uncommon, but can be severe. Accordingly, complete blood counts, including platelets, should be obtained at baseline and periodically thereafter. Carbamazepine induces cytochrome P450 enzymes, and can thereby accelerate its own metabolism and the metabolism of other drugs (eg, oral contraceptives, warfarin, valproate, tricyclic antidepressants). To maintain efficacy, dosages of carbamazepine and these other drugs should be increased as needed.

Drug products containing carbamazepine are available under four trade names: *Carbatrol*, *Equetro*, *Epitol*, and *Tegretol*. Carbamazepine formulations with any of these names can be used for BPD. However, only one product—Equetro—is actually approved for BPD. Equetro is an extended-release formulation, manufactured by Shire Pharmaceuticals, that is identical to Carbatrol, a product approved for seizure control, also manufactured by Shire. Why use two trade names for the same formulation made by the same company? To facilitate marketing, of course. This name game is another good example of why your author wants trade names to be outlawed (see discussion of drug names in Chapter 3).

Lamotrigine

Lamotrigine [Lamictal] is indicated for long-term maintenance therapy of BPD. The goal is to prevent affective relapses into mania or depression. Lamotrigine may be used alone or in combination with other mood-stabilizing

agents. Side effects include headache, dizziness, double vision, and, rarely, life-threatening rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis). To minimize the risk of serious rash, dosage should be low initially (25 to 50 mg/day) and then gradually increased. The target maintenance dosage is 200 mg/day (if used alone), 100 mg/day (if combined with valproate), or 400 mg/day (if combined with carbamazepine or some other inducer of P450).

ANTIPSYCHOTIC DRUGS

In patients with BPD, antipsychotic drugs are used *acutely* to control symptoms during manic episodes, and *long term* to help stabilize mood. These drugs benefit patients with or without psychotic symptoms. Although antipsychotics can be used alone, they are usually employed in combination with a mood stabilizer, typically lithium or valproate.

Which antipsychotics are preferred? As discussed in Chapter 31, the antipsychotic drugs fall into two major groups: first-generation antipsychotics (conventional antipsychotics) and second-generation antipsychotics (atypical antipsychotics). Compared with the conventional agents, the atypical agents carry a lower risk of extrapyramidal side effects, including tardive dyskinesia. Accordingly, the atypical agents are preferred for BPD.

Five atypical antipsychotics—*olanzapine* [Zyprexa], *quetiapine* [Seroquel], *risperidone* [Risperdal], *aripiprazole* [Abilify], and *ziprasidone* [Geodon]—are approved for BPD. (Another one—*clozapine* [Clozaril]—although highly effective in BPD, is not used owing to a risk of agranulocytosis.) All of these drugs are effective against acute mania, when used alone or combined with lithium or valproate. Currently, only three atypical agents—aripiprazole, olanzapine, and ziprasidone—are approved for long-term use to prevent recurrence of mood episodes. Dosages for patients with BPD are summarized in Table 33-5.

The pharmacology of the antipsychotics is presented in Chapter 31.

KEY POINTS

- Bipolar disorder is treated with three kinds of drugs: mood stabilizers, antipsychotic drugs, and antidepressants.
- Mood stabilizers are drugs that (1) relieve symptoms during manic and depressive episodes; (2) prevent recurrence of manic and depressive episodes; and (3) do not worsen symptoms of mania or depression, and do not accelerate the rate of cycling.
- Antipsychotic drugs are used acutely to treat manic episodes, and long term to help stabilize mood. Benefits occur in patients with and without psychotic symptoms.
- In patients with bipolar depression, using an antidepressant alone may induce mania—although the risk appears lower than previously believed. Nonetheless, to minimize any risk of mania, antidepressants should not be used alone; rather, they should be combined with a mood-stabilizing drug.
- Lithium and valproate are the preferred mood stabilizers for BPD.
- To minimize the risk of toxicity, lithium levels must be monitored. The trough level, measured 12 hours after the evening dose, should be less than 1.5 mEq/L.
- Common side effects that occur at therapeutic lithium levels include tremor, goiter, and polyuria.
- Lithium may be teratogenic, and hence should be avoided during the first trimester of pregnancy. Also, unless the benefits outweigh the risks, lithium should be avoided during the second and third trimesters too.
- A reduction in sodium levels will reduce lithium excretion, causing lithium to accumulate—possibly to toxic levels. Patients must maintain normal sodium intake and levels.
- Lithium levels can be increased by diuretics (especially thiazides) and by several nonsteroidal anti-inflammatory drugs.

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LITHIUM

Preadministration Assessment

Therapeutic Goal

Control of acute manic episodes in patients with BPD, and prophylaxis against recurrent mania and depression in patients with BPD.

Baseline Data

Make baseline determinations of cardiac status (electrocardiogram, blood pressure, pulse), hematologic status (complete blood counts with differential), serum electrolytes, renal function (serum creatinine, creatinine clearance, urinalysis), and thyroid function (T_3 , T_4 , and TSH).

Identifying High-Risk Patients

Lithium should be *avoided* during the first trimester of pregnancy, and used with *caution* during the remainder of pregnancy, and in the presence of renal disease, cardiovascular disease, dehydration, sodium depletion, and concurrent therapy with diuretics.

Implementation: Administration

Route

Oral.

Administration

Advise patients to administer lithium with meals or milk to decrease gastric upset. Instruct patients to swallow slow-release tablets intact, without crushing or chewing.

Promoting Adherence

Rigid adherence to the prescribed regimen is important. Deviations in dosage size and timing can cause toxicity. Inadequate dosing may cause relapse.

To promote adherence, educate patients and families about the nature of BPD and the importance of taking lithium as prescribed. Encourage family members to oversee lithium use, and advise them to urge the patient to visit the prescriber or a psychiatric clinic if a pattern of nonadherence develops.

When medicating inpatients, observe the patient to make certain each lithium dose is ingested.

Ongoing Evaluation and Interventions

Monitoring Summary

Lithium Levels. Monitor lithium levels to ensure that they remain within the therapeutic range (0.8 to 1.4 mEq/L for initial therapy and 0.4 to 1 mEq/L for maintenance). Levels should be measured every 2 to 3 days during initial therapy, and every 3 to 6 months during maintenance. Blood for lithium determination should be drawn in the morning, 12 hours after the evening dose.

Other Parameters to Monitor. Evaluate the patient at least once a year for hematologic status (complete blood

count with differential), serum electrolytes, renal function (serum creatinine, creatinine clearance, urinalysis), and thyroid function (T_3 , T_4 , and TSH).

Evaluating Therapeutic Effects

Evaluate the patient for abatement of manic symptoms (eg, flight of ideas, pressured speech, hyperactivity) and for mood stabilization.

Minimizing Adverse Effects

Effects Caused by Excessive Drug Levels. Excessive lithium levels can result in serious adverse effects (see Table 33-3). Lithium levels must be monitored (see *Monitoring Summary* above) and dosage adjusted accordingly.

Teach patients the signs of toxicity, and instruct them to withhold medication and notify the prescriber if they develop.

Renal impairment can cause lithium accumulation. Kidney function should be assessed prior to treatment and once yearly thereafter.

Sodium deficiency can cause lithium to accumulate. Instruct patients to maintain normal sodium intake. Inform patients that diarrhea can cause significant sodium loss. Diuretics promote sodium excretion and must be used with caution.

In the event of severe toxicity, hospitalization may be required. If lithium levels exceed 2.5 mEq/L, hemodialysis should be considered.

Tremor. Lithium can cause fine hand tremor that can interfere with motor skills. Tremor can be reduced with a beta blocker (eg, propranolol) and by measures that reduce peak lithium levels (dosage reduction; use of divided doses or a sustained-release formulation).

Hypothyroidism and Goiter. Lithium can promote goiter (thyroid enlargement) and frank hypothyroidism. Plasma levels of T_3 , T_4 , and TSH should be measured prior to treatment and yearly thereafter. Treat hypothyroidism with levothyroxine.

Renal Toxicity. Lithium can cause renal damage. Kidney function should be assessed prior to treatment and yearly thereafter. If renal impairment develops, lithium dosage must be reduced.

Polyuria. Lithium increases urine output. Polyuria can be suppressed with amiloride (a potassium-sparing diuretic). Instruct patients to drink 8 to 12 glasses of fluid daily to maintain hydration.

Use in Pregnancy and Lactation. Lithium may cause birth defects. The drug should be avoided during pregnancy, especially in the first trimester. Counsel women of child-bearing age about the importance of avoiding pregnancy. Rule out pregnancy before initiating therapy.

Lithium enters breast milk. Advise patients to avoid breast-feeding.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications—cont'd

Minimizing Adverse Interactions

Diuretics. By promoting sodium loss, diuretics can reduce lithium excretion, thereby causing lithium levels to rise. Monitor closely for signs of toxicity.

Anticholinergic Drugs. By causing urinary hesitancy, drugs with anticholinergic actions (eg, antihistamines, phenothiazine antipsychotics, tricyclic antidepressants)

can intensify discomfort associated with lithium-induced diuresis.

Nonsteroidal Anti-inflammatory Drugs. Several NSAIDs (eg, ibuprofen, naproxen, celecoxib), but *not* aspirin or sulindac, can increase renal reabsorption of lithium, thereby causing lithium levels to rise. If a mild analgesic is needed, aspirin or sulindac would be a good choice.

Benzodiazepines

Benzodiazepine-like Drugs

Zolpidem

Zaleplon

Eszopiclone

Ramelteon: A Melatonin Agonist

Barbiturates

Miscellaneous Sedative-Hypnotics

Management of Insomnia

Sleep Phases

Basic Principles of Management

Major Hypnotics Used for Treatment

Other Hypnotics

 Box 34-1. Melatonin, Keeper of the Circadian Clock

The sedative-hypnotics are drugs that depress central nervous system (CNS) function. With some of these drugs, CNS depression is more generalized than with others. The sedative-hypnotics are used primarily for two common disorders: anxiety and insomnia. Agents given to relieve anxiety are known as *antianxiety agents* or *anxiolytics*; an older term is *tranquilizers*. Agents given to promote sleep are known as *hypnotics*. The distinction between antianxiety effects and hypnotic effects is often a matter of dosage: typically, sedative-hypnotics relieve anxiety in low doses and induce sleep in higher doses. Hence, a single drug may be considered both an antianxiety agent and a hypnotic agent, depending upon the reason for its use and the dosage employed.

There are three major groups of sedative-hypnotics: barbiturates (eg, secobarbital), benzodiazepines (eg, diazepam), and benzodiazepine-like drugs (eg, zolpidem). The barbiturates were introduced in the early 1900s, the benzodiazepines in the 1950s, and the benzodiazepine-like drugs in the 1990s. Although barbiturates were widely used as sedative-hypnotics in the past, they are rarely used for this purpose today, having been replaced by the newer drugs.

Before the benzodiazepines became available, anxiety and insomnia were treated with barbiturates and other *general CNS depressants*—drugs with multiple undesirable qualities. First, these drugs are powerful respiratory depressants that can readily prove fatal in overdose. As a result, they are “drugs of choice” for suicide. Second, because they produce subjective effects that many individuals find desirable, most general CNS depressants have a high potential for abuse. Third, with prolonged use, most of these drugs produce significant tolerance and physical dependence. And fourth, bar-

biturates and some other CNS depressants induce synthesis of hepatic drug-metabolizing enzymes, and can thereby decrease responses to other drugs. Because the benzodiazepines are just as effective as the general CNS depressants, but do not share their undesirable properties, the benzodiazepines are clearly preferred to the general CNS depressants for treating anxiety and insomnia.

We begin the chapter by discussing the basic pharmacology of the sedative-hypnotics, and end by discussing their use in insomnia. Use of these drugs for anxiety disorders is addressed in Chapter 35.

BENZODIAZEPINES

Benzodiazepines are drugs of first choice for anxiety and insomnia. In addition, these drugs are used to induce general anesthesia and to manage seizure disorders, muscle spasm, and withdrawal from alcohol.

Benzodiazepines were introduced in the late 1950s and remain important today. Perhaps the most familiar member of the family is diazepam [Valium]. The most frequently prescribed members are lorazepam [Ativan] and alprazolam [Xanax, Xanax XR, Niravam].

The popularity of the benzodiazepines as sedatives and hypnotics stems from their clear superiority over the alternatives: barbiturates and other general CNS depressants. The benzodiazepines are safer than the general CNS depressants and have a lower potential for abuse. In addition, benzodiazepines produce less tolerance and physical dependence and are subject to fewer drug interactions. Contrasts between the benzodiazepines and barbiturates are summarized in Table 34-1.

Since all of the benzodiazepines produce nearly identical effects, we will consider the family as a group, rather than selecting a representative member as a prototype.

Overview of Pharmacologic Effects

Practically all responses to benzodiazepines result from actions in the CNS. Benzodiazepines have few direct actions outside the CNS. All of the benzodiazepines produce a similar spectrum of responses. However, because of pharmacokinetic differences, individual benzodiazepines may differ in clinical applications.

Central Nervous System. All beneficial effects of benzodiazepines and most adverse effects result from depressant actions in the CNS. With increasing dosage, effects progress from sedation to hypnosis to stupor.

Benzodiazepines depress neuronal function at multiple sites in the CNS. They *reduce anxiety* through effects on the limbic system, a neuronal network associated with emotionality. They *promote sleep* through effects on cortical areas and

TABLE 34-1 ■ Contrasts Between Benzodiazepines and Barbiturates

Area of Comparison	Benzodiazepines	Barbiturates
Relative safety	High	Low
Maximal ability to depress CNS function	Low	High
Respiratory depressant ability	Low	High
Suicide potential	Low	High
Ability to cause physical dependence	Low*	High
Ability to cause tolerance	Low	High
Abuse potential	Low	High
Ability to induce hepatic drug metabolism	Low	High

*Although dependence is low in most patients, significant dependence *can* develop with long-term, high-dose use.

on the sleep-wakefulness "clock." They induce muscle relaxation through effects on supraspinal motor areas, including the cerebellum. Two important side effects—*confusion* and *anterograde amnesia*—result from effects on the hippocampus and cerebral cortex.

Cardiovascular System. When taken orally, benzodiazepines have almost no effect on the heart and blood vessels. In contrast, when administered intravenously, even in therapeutic doses, benzodiazepines can produce profound hypotension and cardiac arrest.

Respiratory System. In contrast to the barbiturates, the benzodiazepines are weak respiratory depressants. When taken alone in therapeutic doses, benzodiazepines produce little or no depression of respiration—and with toxic doses, respiratory depression is moderate at most. With oral therapy, clinically significant respiratory depression occurs only when benzodiazepines are combined with other CNS depressants (eg, opioids, barbiturates, alcohol).

Although benzodiazepines generally have minimal effects on respiration, they can be a problem for patients with respiratory disorders. In patients with chronic obstructive pulmonary disease, benzodiazepines may worsen hypoventilation and hypoxemia. In patients with obstructive sleep apnea (OSA), benzodiazepines may exacerbate apneic episodes. In patients who snore, benzodiazepines may convert partial airway obstruction into OSA.

Molecular Mechanism of Action

Benzodiazepines potentiate the actions of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter found throughout the CNS. These drugs enhance the actions of GABA by binding to specific receptors in a supramolecular structure known as the GABA receptor–chloride channel complex (Fig. 34-1). Please note that benzodiazepines do not act as direct GABA agonists—they simply intensify the effects of GABA.

Because benzodiazepines act by amplifying the actions of endogenous GABA, rather than by directly mimicking GABA, there is a limit to how much CNS depression benzodiazepines can produce. This explains why benzodiazepines are so much safer than the barbiturates—drugs that can directly mimic GABA. Since benzodiazepines simply potentiate the inhibitory effects of endogenous GABA, and since the amount of GABA in the CNS is finite, there is a built-in limit to the depth of CNS depression the benzodiazepines can produce. In

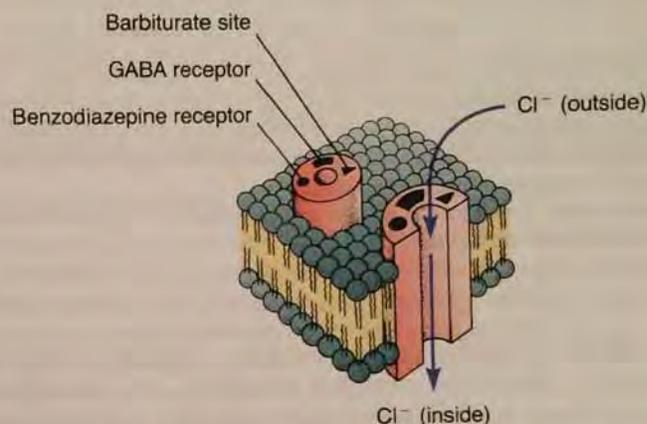


Figure 34-1 ■ Schematic model of the GABA receptor–chloride channel complex showing binding sites for benzodiazepines and barbiturates.

The GABA receptor–chloride channel complex, which spans the neuronal cell membrane, can exist in an open or closed configuration. Binding of GABA to its receptor on the complex causes the chloride channel to open. The resulting inward flow of chloride ions hyperpolarizes the neuron (makes the cell highly negative inside) and thereby decreases its ability to fire. Hence GABA is an *inhibitory* neurotransmitter. Binding of a benzodiazepine to its receptor on the complex increases the frequency of channel opening, thereby increasing chloride influx. Hence, benzodiazepines enhance the inhibitory effects of GABA. In the absence of GABA, benzodiazepines have no effect on channel opening. The benzodiazepine-like drugs (zolpidem, zaleplon, and eszopiclone) have actions much like those of the benzodiazepines. Effects of barbiturates on the chloride channel are dose dependent: at low doses, barbiturates enhance the actions of GABA (by prolonging the duration of channel opening); at high doses, barbiturates directly mimic the actions of GABA.

contrast, since the barbiturates are direct-acting CNS depressants, maximal effects are limited only by the amount of barbiturate administered.

Pharmacokinetics

Absorption and Distribution. Most benzodiazepines are well absorbed following oral administration. Because of their high lipid solubility, benzodiazepines readily cross the blood-brain barrier to reach sites in the CNS.

TABLE 34-2 ■ Applications of the Benzodiazepines

Generic Name [Trade Name]	Approved Applications						
	GAD*	Insomnia	Seizures	Muscle Spasm, Spasticity	Alcohol Withdrawal	Anesthesia Induction or Preanesthesia	Panic Disorder
Alprazolam [Xanax, Xanax XR, Niravam]	✓						✓
Chlordiazepoxide [Librium]	✓				✓		
Clonazepam [Klonopin, Rivotril♦]			✓				✓
Clorazepate [Tranxene]	✓		✓		✓		
Diazepam [Valium, Diastat AcuDial]	✓		✓	✓	✓	✓	
Estazolam (generic only)		✓					
Flurazepam (generic only)		✓					
Lorazepam [Ativan]	✓		✓		✓	✓	✓
Midazolam [Versed]						✓	
Oxazepam (generic only)	✓				✓		
Quazepam [Doral]		✓					
Temazepam [Restoril]		✓					
Triazolam [Halcion]		✓					

*GAD = generalized anxiety disorder.

†Midazolam, in conjunction with an opioid analgesic, is also used to produce *conscious sedation*, a semiconscious state suitable for minor surgeries and endoscopic procedures.

Metabolism. Most benzodiazepines undergo extensive metabolic alterations. With few exceptions, the *metabolites are pharmacologically active*. As a result, responses produced by administering a particular benzodiazepine often persist long after the parent drug has disappeared. Hence, there may be a poor correlation between the plasma half-life of the parent drug and duration of pharmacologic effects. Flurazepam, for example, whose plasma half-life is only 2 to 3 hours, is converted into an active metabolite with a half-life of 50 hours. Hence, giving flurazepam produces long-lasting effects, even though flurazepam itself is gone from the plasma in 8 to 12 hours (about four half-lives).

In patients with liver disease, metabolism of benzodiazepines can decline, thereby prolonging and intensifying responses. Because certain benzodiazepines (oxazepam, temazepam, and lorazepam) undergo very little metabolic alteration, they may be preferred for patients with hepatic impairment.

Time Course of Action. Benzodiazepines differ significantly from one another with respect to time course. Specifically, they differ in onset and duration of action, and tendency to accumulate with repeated dosing.

Because all benzodiazepines have essentially equivalent pharmacologic actions, selection among them is based largely on differences in time course. For example, if a patient needs medication to accelerate falling asleep, a benzodiazepine with a rapid onset (eg, triazolam) would be indicated. However, if medication is needed to prevent waking later in the night, a benzodiazepine with a slower onset (eg, estazolam) would be preferred. For treatment of anxiety, a drug with an intermediate duration is desirable. For treatment of any benzodiazepine-responsive condition in the elderly, a drug such as lorazepam, which is not likely to accumulate with repeated dosing, is generally preferred.

Therapeutic Uses

The benzodiazepines have three principal indications: (1) anxiety, (2) insomnia, and (3) seizure disorders. In addition, they are used as preoperative medications and to treat muscle spasm and withdrawal from alcohol. Although all benzodiazepines share the same pharmacologic properties, and therefore might be equally effective for all applications, not every benzodiazepine is actually employed for all potential uses. The principal factors that determine the actual applications of a particular benzodiazepine are (1) the pharmacokinetic properties of the drug itself and (2) research and marketing decisions of pharmaceutical companies. Specific applications of individual benzodiazepines are summarized in Table 34-2.

Anxiety. Benzodiazepines are drugs of first choice for anxiety. Although all benzodiazepines have anxiolytic actions, only six are marketed for this indication (see Table 34-2). Anxiolytic effects result from depressing neurotransmission in the limbic system and cortical areas. Use of benzodiazepines to treat anxiety disorders is discussed in Chapter 35.

Insomnia. Benzodiazepines are preferred drugs for insomnia. These drugs decrease latency time to falling asleep, reduce awakenings, and increase total sleeping time. The role of benzodiazepines in managing insomnia is discussed in depth later.

Seizure Disorders. Four benzodiazepines—diazepam, clonazepam, lorazepam, and clorazepate—are employed for seizure disorders. Antiseizure applications are discussed in Chapter 24.

Muscle Spasm. One benzodiazepine—diazepam—is used to relieve muscle spasm and spasticity (see Chapter 25). Effects on muscle tone are secondary to actions in the CNS. Diazepam cannot relieve spasm without causing sedation.

Alcohol Withdrawal. Diazepam and other benzodiazepines may be administered to ease withdrawal from alcohol (see Chapter 38). Benefits de-

rive from cross-dependence with alcohol, which enables benzodiazepines to suppress symptoms brought on by alcohol abstinence.

Perioperative Applications. Three benzodiazepines—diazepam [Valium], lorazepam [Ativan], and midazolam [Versed]—are given IV for induction of anesthesia. In addition, midazolam (in combination with an opioid analgesic) can be used to produce conscious sedation, a semiconscious state suitable for endoscopic procedures and minor surgeries. Benzodiazepines are also used for preoperative sedation. All of these applications are discussed in Chapter 27.

Adverse Effects

Benzodiazepines are generally well tolerated, and serious adverse reactions are rare. In contrast to barbiturates and other general CNS depressants, benzodiazepines are remarkably safe.

CNS Depression. When taken to promote sleep, benzodiazepines cause drowsiness, lightheadedness, incoordination, and difficulty concentrating. When these effects occur at bedtime, they are generally inconsequential. However, if sedation and other manifestations of CNS depression persist beyond waking, interference with daytime activities can result.

Anterograde Amnesia. Benzodiazepines can cause anterograde amnesia (impaired recall of events that take place after dosing). Anterograde amnesia has been especially troublesome with triazolam [Halcion]. If patients complain of forgetfulness, the possibility of drug-induced amnesia should be evaluated.

Sleep Driving and Other Complex Sleep-Related Behaviors. Patients taking benzodiazepines in sleep-inducing doses may carry out complex behaviors, and then have no memory of their actions. Reported behaviors include sleep driving, preparing and eating meals, making phone calls, and having sexual intercourse. Although these events can occur with normal doses, they are more likely when doses are excessive, and when benzodiazepines are combined with alcohol and other CNS depressants. Because of the potential for harm, benzodiazepines should be withdrawn if sleep driving is reported. To minimize withdrawal symptoms, dosing should be tapered slowly, rather than discontinued abruptly.

Paradoxical Effects. When employed to treat anxiety, benzodiazepines sometimes cause paradoxical responses, including insomnia, excitation, euphoria, heightened anxiety, and rage. If these occur, the benzodiazepine should be withdrawn.

Respiratory Depression. Benzodiazepines are weak respiratory depressants. Death from overdose with oral benzodiazepines alone has never been documented. Hence, in contrast to the barbiturates, benzodiazepines present little risk as vehicles for suicide. It must be emphasized, however, that although respiratory depression with oral therapy is rare, benzodiazepines can cause severe respiratory depression when administered intravenously. In addition, substantial respiratory depression can result from combining oral benzodiazepines with other CNS depressants (eg, alcohol, barbiturates, opioids).

Abuse. Benzodiazepines have a lower abuse potential than barbiturates and most other general CNS depressants. The behavior pattern that constitutes "addiction" is uncommon among people who take benzodiazepines for therapeutic purposes. When asked about their drug use, individuals who regularly abuse drugs rarely express a preference for benzodiazepines over barbiturates. Because their potential for abuse is low, the benzodiazepines are classified under Schedule IV of the Con-

trolled Substances Act. This contrasts with the barbiturates, most of which are classified under Schedule II or III.

Use in Pregnancy and Lactation. Benzodiazepines are highly lipid soluble and can readily cross the placental barrier. Use of benzodiazepines during the first trimester of pregnancy is associated with an increased risk of congenital malformations, such as cleft lip, inguinal hernia, and cardiac anomalies. Use near term can cause CNS depression in the neonate. Because they may represent a risk to the fetus, most benzodiazepines are classified in Food and Drug Administration (FDA) Pregnancy Risk Category D. Five of these drugs—estazolam, flurazepam, quazepam, temazepam, and triazolam—are in Category X. Women of child-bearing age should be warned about the potential for fetal harm and instructed to discontinue benzodiazepines if pregnancy occurs.

Benzodiazepines enter breast milk with ease and may accumulate to toxic levels in the breast-fed infant. Accordingly, these drugs should be avoided by nursing mothers.

Other Adverse Effects. Occasional reactions include weakness, headache, blurred vision, vertigo, nausea, vomiting, epigastric distress, and diarrhea. Neutropenia and jaundice occur rarely. Rarely, benzodiazepines may cause severe allergic reactions, including angioedema and anaphylaxis.

Drug Interactions

Benzodiazepines undergo very few important interactions with other drugs. Unlike barbiturates, benzodiazepines do not induce hepatic drug-metabolizing enzymes. Hence, benzodiazepines do not accelerate the metabolism of other drugs.

CNS Depressants. The CNS-depressant actions of benzodiazepines add with those of other CNS depressants (eg, alcohol, barbiturates, opioids). Hence, although benzodiazepines are very safe when used alone, they can be extremely hazardous in combination with other depressants. Combined overdose with a benzodiazepine plus another CNS depressant can cause profound respiratory depression, coma, and death. Patients should be warned against use of alcohol and all other CNS depressants.

Tolerance and Physical Dependence

Tolerance. With prolonged use of benzodiazepines, tolerance develops to some effects but not to others. No tolerance develops to anxiolytic effects, and tolerance to hypnotic effects is generally low. In contrast, significant tolerance develops to antiseizure effects. Patients tolerant to barbiturates, alcohol, and other general CNS depressants show some cross-tolerance to benzodiazepines.

Physical Dependence. Benzodiazepines can cause physical dependence—but the incidence of substantial dependence is low. When benzodiazepines are discontinued following short-term use at therapeutic doses, the resulting withdrawal syndrome is generally mild and often goes unrecognized. Symptoms include anxiety, insomnia, sweating, tremors, and dizziness. Withdrawal from long-term, high-dose therapy can elicit more serious reactions, such as panic, paranoia, delirium, hypertension, muscle twitches, and outright convulsions. Symptoms of withdrawal are usually more intense with benzodiazepines that have a short duration of action. With one agent—alprazolam [Xanax, Xanax XR, Niravam]—dependence may be a greater problem than with other benzodiazepines. Because the benzodiazepine withdrawal syndrome can resemble an anxiety disorder, it is important to differentiate withdrawal symptoms from the return of original anxiety symptoms.

The intensity of withdrawal symptoms can be minimized by discontinuing treatment gradually. Doses should be slowly tapered over several weeks or months. Substituting a benzodiazepine with a long half-life for one with a short half-life is also helpful. Patients should be warned against abrupt cessation of treatment. Following discontinuation of treatment, patients should be monitored for 3 weeks for indications of withdrawal or recurrence of original symptoms.

Acute Toxicity

Oral Overdose. When administered in excessive dosage by mouth, benzodiazepines rarely cause serious toxicity. Symptoms include drowsiness, lethargy, and confusion. Significant cardiovascular and respiratory effects are uncommon. If an individual known to have taken an overdose of benzodiazepines does exhibit signs of serious toxicity, it is probable that another drug was taken too.

Intravenous Toxicity. When injected IV, even in therapeutic doses, benzodiazepines can cause severe adverse effects. Life-threatening reactions (eg, profound hypotension, respiratory arrest, cardiac arrest) occur in about 2% of patients.

General Treatment Measures. Benzodiazepine-induced toxicity is managed the same as toxicity from barbiturates and other general CNS depressants. Oral benzodiazepines can be removed from the body with gastric lavage followed by ingesting activated charcoal and a saline cathartic; dialysis may be helpful if symptoms are especially severe. Respiration should be monitored and the airway kept patent. Support of blood pressure with IV fluids and norepinephrine may be required.

Treatment with Flumazenil. Flumazenil [Romazicon, Anexate] is a competitive benzodiazepine receptor antagonist. The drug can reverse the sedative effects of benzodiazepines but may not reverse respiratory depression. Flumazenil is approved for benzodiazepine overdose and for reversing the effects of benzodiazepines following general anesthesia. The principal adverse effect is precipitation of convulsions. This is most likely in patients taking benzodiazepines to treat epilepsy and in patients who are physically dependent on benzodiazepines. Flumazenil is administered IV. Doses are injected slowly (over 30 seconds) and may be repeated every minute as needed. The first dose is 0.2 mg, the second is 0.3 mg, and all subsequent doses are 0.5 mg. Effects of flumazenil fade in about 1 hour, hence repeated doses may be required.

Preparations, Dosage, and Administration

Preparations and Dosage. Preparations and dosages for insomnia are presented later in the chapter. Preparations and dosages of benzodiazepines used for other disorders are presented in Chapter 24 (Drugs for Epilepsy), Chapter 25 (Drugs for Muscle Spasm and Spasticity), Chapter 27 (General Anesthetics), and Chapter 35 (Management of Anxiety Disorders).

Routes. All benzodiazepines can be administered orally. In addition, three agents—diazepam, chlorthalidopoxide, and lorazepam—may be administered parenterally (IM and IV). When used for sedation or induction of sleep, benzodiazepines are almost always administered by mouth. Parenteral administration is reserved for emergencies, including acute alcohol withdrawal, severe anxiety, and status epilepticus.

Oral. Patients should be advised to take oral benzodiazepines with food if gastric upset occurs. Also, they should be instructed to swallow sustained-release formulations intact, without crushing or chewing. Patients should be warned not to increase the dosage or discontinue therapy without consulting the prescriber.

For treatment of insomnia, benzodiazepines should be given on an intermittent schedule (eg, 3 or 4 days a week) in the lowest effective dosage for

the shortest duration required. This will minimize physical dependence and associated drug-dependency insomnia.

Intravenous. Intravenous administration is hazardous and must be performed with care. Life-threatening reactions (severe hypotension, respiratory arrest, cardiac arrest) have occurred. In addition, IV administration carries a risk of venous thrombosis, phlebitis, and vascular impairment.

To reduce complications, the following precautions should be taken: (1) inject the drug slowly; (2) take care to avoid intra-arterial injection and extravasation; (3) if direct venous injection is impossible, make the injection into infusion tubing as close to the vein as possible; (4) follow the manufacturer's instructions regarding suitable diluents for preparing solutions; and (5) have facilities for resuscitation available.

Intramuscular. If IM administration is needed, lorazepam is the preferred benzodiazepine to use, owing to consistent absorption from IM sites. Absorption of IM diazepam is erratic and may be delayed. Accordingly, IM diazepam should be avoided.

BENZODIAZEPINE-LIKE DRUGS

Three benzodiazepine-like drugs are available: zolpidem, zaleplon, and eszopiclone. All three are preferred agents for insomnia. They are not indicated for anxiety. These drugs are structurally different from benzodiazepines, but nonetheless share the same mechanism of action: They all act as agonists at the benzodiazepine receptor site on the GABA receptor-chloride channel complex. Like the benzodiazepines, these drugs have a low potential for tolerance, dependence, and abuse, and are classified as Schedule IV substances.

Zolpidem

Zolpidem [Ambien, Ambien CR, Edluar, Tovalt ODT, Zolpimist], our most widely used hypnotic, is approved only for short-term management of insomnia. However, although approval is limited to short-term use, many patients have taken the drug long term with no apparent tolerance or increase in adverse effects. All zolpidem formulations have a rapid onset, and hence can help people who have difficulty falling asleep. In addition, the extended-release formulation—Ambien CR—can help people who have difficulty maintaining sleep.

Although structurally unrelated to the benzodiazepines, zolpidem binds to the benzodiazepine receptor site on the GABA receptor-chloride channel complex and shares some properties of the benzodiazepines. Like the benzodiazepines, zolpidem can reduce sleep latency and awakenings and can prolong sleep duration. The drug does not significantly reduce time in rapid-eye-movement (REM) sleep and causes little or no rebound insomnia when therapy is discontinued. In contrast to the benzodiazepines, zolpidem lacks anxiolytic, muscle relaxant, and anticonvulsant actions. Why? Because zolpidem doesn't bind with all benzodiazepine receptors. Rather, binding is limited to the benzodiazepine₁ subtype of benzodiazepine receptors.

Zolpidem is rapidly absorbed following oral dosing. Plasma levels peak in 2 hours. The drug is widely distributed, although levels in the brain remain low. Zolpidem is extensively metabolized to inactive compounds that are excreted in the bile, urine, and feces. The elimination half-life is 2.4 hours.

Zolpidem has a side effect profile like that of the benzodiazepines. Daytime drowsiness and dizziness are most common, and these occur in only 1% to 2% of patients. Like the benzodiazepines, zolpidem has been associated with sleep-driving and other sleep-related complex behaviors. At these

peptic doses, zolpidem causes little or no respiratory depression. Safety in pregnancy has not been established. According to the FDA, zolpidem may pose a small risk of anaphylaxis and angioedema.

Short-term treatment is not associated with significant tolerance or physical dependence. Withdrawal symptoms are minimal or absent. Similarly, the abuse liability of zolpidem is low. Accordingly, the drug is classified under Schedule IV of the Controlled Substances Act.

Like other sedative-hypnotics, zolpidem can intensify the effects of other CNS depressants. Accordingly, patients should be warned against combining zolpidem with alcohol and all other drugs that depress CNS function.

Zolpidem is available in five formulations: (1) immediate-release tablets (5 and 10 mg) sold as *Ambien*, (2) extended-release tablets (6.25 and 12.5 mg) sold as *Ambien CR*, (3) orally disintegrating tablets (5 and 10 mg) sold as *Tovolt ODT*, (4) an oral spray (5 and 10 mg) sold as *Zolpimist*, and (5) sublingual tablets (5 and 10 mg) sold as *Eduar*. With the immediate-release tablets, sublingual tablets, orally disintegrating tablets, and oral spray, the usual dose is 10 mg. The initial dose should be reduced to 5 mg for elderly and debilitated patients and for those with hepatic insufficiency. With the extended-release tablets, the usual dose is 12.5 mg (or 6.25 mg for elderly or debilitated patients). All formulations have a rapid onset, and hence should be taken just before bedtime. This timing will promote sleep while minimizing daytime sedation.

Zaleplon

Zaleplon [Sonata] is the first representative of a new class of hypnotics, the pyrazolopyrimidines. The drug is approved only for short-term management of insomnia, but prolonged use does not appear to cause tolerance. Like zolpidem, zaleplon binds to the benzodiazepine₁ receptor site on the GABA receptor-chloride channel complex, and thereby enhances the depressant actions of endogenous GABA. In contrast to zolpidem, zaleplon has a very rapid onset and short duration of action, and hence is good for helping patients fall asleep, but not for maintaining sleep.

Zaleplon is rapidly and completely absorbed after oral dosing. However, because of extensive first-pass metabolism, bioavailability is only 30%. A large or high-fat meal can delay absorption substantially. Plasma levels peak about 1 hour after administration and then rapidly decline, returning to baseline in 4 to 5 hours. Zaleplon is metabolized by hepatic aldehyde oxidase prior to excretion in the urine. Its half-life is just 1 hour.

Because of its kinetic profile, zaleplon is well suited for people who have trouble falling asleep, but not for people who can't maintain sleep. The drug can also help people who need a sedative in the middle of the night: Because of its short duration, zaleplon can be taken at 3:00 AM without causing hangover when the alarm goes off at 7:00 AM.

Zaleplon is well tolerated. The most common side effects are headache, nausea, drowsiness, dizziness, myalgia, and abdominal pain. Like the benzodiazepines, zaleplon has been associated with rare cases of sleep driving and other complex sleep-related behaviors. Respiratory depression has not been observed. Physical dependence is minimal, the only sign being mild rebound insomnia the first night after drug withdrawal. Next-day sedation and hangover have not been reported. Like the benzodiazepines, zaleplon has a low potential for abuse, and hence is classified as a Schedule IV drug.

Cimetidine (a drug for peptic ulcer disease) inhibits hepatic aldehyde oxidase, and can thereby greatly increase levels of zaleplon. Accordingly, dosage of zaleplon must be reduced if these drugs are used concurrently.

Zaleplon is available in 5- and 10-mg capsules. The usual dose is 10 mg. The dose should be reduced to 5 mg for (1) the elderly, (2) small individuals, (3) patients with liver impairment, and (4) patients taking cimetidine. The maximum dose is 20 mg. Dosing is usually done just before retiring. However, dosing may also be done after going to bed on nights when sleep fails to come.

Eszopiclone

Eszopiclone [Lunesta], approved in 2005, is the *S*-isomer of zopiclone, a drug used for years in Canada and Europe. Like zaleplon and zolpidem, eszopiclone binds selectively with the benzodiazepine₁ receptor on the GABA receptor-chloride channel complex, and thereby enhances the depressant actions of endogenous GABA.

Eszopiclone is approved for treating insomnia, with no limitation on how long it can be used. This contrasts with zaleplon and zolpidem, which are approved for short-term use only. Does this mean that eszopiclone is safer than the other two drugs, or less likely to promote tolerance? Not necessarily. It only means that the manufacturer of eszopiclone conducted a prolonged (6-month) study, whereas the manufacturers of the other two drugs did not. In that prolonged study, eszopiclone reduced sleep latency and nighttime awakening, increased total sleep time and sleep quality, had no significant effect on sleep architecture, and showed no indication of tolerance.

Eszopiclone is rapidly absorbed after oral dosing, reaching peak blood levels in 1 to 2 hours. The drug undergoes extensive hepatic metabolism, primarily by CYP3A4 (the 3A4 isozyme of cytochrome P450). The resulting inactive (or weakly active) metabolites are excreted in the urine. The elimination half-life is 6 hours.

Eszopiclone is generally well tolerated. The most common adverse effect is a bitter aftertaste, reported by 17% of patients dosed with 2 mg and 34% of those dosed with 3 mg. Other common effects are headache, somnolence, dizziness, and dry mouth. Rebound insomnia may occur on the first night after discontinuing the drug. Like the benzodiazepines and the other benzodiazepine-like drugs, eszopiclone has been associated with cases of sleep driving and other sleep-related complex behaviors. Rarely, eszopiclone may cause anaphylaxis or angioedema. Eszopiclone has a low potential for abuse and hence is classified as a Schedule IV drug.

Eszopiclone [Lunesta] is available in 1-, 2-, and 3-mg tablets. For nonelderly adults, the recommended starting dose is 2 mg, taken just before bedtime. The dose can be raised to 3 mg if needed. For patients with severe hepatic impairment, and for those taking inhibitors of CYP3A4 (eg, ketoconazole), the starting dose is 1 mg. For elderly patients, the starting dose is 1 mg (for those who can't fall asleep) or 2 mg (for those who can't stay asleep).

RAMELTEON: A MELATONIN AGONIST

Ramelteon [Rozerem] is a relatively new hypnotic with a unique mechanism of action: activation of receptors for melatonin. The drug is approved for treating chronic insomnia characterized by difficulty with sleep onset, but not with sleep

MELATONIN, KEEPER OF THE CIRCADIAN CLOCK

Melatonin is a hormone that helps regulate our circadian clock, the time-keeping mechanism that controls our sleep-wakefulness cycle. Principal uses for melatonin are insomnia and jet lag. Of note, melatonin is the only hormone that can be purchased without a prescription. The compound is available in health-food stores, vitamin shops, and even airport newsstands.

Melatonin is produced by the pineal gland, a structure located at the base of the brain. Secretion is suppressed by environmental light and stimulated by darkness. Normally, secretion is low during the day, begins to rise around 9:00 PM, reaches a peak between 2:00 AM and 4:00 AM, and returns to baseline by morning. Signals that control secretion travel along a multineuron pathway that connects the retina to the pineal gland. Nocturnal secretion peaks early in life, and then remains steady from adolescence through old age. In blind people, melatonin secretion has no predictable pattern. In insomniacs, melatonin levels are low.

When taken to promote sleep, melatonin has two beneficial actions. First, low doses can reset the circadian clock. Second, higher doses exert direct hypnotic effects. Melatonin receptors on the suprachiasmatic nucleus (the anatomic site of the circadian clock), probably mediate clock resetting by exogenous melatonin. Whether these receptors also mediate direct hypnotic effects is unknown.

What's the effect of melatonin on insomnia? Several trials indicate that it promotes sleep. For example, doses of 0.3 to 1 mg taken 1 to 2 hours before bedtime can hasten sleep onset and the time to REM sleep, without reducing total time in REM sleep. During a 6-month study, patients taking *Circadin**—a 2-mg sustained-release formulation—experienced consistent improvements in sleep latency, sleep quality, and morning alertness, with no withdrawal symptoms or rebound insomnia when dosing was stopped. In blind insomniacs, taking melatonin for

3 weeks normalized the melatonin production cycle and relieved insomnia.

Can melatonin ease symptoms of jet lag? Probably. Of all treatments for jet lag, melatonin is the most widely studied. To date, there have been 11 double-blind, placebo-controlled trials. In eight of these trials, melatonin produced significant benefit. Of the three negative studies, two were too small to permit firm conclusions, and one involved subjects whose baseline circadian rhythm may have been inappropriate for evaluation. How does melatonin help ease jet lag? It resets the circadian clock to the new time zone.

What side effects does melatonin have? When used short term in low doses (eg, under 2 mg), melatonin has no observable adverse effects. However, short-term use of large doses can cause hangover, headache, nightmares, hypothermia, and transient depression. In one case, reversible psychosis occurred with a huge daytime dose. Possible adverse effects of long-term use are unknown.

Two melatonin formulations are available: immediate release (IR) and sustained release (SR). The IR products are best for people with trouble falling asleep, and the SR products are best for people with trouble staying asleep. For both types of product, strengths typically range from 0.3 to 3 mg. Today, most commercial melatonin is synthesized in the laboratory. Melatonin from animal sources should be avoided, owing to a risk of contamination.

Although melatonin is a hormone, it is marketed as a dietary supplement—not as a drug. As a result, melatonin is not regulated by the FDA and has not been reviewed for safety and efficacy. Because melatonin is not regulated, commercial preparations may have impurities and may not contain the exact amount of melatonin advertised on the label.

*Not available in the United States.

maintenance. Long-term use is permitted. Of the major drugs for insomnia, ramelteon is the only one not regulated as a controlled substance.

Therapeutic Use. Ramelteon has a rapid onset (about 30 minutes) and short duration, and hence is good for inducing sleep but not maintaining sleep. There are no significant residual effects on the day after dosing. Nor is there any rebound insomnia when treatment is stopped after 35 consecutive nights of use. When approving the drug, the FDA put no limit on how long it may be used.

Mechanism of Action. Ramelteon activates receptors for melatonin—specifically the MT₁ and MT₂ subtypes, which are key mediators of the normal sleep-wakefulness cycle. Sleep promotion derives primarily from activating MT₁ receptors. (Under physiologic conditions, activation of MT₁ receptors by endogenous melatonin induces sleepiness.) Ramelteon does not activate MT₃ receptors, which help regulate numerous systems unrelated to sleep. Selectivity for MT₁ and MT₂ receptors explains why ramelteon is superior to melatonin it-

self for treating insomnia (Box 34-1). Ramelteon does not bind with the GABA receptor-chloride channel complex, or with receptors for neuropeptides, benzodiazepines, dopamine, serotonin, norepinephrine, acetylcholine, or opioids.

Pharmacokinetics. Absorption is rapid and nearly complete, although food can reduce both the rate and extent of absorption. Despite generally good absorption, the absolute bioavailability of ramelteon is very low—only 1.8%, owing to extensive first-pass metabolism, primarily by hepatic CYP1A2 (the 1A2 isozyme of cytochrome P450). Much of each dose is converted to an active metabolite, designated M-II, that contributes to therapeutic effects. The half-lives of the parent drug and active metabolite average 2 to 5 hours. In patients with hepatic impairment, elimination is delayed and drug levels can rise. Renal impairment does not affect drug levels.

Adverse Effects. Ramelteon is very well tolerated. In clinical trials, the incidence of adverse effects was nearly identical to that of placebo. The most common side effects are somnolence (5% vs. 3% with placebo), dizziness (5% vs.

3%), and fatigue (4% vs. 2%). According to the FDA, ramelteon may share the ability of benzodiazepines to cause sleep driving and other sleep-related complex behaviors. Very rarely, patients have reported hallucinations, agitation, and mania.

Ramelteon can increase levels of prolactin and reduce levels of testosterone. As a result, the drug has the potential to cause amenorrhea, galactorrhea, reduced libido, and fertility problems. If these occur, the prescriber should be consulted.

Postmarketing reports indicate a small risk of severe allergic reactions. Rarely, patients have experienced angioedema of the tongue, glottis, or larynx. Some patients also experienced dyspnea and throat constriction, suggestive of anaphylaxis. Patients who experience these symptoms should discontinue ramelteon and never use it again.

Physical Dependence and Abuse. There is no evidence that taking ramelteon leads to physical dependence or abuse. As a result, ramelteon is the first FDA-approved sleep remedy that is not regulated under the Controlled Substances Act.

Drug Interactions. Fluvoxamine [Luvox], a strong inhibitor of CYP1A2, can increase levels of ramelteon more than 50-fold. Accordingly, the combination should be avoided. Weaker inhibitors of CYP1A2 should be used with caution. Alcohol can intensify sedation, and hence should be avoided.

Precautions. Ramelteon should be used with caution by patients with moderate hepatic impairment, and should be avoided by those with severe hepatic impairment. Because ramelteon promotes sedation, patients should be advised to avoid dangerous activities, such as driving or operating heavy machinery.

Use in Pregnancy and Breast-Feeding. Very high doses (197 times the human dose) are teratogenic in rats. Effects during human pregnancy have not been studied. Until more is known, prudence dictates avoiding the drug during pregnancy (or at least using it with caution). Ramelteon is not recommended for use by nursing mothers.

Preparations, Dosage, and Administration. Ramelteon [Rozerem] is available in 8-mg tablets. The usual dosage is 8 mg taken 30 minutes before bedtime. Because food reduces absorption, ramelteon should not be taken with or immediately after a high-fat meal.

BARBITURATES

The barbiturates (pronounced bahr-bih-TEWR-ates or bahr-BITCH-oo-rates) have been available for more than 100 years. These drugs cause relatively nonselective depression of CNS function and are the prototypes of the general CNS depressants. Because they depress multiple aspects of CNS function, barbiturates can be used for daytime sedation, in-

duction of sleep, suppression of seizures, and general anesthesia. Barbiturates cause tolerance and dependence, have a high abuse potential, and are subject to multiple drug interactions. Moreover, barbiturates are powerful respiratory depressants that can be fatal in overdose. Because of these undesirable properties, barbiturates are used much less than in the past, having been replaced by newer and safer drugs—primarily the benzodiazepines and benzodiazepine-like drugs (eg, zolpidem). However, although their use has declined greatly, barbiturates still have important applications in seizure control and anesthesia. Moreover, barbiturates are valuable from an instructional point of view: By understanding these prototypic agents, we gain an understanding of the general CNS depressants as a group, along with an appreciation of why barbiturates are no longer used for anxiety and insomnia.

Classification

The barbiturates fall into three groups—ultrashort-acting, short- to intermediate-acting, and long-acting—based on duration of action. As indicated in Table 34-3, their duration of action is inversely related to their lipid solubility. Barbiturates with the highest lipid solubility have the shortest duration of action. Conversely, barbiturates with the lowest lipid solubility have the longest duration.

Duration of action influences the clinical applications of barbiturates. The ultrashort-acting agents (eg, thiopental) are used for induction of anesthesia. The short- to intermediate-acting agents (eg, secobarbital) are used as sedatives and hypnotics. The long-acting agents (eg, phenobarbital) are used primarily as antiseizure drugs.

Mechanism of Action

Like benzodiazepines, barbiturates bind to the GABA receptor-chloride channel complex (see Fig. 34-1). By doing so, these drugs can (1) enhance the inhibitory actions of GABA and (2) directly mimic the actions of GABA.

Since barbiturates can directly mimic GABA, there is no ceiling to the degree of CNS depression they can produce. Hence, in contrast to the benzodiazepines, these drugs can readily cause death by overdose. Although barbiturates can cause general depression of the CNS, they show some selectivity for depressing the *reticular activating system* (RAS), a neuronal network that helps regulate the sleep-wakefulness cycle. By depressing the RAS, barbiturates produce sedation and sleep.

Pharmacologic Effects

CNS Depression. Most effects of barbiturates—both therapeutic and adverse—result from generalized depression of CNS function. With increasing dosage, responses progress from sedation to sleep to general anesthesia.

Most barbiturates can be considered nonselective CNS depressants. The main exception is phenobarbital, a drug used to control seizures. Seizure control is achieved at doses that have minimal effects on other aspects of CNS function.

Cardiovascular Effects. At hypnotic doses, barbiturates produce modest reductions in blood pressure and heart rate. In contrast, toxic doses can cause profound hypotension and shock. How? At high doses, barbiturates depress the myocardium and vascular smooth muscle, along with all other electrically excitable tissues.

Induction of Hepatic Drug-Metabolizing Enzymes. Barbiturates stimulate synthesis of hepatic microsomal enzymes, the principal drug-metabolizing enzymes of the liver. As a result, barbiturates can accelerate their own metabolism and the metabolism of many other drugs.

TABLE 34-3 • Characteristics of Barbiturate Subgroups

Barbiturate Subgroup	Representative Drug	Lipid Solubility	Time Course		Applications
			Onset (min)	Duration (hr)	
Ultrashort-acting	Thiopental	High	0.5	0.2	Induction of anesthesia; treatment of seizures
Short- to intermediate-acting	Secobarbital	Moderate	10–15	3–4	Treatment of insomnia
Long-acting	Phenobarbital	Low	60 or less	10–12	Treatment of seizures

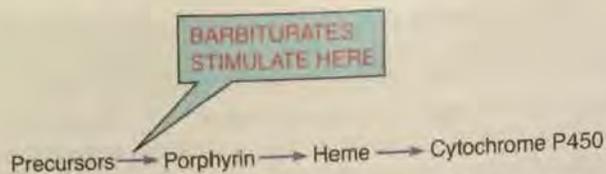


Figure 34-2 = Induction of hepatic microsomal enzymes by barbiturates.

By increasing synthesis of porphyrin, barbiturates increase production of cytochrome P450, a key component of the hepatic drug-metabolizing system.

How do barbiturates stimulate drug metabolism? By promoting synthesis of porphyrin (Fig. 34-2). Porphyrin is then converted into cytochrome P450, a key component of the hepatic drug-metabolizing system.

Tolerance and Physical Dependence

Tolerance. Tolerance is defined as reduced drug responsiveness that develops over the course of repeated drug use. When barbiturates are taken regularly, tolerance develops to many—but not all—of their CNS effects. Specifically, tolerance develops to sedative and hypnotic effects and to other effects that underlie barbiturate abuse. However, even with chronic use, *very little tolerance develops to toxic effects.*

In the tolerant user, doses must be increased to produce the same intensity of response that could formerly be achieved with smaller doses. Hence, individuals who take barbiturates for prolonged periods—be it for therapy or recreation—require steadily increasing doses to achieve the effects they desire.

It is important to note that *very little tolerance develops to respiratory depression.* Because tolerance to respiratory depression is minimal, and because tolerance does develop to therapeutic effects, with continued treatment, the lethal (respiratory-depressant) dose remains relatively constant while the therapeutic dose climbs higher and higher (Fig. 34-3). As tolerance to therapeutic effects increases, the therapeutic dose grows steadily closer to the lethal dose—a situation that is clearly hazardous.

As a rule, tolerance to one general CNS depressant bestows tolerance to all other general CNS depressants. Hence, there is cross-tolerance among barbiturates, alcohol, benzodiazepines, general anesthetics, chloral hydrate, and certain other agents. Tolerance to barbiturates and the other general CNS depressants does *not* produce significant cross-tolerance with opioids (eg, morphine).

Physical Dependence. Prolonged use of barbiturates results in physical dependence, a state in which continued use is required to avoid an abstinence syndrome. Physical dependence results from adaptive neurochemical changes that occur in response to chronic drug exposure.

Individuals who are physically dependent on barbiturates exhibit cross-dependence with other general CNS depressants. Because of cross-dependence, a person physically dependent on barbiturates can prevent withdrawal symptoms by taking any other general CNS depressant (eg, alcohol, benzodiazepines). As a rule, cross-dependence exists among all of the general CNS depressants. However, there is no significant cross-dependence with opioids.

The general CNS-depressant abstinence syndrome can be severe. Contrary to popular understanding, abrupt withdrawal from general CNS depressants is more dangerous than withdrawal from opioids. Although withdrawal from opioids is certainly unpleasant, the risk of serious injury is low. In contrast, the abstinence syndrome associated with general CNS depressants can be fatal.

The following description illustrates how dangerous withdrawal from general CNS depressants can be. Early reactions include weakness, restlessness, insomnia, hyperthermia, orthostatic hypotension, confusion, and disorientation. By the third day, major convulsive episodes may develop. Approximately 75% of patients experience psychotic delirium (a state similar to alcoholic delirium tremens). In extreme cases, these symptoms may be followed by exhaustion, cardiovascular collapse, and death. The entire abstinence syndrome evolves over approximately 8 days. Symptom intensity can be greatly reduced by withdrawing barbiturates and other general CNS depressants slowly.

A long-acting barbiturate (eg, phenobarbital) may be administered to facilitate the withdrawal process. Because of cross-dependence, phenobarbital can substitute for other CNS depressants, and can thereby suppress symptoms of withdrawal. Because phenobarbital leaves the body slowly, treatment per-

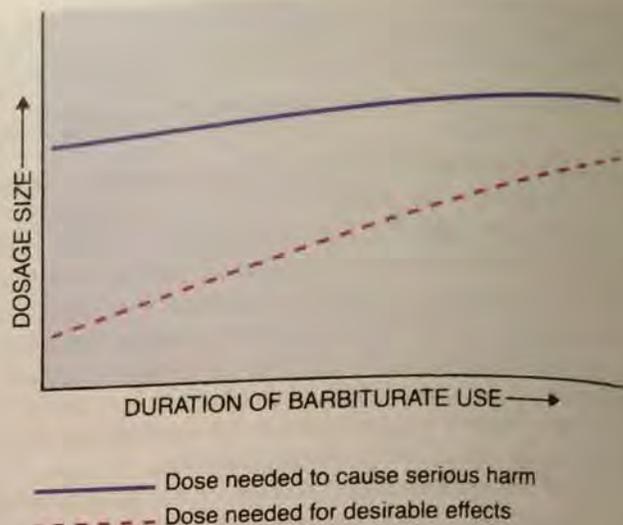


Figure 34-3 = Development of tolerance to the toxic and subjective effects of barbiturates.

With prolonged barbiturate use, tolerance develops. However, less tolerance develops to toxic effects than to desired effects. Consequently, as duration of use increases, the difference between the dose producing desirable effects and the dose producing toxicity becomes progressively smaller, thereby increasing the risk of serious harm.

mits a gradual transition from a drug-dependent state to a drug-free state. When phenobarbital is given to aid withdrawal, its dosage should be reduced gradually over 10 days to 3 weeks.

It is important to note that physical dependence should not be equated with addiction. Addiction is defined as a behavior pattern characterized by continued drug use despite physical, psychologic, or social harm. Although physical dependence can contribute to this behavior pattern, physical dependence, by itself, will neither cause nor sustain addictive behavior. The distinction between addiction and physical dependence is discussed further in Chapter 37 (Drug Abuse: Basic Considerations).

Pharmacokinetics

Lipid solubility has a significant impact on the pharmacokinetic properties of individual barbiturates. As noted, barbiturates with high lipid solubility have a rapid onset and brief duration. Onset is rapid because lipid solubility allows these drugs to penetrate the blood-brain barrier with ease, thereby reaching sites of action quickly. As they undergo uptake by tissues other than the brain, levels in plasma fall, creating a concentration gradient favoring movement from the brain back into the blood. As a result, highly lipid-soluble barbiturates undergo rapid redistribution from the brain back into the blood and then into other tissues. This redistribution terminates CNS effects.

In comparison to the highly lipid-soluble agents, barbiturates of lower lipid solubility have effects of relatively slow onset but prolonged duration. Onset is delayed because low lipid solubility impedes passage across the blood-brain barrier. Effects are prolonged because termination is dependent on renal excretion and hepatic metabolism—processes that are slower than simple redistribution from the brain to other tissues.

With the exception of the highly lipid-soluble agents, all of the barbiturates have long half-lives. These half-lives are so long, in fact, that significant amounts remain in plasma more than 24 hours after giving a single dose. This persistence has two clinical consequences. First, when barbiturates are taken at night to promote sleep, residual drug may cause sedation the following day. And second, since barbiturates are not eliminated entirely in 24 hours, daily administration produces accumulation. As a result, the brain undergoes continuous exposure to progressively higher levels of drug—a phenomenon that promotes tolerance.

Therapeutic Uses

Seizure Disorders. Two barbiturates—phenobarbital and mephobarbital—are used for seizure disorders (see Chapter 24). These drugs suppress seizures at doses that are essentially nonsedative.

Induction of Anesthesia. Two highly lipid-soluble barbiturates—thiopental sodium [Pentothal] and methohexital sodium [Brevital]—are used to induce general anesthesia (see Chapter 27). Unconsciousness develops within seconds of IV injection.

Insomnia. By depressing the CNS, barbiturates can promote sleep. However, because they can cause multiple undesired effects, barbiturates have been replaced by benzodiazepines and related drugs as treatments of choice for insomnia.

Other Uses. Barbiturates have been used to treat acute manic states and delirium. In children, they can decrease restlessness secondary to colic, pylorospasm, and whooping cough. In addition, they can help reduce anxiety in children prior to minor dental and medical procedures. Excessive excitation from overdose with CNS stimulants (eg, amphetamine, theophylline, ephedrine) can be decreased with barbiturates. They can also be employed for emergency treatment of convulsions caused by tetanus, eclampsia, and epilepsy. When administered in anesthetic doses, barbiturates can help reduce mortality from head injury; deep anesthesia reduces the brain's requirements for oxygen and glucose and thereby helps preserve CNS function. However, until anesthetic levels are achieved, barbiturates increase sensitivity to pain, and hence should not be used until pain is under control.

Adverse Effects

Respiratory Depression. Barbiturates reduce ventilation by two mechanisms: (1) depression of brainstem neurogenic respiratory drive and (2) depression of chemoreceptive mechanisms that control respiratory drive. Doses only 3 times greater than those needed to induce sleep can cause complete suppression of the neurogenic respiratory drive. With severe overdose, barbiturates can cause apnea and death.

For most patients, the degree of respiratory depression produced at therapeutic doses is not significant. However, in elderly patients and those with respiratory disease, therapeutic doses can compromise respiration substantially. Combining a barbiturate with another CNS depressant intensifies respiratory depression.

Suicide. Barbiturates have a low therapeutic index. Accordingly, overdose can readily cause death. Because of their toxicity, the barbiturates are frequently employed as vehicles for suicide, and hence should not be dispensed to patients with suicidal tendencies.

Abuse. Barbiturates produce subjective effects that many individuals find desirable. As a result, they are popular drugs of abuse. The barbiturates that are most prone to abuse are those in the short- to intermediate-acting group (eg, secobarbital). Individual barbiturates within the group are classified under Schedule II or III of the Controlled Substances Act, reflecting their high potential for abuse. Although barbiturates are frequently abused in non-medical settings, they are rarely abused during medical use.

Use in Pregnancy. Barbiturates readily cross the placenta and can injure the developing fetus. Women of child-bearing age should be informed about the potential for fetal harm and warned against becoming pregnant. Use of barbiturates during the third trimester may cause drug dependence in the infant.

Exacerbation of Intermittent Porphyria. Barbiturates can intensify attacks of acute intermittent porphyria, a condition brought on by excessive synthesis of porphyrin. Symptoms include nausea, vomiting, abdominal colic, neuromuscular disturbances, and disturbed behavior. Barbiturates exacerbate porphyria by stimulating porphyrin synthesis (see Fig. 34-2). Because they intensify porphyria, barbiturates are absolutely contraindicated for individuals with a history of the disorder.

Hangover. Barbiturates have long half-lives, and therefore can produce residual effects (hangover) when taken for insomnia. Hangover can manifest as sedation, impaired judgment, and reduced motor skills. Patients should be forewarned that their ability to perform complex tasks, both manual and intellectual, may be significantly impaired the day after taking a barbiturate to induce sleep.

Paradoxical Excitement. In some patients, especially the elderly and debilitated, barbiturates may cause excitation. The mechanism of this paradoxical response is unknown.

Hyperalgesia. Barbiturates can intensify sensitivity to pain. In addition, they may cause pain directly. These drugs have caused muscle pain, joint pain, and pain along nerves.

Drug Interactions

CNS Depressants. Drugs with CNS-depressant properties (eg, barbiturates, benzodiazepines, alcohol, opioids, antihistamines) intensify each other's effects. If these agents are combined, fatal CNS depression can result. Accordingly, patients should be warned emphatically against combining barbiturates with alcohol and other drugs that can depress CNS function.

Interactions Resulting from Induction of Drug-Metabolizing Enzymes.

As discussed above, barbiturates stimulate synthesis of hepatic drug-metabolizing enzymes, thereby accelerating metabolism of other drugs. Increased metabolism is of particular concern with *warfarin* (an anticoagulant), *oral contraceptives*, and *phenytoin* (an antiseizure agent). When these drugs are taken concurrently with a barbiturate, their dosages should be increased.

Following barbiturate withdrawal, rates of drug metabolism gradually decline to baseline values. Several weeks are required for this to occur. Drug dosages that had been increased to account for augmented metabolism must now be reduced to their prebarbiturate amount.

Acute Toxicity

Acute intoxication with barbiturates is a medical emergency: Left untreated, overdose can be fatal. Poisoning is often the result of attempted suicide, although it can also occur by accident (usually in children and drug abusers). Since acute toxicity from barbiturates and other general CNS depressants is very similar, the discussion below applies to all of these drugs.

Symptoms. Acute overdose produces a classic triad of symptoms: *respiratory depression*, *coma*, and *pinpoint pupils*. (Pupils may later dilate as hypoxia caused by respiratory depression sets in.) The three classic symptoms are frequently accompanied by *hypotension* and *hypothermia*. Death is likely to result from pulmonary complications and renal failure.

Treatment. Proper management requires an intensive care unit. With vigorous treatment, most patients recover fully.

Treatment has two main objectives: (1) removal of barbiturate from the body and (2) maintenance of an adequate oxygen supply to the brain. Oxygenation can be maintained by keeping the airway patent and giving oxygen.

Several measures can promote barbiturate removal. Unabsorbed drug can be removed from the stomach (using gastric lavage) and from the intestine (using a saline cathartic). Drug that has already been absorbed can be removed with hemodialysis. For phenobarbital and other barbiturates that are excreted intact in the urine, forced diuresis and alkalinizing the urine may facilitate their renal excretion.

Steps should be taken to prevent hypotension and loss of body heat. Blood pressure can be supported with fluid replacement and dopamine. Body heat can be maintained with blankets and warming devices.

Barbiturate poisoning has no specific antidote. CNS stimulants should definitely *not* be employed. Not only are stimulants ineffective, they are dangerous: Their use in barbiturate poisoning has been associated with a significant increase in mortality. Naloxone, a drug that can reverse poisoning by opioids, is *not* effective against poisoning by barbiturates.

Administration

Oral. Oral administration is employed for daytime sedation and to treat insomnia. Patients should be warned not to increase their dosage or discontinue treatment without consulting the prescriber. Dosages should be reduced for elderly patients. When terminating therapy, the dosage should be gradually tapered.

Intravenous. Intravenous administration is reserved for general anesthesia and emergency treatment of convulsions. Injections should be made slowly to minimize respiratory depression and hypotension. Blood pressure, pulses, and respiration should be monitored, and facilities for resuscitation should be available. The patient should be under continuous observation. Extravasation may result in local necrosis, hence care must be taken to ensure that extravasation does not occur. Solutions that are cloudy or contain a precipitate should not be used. Intra-arterial injection should be avoided, owing to a risk of gangrene secondary to prolonged arteriospasm.

Intramuscular. Barbiturate solutions are highly alkaline and can cause pain and necrosis when injected IM. Consequently, IM injection is generally avoided. Injection in the vicinity of peripheral nerves can cause irreversible neurologic injury.

MISCELLANEOUS SEDATIVE-HYPNOTICS

Basic Pharmacologic Profile

The drugs discussed in this section—chloral hydrate and meprobamate—are nonselective CNS depressants with actions much like those of the barbiturates. At therapeutic doses, these drugs cause substantial drowsiness, and hence patients should avoid driving and other hazardous activities. Combining these drugs with other CNS depressants (eg, alcohol, barbiturates, benzodiazepines, opioids, antihistamines) can produce profound CNS depression, and hence must be avoided. Prolonged use can produce tolerance and physical dependence. Consequently, these agents should be reserved for short-term therapy.

In general, acute overdose resembles poisoning with barbiturates. Characteristic signs are respiratory depression, coma, miosis, and hypotension. Management is the same as with barbiturate poisoning. Because overdose can cause potentially fatal respiratory depression, these drugs should not be given to patients suspected of suicidal tendencies.

Nonselective CNS depressants should be avoided during pregnancy and lactation. Infants exposed late in gestation may be born drug dependent. Accumulation in breast milk may cause lethargy in the nursing infant.

Chloral Hydrate

Chloral hydrate [Somnote] is a general CNS depressant with properties similar to those of the barbiturates. This agent is a prodrug that undergoes rapid conversion to its active form in the liver. The drug's principal application is induction of sleep. However, tolerance to hypnotic effects develops quickly, and withdrawal is associated with sleep disruption and nightmares.

Chloral hydrate is supplied in capsules (500 mg) and as a syrup (50 and 100 mg/mL). Patients should be instructed to swallow the capsules intact, without crushing or chewing. The syrup should be diluted with water, fruit juice, or ginger ale. With oral administration, epigastric distress, nausea, and flatulence are common.

The recommended dosage is 0.5 to 1 gm 30 minutes before bedtime. However, doses in this range are frequently too low to induce sleep. To elicit an adequate response, as much as 2 gm may be needed.

Chloral hydrate is subject to abuse and is classified as a Schedule IV drug. Abuse is similar to that seen in alcoholism. Prolonged consumption of chloral hydrate results in substantial tolerance and physical dependence. As a result, chloral hydrate addicts may ingest extremely large amounts of the drug. Abrupt withdrawal can cause delirium and seizures. Left untreated, the abstinence syndrome can be fatal.

Meprobamate

Meprobamate [Miltown] has only one indication: short-term management of anxiety. However, it is rarely used today. The drug has pharmacologic properties that lie between those of barbiturates and benzodiazepines. As a CNS depressant, meprobamate is more selective than barbiturates but less selective than benzodiazepines. Meprobamate induces hepatic drug-metabolizing enzymes and can exacerbate intermittent porphyria. Use in the first trimester of pregnancy has been associated with fetal malformations, and hence use during pregnancy should be avoided. Meprobamate is available in 200- and 400-mg tablets. The usual adult dosage is 1.2 to 1.6 gm/day in three or four divided doses. Meprobamate is a Schedule IV drug.

MANAGEMENT OF INSOMNIA

Insomnia can be defined as an inability to sleep well. Some people have difficulty falling asleep, some have difficulty maintaining sleep, some are troubled by early morning awakening, and some have sleep that is not refreshing. Insomnia is transient for some people and chronic for others. In any given year, about 30% of Americans experience intermittent insomnia, and about 10% experience chronic insomnia. In the United States, the direct costs of insomnia total about \$16 billion a year—a figure that includes the costs of testing, prescriber visits, and hypnotic drugs.

As a result of sleep loss, insomniacs experience daytime drowsiness along with impairment of mood, memory, coordination, and the ability to concentrate and make decisions. Chronic insomnia is major risk factor for automotive and industrial accidents, marital and social problems, major depression, coronary heart disease, and metabolic and endocrine dysregulation.

Loss of sleep is often the result of a medical condition. Psychiatric disorders often disturb sleep, and pain can keep anyone awake. Sleep is frequently lost owing to concern regarding impending surgery and other procedures.

At one time or another, nearly everyone suffers from situational insomnia. Worry about exams may keep students awake. Job-related pressures may deprive workers of sleep.

Deadlines may keep pharmacology writers awake. Unfamiliar surroundings may keep travelers awake. Major life stressors (bereavement, divorce, loss of job) frequently disrupt sleep. Other factors, such as uncomfortable bedding, excessive noise, and bright light, can rob us of sound sleep.

Sleep Phases

The sleeping state has two primary phases: *rapid-eye-movement* (REM) sleep and *non-rapid-eye-movement* (NREM) sleep. NREM sleep is further divided into four stages, labeled I, II, III, and IV. Sleep is relatively light in stages I and II, and deep in stages III and IV. REM sleep is the phase when most recallable dreams occur. In a typical night, we go through four to six REM periods. Males often experience penile erection during REM sleep, a curious phenomenon unrelated to dream content. The percentage of time spent in each sleep phase is as follows:

- Stage I: 5%
- Stage II: 50% to 60%
- Stages III and IV: 10% to 20%
- REM: 20% to 25%

Basic Principles of Management Cause-Specific Therapy

Treatment is highly dependent on the cause of insomnia. Accordingly, if therapy is to succeed, the underlying reason for sleep loss must be determined. To make this assessment, a thorough history is required.

When the cause of insomnia is a known medical disorder, primary therapy should be directed at the underlying illness; hypnotics should be employed only as adjuncts. For example, if pain is the reason for lost sleep, analgesics should be prescribed. If insomnia is secondary to major depression, antidepressants are the appropriate treatment. If anxiety is the cause of insomnia, the patient should receive an anxiolytic.

Nondrug Therapy

For many insomniacs, nondrug measures may be all that is needed to promote sleep. For some individuals, avoidance of naps and adherence to a regular sleep schedule is sufficient. For others, decreased consumption of caffeine-containing beverages (eg, coffee, tea, cola drinks) may fix the problem. Still others may benefit from restful activity as bedtime nears. If environmental factors are responsible for lack of sleep, the patient should be taught how to correct them or compensate for them. All patients should be counseled about sleep fitness (also known as sleep hygiene). Rules for sleep fitness are summarized in Table 34-4.

Research has shown that *cognitive behavioral therapy* is superior to drug therapy for both short-term and long-term management of chronic insomnia in older adults. Cognitive and behavioral interventions include sleep restriction, control of bedroom environment, progressive relaxation, and education about sleep hygiene. The American Academy of Sleep Medicine considers these interventions both effective and reliable, and hence recommends them as first-line therapy for chronic insomnia, even if drug therapy is also employed.

TABLE 34-4 • Rules for Sleep Fitness

- Establish a regular time to go to bed and a regular time to rise—even on weekends. This will help reset your biologic clock.
- Sleep only as long as needed to feel refreshed. Too much time in bed causes fragmented and shallow sleep. In contrast, restricting time in bed helps consolidate and deepen sleep.
- Insulate your bedroom against light and sounds that disturb your sleep (eg, install carpeting and insulated curtains).
- Keep your bedroom temperature moderate. High temperature may disturb sleep.
- Exercise daily, but not later than 7:00 PM. Regular exercise helps deepen sleep.
- Schedule outdoor time at the same time each day.
- Avoid daytime naps. Staying awake during the day helps you sleep at night.
- Avoid caffeine, especially in the evening.
- Avoid consuming too much fluid in the evening so as to minimize nighttime trips to the bathroom.
- Avoid alcohol in the evening. Although alcohol can help you fall asleep, it causes sleep to be fragmented.
- Avoid tobacco; it disturbs sleep (and shortens your life, too).
- Try having a light snack near bedtime, since hunger can disturb sleep—but don't eat heavily.
- Relax before bedtime with soft music, mild stretching, yoga, or pleasurable reading.
- Avoid bright light—including television, computers, and video games—before going to bed.
- Leave your problems outside the bedroom. Reserve time earlier in the evening to work on problems and to plan tomorrow's activities.
- Reserve your bedroom for sleeping (and sex). This will help condition your brain to see the bedroom as a place where sleep happens. Don't eat, read, or watch TV in bed.
- If you don't fall asleep within 20 minutes or so, get up and do something relaxing (eg, read, listen to music, watch TV), and then return to bed when you feel drowsy. Repeat as often as required.
- Don't look at the clock if you wake up during the night. If necessary, turn its face away from the bed.

Therapy with Hypnotic Drugs

Hypnotics should be used only when insomnia cannot be managed by other means. Hence, before resorting to drugs, we should implement nondrug measures, and we should treat any pathology that may underlie inadequate sleep.

Drug therapy of transient insomnia should be short term (just 2 to 3 weeks). The patient should be reassessed on a regular basis to determine if drug therapy is still needed.

Escalation of dosage should be avoided. A need for increased dosage suggests development of tolerance. If hypnotic effects are lost in the course of treatment, it is preferable to interrupt therapy rather than elevate dosage. Interruption will allow tolerance to decline, thereby restoring responsiveness to treatment.

In certain patients, hypnotics must be employed with special caution. Patients who snore heavily and those with respiratory disorders have reduced respiratory reserve, which can be further compromised by the respiratory-depressant actions of hypnotics. Hypnotic agents are generally contraindicated for use during pregnancy; these drugs have

the potential to cause fetal harm, and their use is never an absolute necessity.

Patients taking hypnotics should be forewarned that residual CNS depression may persist the next day. Although CNS depression may not be pronounced, it may still compromise intellectual or physical performance.

When hypnotics are employed, care must be taken to prevent *drug-dependency insomnia*, a condition that can lead to inappropriate prolongation of therapy. Drug-dependency insomnia is a particular problem with older hypnotics (eg, barbiturates), and develops as follows: (1) Insomnia motivates treatment with hypnotics. (2) With continuous drug use, low-level physical dependence develops. (3) Upon cessation of treatment, a mild withdrawal syndrome occurs and disrupts sleep. (4) Failing to recognize that the inability to sleep is a manifestation of drug withdrawal, the patient becomes convinced that insomnia has returned and resumes drug use. (5) Continued drug use leads to heightened physical dependence, making it even more difficult to withdraw medication without producing another episode of drug-dependency insomnia. To minimize drug-dependency insomnia, hypnotics should be employed judiciously. That is, they should be used in the lowest effective dosage for the shortest time required.

Major Hypnotics Used for Treatment

Insomnia can be treated with prescription drugs, nonprescription drugs, and alternative medicines. Among the prescription drugs, benzodiazepines and the benzodiazepine-like drugs (zolpidem, zaleplon, and eszopiclone) are drugs of choice. Older sedative-hypnotics, such as barbiturates and chloral hydrate, are rarely used. Nonprescription drugs and alternative medicines are much less effective than the first-choice drugs, and hence should be reserved for people whose insomnia is mild.

As shown in Table 34-5, hypnotic drugs differ with respect to onset and duration of action, and hence differ in their applications. Drugs with a rapid onset (eg, zolpidem) are good for patients who have difficulty falling asleep, whereas drugs with a long duration (eg, estazolam) are good for patients who have difficulty maintaining sleep. Drugs such as flurazepam, which have both a rapid onset and long duration, are good for patients with both types of sleep problems.

Benzodiazepines

Benzodiazepines are drugs of first choice for short-term treatment of insomnia. These agents are safe and effective and lack the undesirable properties that typify barbiturates and other older hypnotics. Benzodiazepines have a low abuse potential, cause minimal tolerance and physical dependence, present a minimal risk of suicide, and undergo few interactions with other drugs. Only five benzodiazepines are marketed specifically for use as hypnotics (see Table 34-5). However, any benzodiazepine with a short to intermediate onset could be employed.

Benzodiazepines have multiple desirable effects on sleep: they decrease the latency to sleep onset, decrease the number of awakenings, and increase total sleeping time. In addition, they impart a sense of deep and refreshing sleep. With most benzodiazepines, tolerance to hypnotic actions develops slowly, allowing them to be used nightly for several weeks

TABLE 34-5 Major Drugs for Insomnia

Drug	Time Course		Use in Insomnia*		Bedtime Dosage (mg)	
	Onset (min)	Duration	DFA	DMS	Nonelderly	Elderly
Benzodiazepines					0.125–0.25	0.13
Triazolam [Halcion]	15–30	Short	✓		30	7.5
Flurazepam [†] (generic only)	30–60	Long	✓	✓	15	7.5
Quazepam [†] [Doral]	20–45	Long	✓	✓	1–2	0.5–1
Estazolam (generic only)	15–60	Intermediate		✓	15–30	7.5–15
Temazepam [Restoril]	45–60	Intermediate		✓		
Benzodiazepine-like Drugs					2–3	1–2
Eszopiclone [Lunesta]	30	Intermediate	✓	✓		
Zolpidem					12.5	6.25
Extended-release tablets [Ambien CR]	30	Intermediate	✓	✓	10	5
Immediate-release tablets [Ambien]	30	Short	✓		10	5
Orally disintegrating tablets [Tovalt ODT]	30	Short	✓		10	5
Sublingual [Edluar]	30	Short	✓		5–10	5
Oral spray [Zolpimist]	30	Short	✓		10–20	5
Zaleplon [Sonata]	15–30	Ultrashort	✓			
Melatonin Receptor Agonist					8	8
Ramelteon [Rozerem]	30	Short	✓			

*DFA = difficulty falling asleep, DMS = difficulty maintaining sleep.

[†]Because of its long duration, this drug is not generally recommended.

without a noticeable loss in hypnotic effects. Furthermore, with most benzodiazepines, treatment does not significantly reduce the amount of time spent in REM sleep, and withdrawal is not associated with significant rebound insomnia.

Two agents—*triazolam* [Halcion] and *flurazepam* (formerly available as Dalmane)—can be considered prototypes of the benzodiazepines used to promote sleep. Triazolam has a rapid onset and short duration, making it a good choice for patients who have difficulty falling asleep (as compared with difficulty maintaining sleep). Flurazepam has a delayed onset and more prolonged duration, making it an effective agent for patients who have difficulty maintaining sleep. However, because flurazepam has a relatively long half-life, the drug is likely to cause daytime drowsiness, and hence is not used widely today. Triazolam has a much shorter half-life than flurazepam, which is both good news and bad news. The good news is that, because it leaves the body rapidly, triazolam does not cause daytime sedation. The bad news is that, because triazolam is rapidly cleared, treatment is associated with two problems: (1) tolerance to hypnotic effects can develop quickly—in 11 to 18 days, which is much faster than with other benzodiazepines; and (2) triazolam causes more rebound insomnia than other benzodiazepines.

The pharmacology of the benzodiazepines is discussed above.

Benzodiazepine-like Drugs: Zolpidem, Zaleplon, and Eszopiclone

Zolpidem [Ambien, Ambien CR, Edluar, Zolpimist], zaleplon [Sonata], and eszopiclone [Lunesta] are drugs of first choice for insomnia. In fact, one of these drugs—zolpidem—is prescribed more often than any other hypnotic. All three drugs have the same mechanism as the benzodiazepines—and all

three are as effective as the benzodiazepines, and may be safer for long-term use. Furthermore, whereas benzodiazepines are contraindicated during pregnancy, the benzodiazepine-like drugs are not (although use during pregnancy should be discouraged). All three drugs have a rapid onset, and hence can help people with difficulty *falling* asleep. Also, with zolpidem and eszopiclone, effects persist long enough to help people who have difficulty *staying* asleep. In contrast, effects of zaleplon fade too rapidly to help people with trouble staying asleep. However, zaleplon is great for people who wake up in the middle of the night. Why? Owing to its ultrashort duration, zaleplon can be taken a few hours before arising and still not cause drowsiness during the day. Of the three drugs, only eszopiclone has been *proved* effective for long-term use. However, even though long-term studies for zaleplon and zolpidem are lacking, it seems likely that they too would retain efficacy when taken long term. The pharmacology of the benzodiazepine-like drugs is discussed above.

Ramelteon

Ramelteon [Rozerem] is a melatonin agonist approved for long-term therapy of insomnia. The drug has a rapid onset and short duration, and hence is good for inducing sleep, but not maintaining sleep. Ramelteon does not cause tolerance or dependence, and is not regulated as a controlled substance. The pharmacology of ramelteon is discussed above.

Other Hypnotics

Antidepressants

Trazodone. Trazodone [Oleptro] is an atypical antidepressant with strong sedative actions. The drug can decrease sleep latency and prolong sleep duration, and does not cause tolerance or physical dependence. Trazodone is especially useful for treating insomnia resulting from use of anti-

pressants that cause significant CNS stimulation (eg, fluoxetine [Prozac], bupropion [Wellbutrin]). Principal adverse effects are daytime grogginess and postural hypotension. (Hypotension results from alpha-adrenergic blockade.) The basic pharmacology of trazodone is presented in Chapter 32.

Doxepin. Doxepin is an old tricyclic antidepressant (TCA) with strong sedative actions. In 2010, the FDA approved a new low-dose formulation for treating patients who have trouble staying asleep. The new formulation (3- and 6-mg tablets) is sold as *Silenor*. High-dose formulations for depression are sold as *Sinequan*. In clinical trials of adults with chronic insomnia, *Silenor* increased total sleep time, and maintained the effect for over 12 weeks. These benefits probably derive from blocking receptors for histamine. The initial dosage for patients age 65 and older is 3 mg, taken within 30 minutes of bedtime. The initial dosage for patients under age 65 is 6 mg. Both dosages are much lower than the dosages used for depression (75 to 150 mg/day). Unfortunately, although *Silenor* is effective, treatment is expensive, costing about \$180 a month.

In the low doses used for sleep maintenance, doxepin is well tolerated. The most common adverse effects are sedation, nausea, and upper respiratory infection. In the high doses used for depression, doxepin can cause hypotension, dysrhythmias, and anticholinergic effects (eg, dry mouth, constipation, urinary retention, blurred vision). Owing to the risk of anticholinergic effects, *Silenor* is contraindicated for patients with untreated narrow-angle glaucoma

or severe urinary retention. In addition, *Silenor* is contraindicated for patients who have taken a monoamine oxidase (MAO) inhibitor within the past 2 weeks. Unlike the benzodiazepines and benzodiazepine-like drugs, *Silenor* has little or no potential for abuse, and hence is not regulated under the Controlled Substances Act. Accordingly, the drug may be especially appropriate when drug abuse is a concern.

The basic pharmacology of doxepin and other TCAs is presented in Chapter 32.

Antihistamines

Two antihistamines—diphenhydramine [Nytol, Somnex, others] and doxylamine [Unisom]—are FDA approved for use as “sleep aids,” and can be purchased without a prescription. These drugs are less effective than benzodiazepines and benzodiazepine-like drugs, and tolerance develops quickly (in 1 to 2 weeks). Daytime drowsiness and anticholinergic effects (eg, dry mouth, blurred vision, urinary hesitancy, constipation) are common.

Alternative Medicines

Of the alternative medicines employed to promote sleep, only one—melatonin—appears moderately effective. Several others—valerian root, chamomile, passionflower, lemon balm, and lavender—have very mild sedative effects, and proof of benefits in insomnia is lacking. Melatonin is discussed in Box 34-1.

KEY POINTS

- Drugs used to treat anxiety disorders are called anti-anxiety agents, anxiolytics, or tranquilizers.
- Drugs that promote sleep are called hypnotics.
- Barbiturates and other general CNS depressants are undesirable in that they can cause fatal respiratory depression, have a high potential for abuse, cause significant tolerance and physical dependence, and often induce hepatic drug-metabolizing enzymes.
- Benzodiazepines are preferred to barbiturates and other general CNS depressants because they are much safer, have a low abuse potential, cause less tolerance and dependence, and don't induce drug-metabolizing enzymes.
- Although benzodiazepines can cause physical dependence, the withdrawal syndrome is usually mild (except in patients who have undergone prolonged, high-dose therapy).
- To minimize withdrawal symptoms, benzodiazepines should be discontinued gradually, over several weeks or even months.
- Benzodiazepines cause minimal respiratory depression when used alone, but can cause profound respiratory depression when combined with other CNS depressants (eg, opioids, barbiturates, alcohol).
- Benzodiazepines produce their effects by enhancing the actions of GABA, the principal inhibitory neurotransmitter in the CNS.
- Although benzodiazepines undergo extensive metabolism, in most cases the metabolites are pharmacologically active. As a result, responses produced by administering a particular benzodiazepine often persist long after the parent drug has disappeared from the blood.
- All of the benzodiazepines have essentially equivalent pharmacologic actions; hence, selection among them is based in large part on differences in time course.
- The principal indications for benzodiazepines are anxiety, insomnia, and seizure disorders.
- The principal adverse effects of benzodiazepines are daytime sedation and anterograde amnesia.
- Rarely, patients taking benzodiazepines to promote sleep carry out sleep driving and other complex behaviors, and then have no memory of their actions.
- Flumazenil, a benzodiazepine receptor antagonist, can be used to treat benzodiazepine overdose.
- Like the benzodiazepines, the benzodiazepine-like drugs—zaleplon [Sonata], eszopiclone [Lunesta], and zolpidem [Ambien, others]—produce their effects by enhancing the actions of GABA.
- When insomnia has a treatable cause (eg, pain, depression, schizophrenia), primary therapy should be directed at the underlying illness; hypnotics should be used only as adjuncts.
- Cognitive behavioral therapy is highly effective for insomnia, and hence is considered first-line treatment, even if drugs are also employed.
- Benzodiazepines and the benzodiazepine-like drugs (zolpidem, zaleplon, eszopiclone) are drugs of choice for insomnia.
- When benzodiazepines are used for transient insomnia, treatment should last only 2 to 3 weeks.

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Summary of Major Nursing Implications*

BENZODIAZEPINES

Alprazolam
Chlordiazepoxide
Clorazepate
Diazepam
Estazolam
Flurazepam
Lorazepam
Oxazepam
Quazepam
Temazepam
Triazolam

The nursing implications summarized here apply to the sedative-hypnotic benzodiazepines and their use in insomnia.

Preadministration Assessment

Therapeutic Goal

Benzodiazepines are used to promote sleep, relieve symptoms of anxiety (see Chapter 35), suppress seizure disorders (see Chapter 24), relax muscle spasm (see Chapter 25), and ease withdrawal from alcohol (see Chapter 38). They are also used for preanesthetic medication and to induce general anesthesia (see Chapter 27).

Baseline Data

Determine the nature of the sleep disturbance (prolonged latency, frequent awakenings, early morning awakening) and how long it has lasted. Assess for a possible underlying cause (eg, medical illness, psychiatric illness, use of caffeine and other stimulants, poor sleep hygiene, major life stressor).

Identifying High-Risk Patients

Benzodiazepines are *contraindicated* during pregnancy and for patients who experience sleep apnea. Use with *caution* in patients with suicidal tendencies or a history of substance abuse.

Implementation: Administration

Routes

Oral. All benzodiazepines.

IM and IV. Diazepam, chlordiazepoxide, and lorazepam.

Rectal. Diazepam.

Administration

Oral. Advise patients to administer benzodiazepines with food if gastric upset occurs. Instruct patients to swallow sustained-release formulations intact, without crushing or chewing.

Warn patients not to increase the dosage or discontinue treatment without consulting the prescriber.

To minimize physical dependence when treating insomnia, use intermittent dosing (3 or 4 nights a week) and the lowest effective dosage for the shortest duration required.

To minimize abstinence symptoms, taper the dosage gradually (over several weeks or even months).

Intravenous. Perform IV injections with care. Life-threatening reactions (severe hypotension, respiratory arrest, cardiac arrest) have occurred, along with less serious reactions (venous thrombosis, phlebitis, vascular impairment). To reduce complications, follow these guidelines: (1) make injections slowly; (2) take care to avoid intra-arterial injection and extravasation; (3) if direct venous injection is impossible, inject into infusion tubing as close to the vein as possible; (4) follow the manufacturer's instructions regarding suitable diluents for preparing solutions; and (5) have facilities for resuscitation available.

Implementation: Measures to Enhance Therapeutic Effects

Educate patients about sleep fitness (see Table 34-4). Reassure patients with situational insomnia that sleep patterns will normalize once the precipitating stressor has been eliminated. Ensure that correctable underlying causes of insomnia (psychiatric or medical illness, use of stimulant drugs) are being managed.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Insomnia is usually self-limiting. Consequently, drug therapy is usually short term. Benzodiazepines should be discontinued periodically to determine if they are still required. If insomnia is long term, make a special effort to identify possible underlying causes (eg, psychiatric illness, medical illness, use of caffeine and other stimulants).

Minimizing Adverse Effects

CNS Depression. Drowsiness may be present the next day when benzodiazepines are used for insomnia. Warn patients about possible residual CNS depression and advise them to avoid hazardous activities (eg, driving) if daytime sedation is significant.

Sleep Driving and Other Complex Sleep-Related Behaviors. Rarely, patients taking benzodiazepines to promote sleep may carry out complex behaviors (eg, sleep driving, eating, making phone calls), and then have no memory of the event. To reduce the risk of these events, dosage should be as low as possible, and alcohol and other CNS depressants should be avoided. Inform patients about the possibility of complex sleep-related behaviors and instruct them to notify the prescriber if they occur. If the patient reports driving while asleep, the benzodiazepine should be withdrawn (albeit slowly).

Paradoxical Effects. Inform patients about possible paradoxical reactions (rage, excitement, heightened anxiety), and instruct them to notify the prescriber if these occur. If the reaction is verified, benzodiazepines should be withdrawn.

Physical Dependence. With most benzodiazepines, significant physical dependence is rare. However, with one agent—alprazolam [Xanax, Xanax XR, Niravam]—substantial dependence has been reported. With all benzodiazepines, development of dependence can be minimized by

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

using the lowest effective dosage for the shortest time necessary and by using intermittent dosing when treating insomnia.

When dependence is mild, withdrawal can elicit insomnia and other symptoms that resemble anxiety. These must be distinguished from a return of the patient's original sleep disorder. **Warn patients about possible drug-dependency insomnia during or after benzodiazepine withdrawal.**

When dependence is severe, withdrawal reactions may be serious (panic, paranoia, delirium, hypertension, convulsions). To minimize symptoms, withdraw benzodiazepines slowly (over several weeks or months). **Warn patients against abrupt discontinuation of treatment.** After drug cessation, patients should be monitored for 3 weeks for signs of withdrawal or recurrence of original symptoms.

Abuse. The abuse potential of the benzodiazepines is low. However, some individuals do abuse them. Be alert to requests for increased dosage, since this may reflect an attempt at abuse. Benzodiazepines are classified under Sched-

ule IV of the Controlled Substances Act and must be dispensed accordingly.

Use in Pregnancy and Lactation. Benzodiazepines may injure the developing fetus, especially during the first trimester. **Inform women of child-bearing age about the potential for fetal harm and warn them against becoming pregnant.** If pregnancy occurs, benzodiazepines should be withdrawn.

Benzodiazepines readily enter breast milk and may accumulate to toxic levels in the infant. **Warn mothers against breast-feeding.**

Minimizing Adverse Interactions

CNS Depressants. Combined overdose with a benzodiazepine plus another CNS depressant can cause profound respiratory depression, coma, and death. **Warn patients against use of alcohol and all other CNS depressants (eg, opioids, barbiturates, antihistamines).**

*Patient education information is highlighted as **blue text**.

Generalized Anxiety Disorder
 Panic Disorder
 Obsessive-Compulsive Disorder
 Social Anxiety Disorder (Social Phobia)
 Post-traumatic Stress Disorder

Anxiety is an uncomfortable state that has both psychologic and physical components. The psychologic component can be characterized with terms such as *fear*, *apprehension*, *dread*, and *uneasiness*. The physical component manifests as tachycardia, palpitations, trembling, dry mouth, sweating, weakness, fatigue, and shortness of breath.

Anxiety is a nearly universal experience that often serves an adaptive function. When anxiety is moderate and situationally appropriate, therapy may not be needed or even desirable. In contrast, when anxiety is persistent and disabling, intervention is clearly indicated.

Anxiety disorders are among the most common psychiatric illnesses. In the United States, about 25% of people develop pathologic anxiety at some time in their lives. As a rule, the incidence is higher in women than in men.

In this chapter, we focus on five of the more common anxiety disorders: generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorder. Although each type is distinct, they all have one element in common: an unhealthy level of anxiety. In addition, with all anxiety disorders, depression is frequently comorbid.

Fortunately, anxiety disorders often respond well to treatment—either psychotherapy, drug therapy, or both. For most patients, a combination of psychotherapy and drug therapy is more effective than either modality alone.

As indicated in Table 35-1, two classes of drugs are used most: *benzodiazepines* and *selective serotonin reuptake inhibitors* (SSRIs). Benzodiazepines are used primarily for one condition: generalized anxiety disorder (GAD). In contrast, the SSRIs are now used for *all* anxiety disorders. It should be noted that, although SSRIs were developed as antidepressants, they can be very effective against anxiety—whether or not depression is present.

Diagnostic criteria for the anxiety disorders are set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The criteria now in use, published in the fourth edition of the DSM (DSM-IV), were released in 1994. Revised criteria will appear in fifth edition of the DSM (DSM-5).

TABLE 35-1 ■ First-Line Drugs for Anxiety Disorders

Anxiety Disorder	Benzodiazepines	SSRIs	Others
Generalized Anxiety Disorder	Alprazolam Chlordiazepoxide Clorazepate Diazepam Lorazepam Oxazepam	Escitalopram Paroxetine	Buspirone Venlafaxine Duloxetine
Panic Disorder		Fluoxetine Paroxetine Sertraline	Venlafaxine
Obsessive-Compulsive Disorder		Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	
Social Anxiety Disorder		Fluvoxamine Paroxetine Sertraline	Venlafaxine
Post-traumatic Stress Disorder		Fluoxetine Paroxetine Sertraline	Venlafaxine

SSRIs = selective serotonin reuptake inhibitors.

scheduled for release in 2013. The proposed DSM-5 criteria for anxiety disorders, which are much like the criteria in DSM-IV, are presented in tables throughout this chapter.

GENERALIZED ANXIETY DISORDER

Characteristics

Generalized anxiety disorder is a chronic condition characterized by uncontrollable worrying. Of all anxiety disorders, GAD is the least likely to remit. Most patients with GAD also have another psychiatric disorder, usually depression. GAD should not be confused with *situational anxiety*, which is a normal response to a stressful situation (eg, family problems, exams, financial difficulties); symptoms may be intense, but they are temporary.

The hallmark of GAD is unrealistic or excessive anxiety about several events or activities (eg, work or school performance) that lasts 6 months or longer. Other psychological manifestations include vigilance, tension, apprehension, poor concentration, and difficulty falling or staying asleep. Somatic manifestations include trembling, muscle tension, restlessness, and signs of autonomic hyperactivity, such as palpitations, tachycardia, sweating, and cold clammy hands. Diagnostic criteria for GAD, as proposed for DSM-5, are shown in Table 35-2.

Treatment

GAD can be managed with nondrug therapy and with drugs. Nondrug approaches include supportive therapy, cognitive behavioral therapy (CBT), biofeedback, and relaxation training. These can help relieve symptoms and improve coping skills in anxiety-provoking situations. When symptoms are mild, nondrug therapy may be all that is needed. However, if symptoms are intensely uncomfortable or disabling, drugs are indicated. Current first-line choices are benzodiazepines, buspirone, and four antidepressants: venlafaxine, paroxetine, escitalopram, and duloxetine. With the benzodiazepines, onset of relief is rapid. In contrast, with buspirone and the antidepressants, onset is delayed. Accordingly, benzodiazepines are preferred drugs for immediate stabilization, especially when anxiety is severe. However, for long-term management, buspirone and the antidepressants are preferred. Because GAD is a chronic disorder, initial drug therapy should be prolonged, lasting at least 12 months, and possibly longer. Unfortunately, even after extended treatment, drug withdrawal frequently results in relapse. Hence, for many patients, drug therapy must continue indefinitely.

Benzodiazepines

Benzodiazepines are first-choice drugs for anxiety. As discussed in Chapter 34, benefits derive from enhancing responses to gamma-aminobutyric acid (GABA), an inhibitory

TABLE 35-2 ■ Proposed DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder

- A. Excessive anxiety and worry (apprehensive expectation) about two (or more) domains of activities or events (for example, domains like family, health, finances, and school/work difficulties).
- B. The excessive anxiety and worry occur on more days than not for 3 months or more.
- C. The anxiety and worry are associated with one or more of the following symptoms:
 1. Restlessness or feeling keyed up or on edge
 2. Being easily fatigued
 3. Difficulty concentrating or mind going blank
 4. Irritability
 5. Muscle tension
 6. Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
- D. The anxiety and worry are associated with one or more of the following behaviors:
 1. Marked avoidance of situations in which a negative outcome could occur
 2. Marked time and effort preparing for situations in which a negative outcome could occur
 3. Marked procrastination in behavior or decision-making due to worries
 4. Repeatedly seeking reassurance due to worries
- E. The focus of the anxiety and worry are not restricted to symptoms of another disorder, such as Panic Disorder, Social Anxiety Disorder, Obsessive-Compulsive Disorder, Separation Anxiety Disorder (eg, anxiety about being away from home or close relatives), Anorexia Nervosa (eg, fear of gaining weight), Somatization Disorder (eg, anxiety about multiple physical complaints), Body Dysmorphic Disorder (eg, worry about perceived appearance flaws), Hypochondriasis (eg, belief about having a serious illness), and the anxiety and worry do not occur exclusively during Posttraumatic Stress Disorder.
- F. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- G. The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hyperthyroidism) and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or an Autism Spectrum Disorder.

Modified from the proposed diagnostic criteria for GAD, to be published in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on November 11, 2011.

TABLE 35-3 • Dosages of Benzodiazepines Approved for Anxiety

Generic Name	Trade Name	Dosage	
		Initial	Usual Range (mg/day)
Alprazolam	Xanax, Niravam	0.25–0.5 mg 3 times/day	0.5–6
	Xanax XR	0.5–1 mg once/day	3–6
Chlordiazepoxide	Librium	—	15–100
Clorazepate	Tranxene	—	15–60
Diazepam	Valium	—	4–40
Lorazepam	Ativan	0.5–1 mg 3 times/day	2–6
Oxazepam	—	—	30–120

neurotransmitter. Onset of benefits is immediate, and the margin of safety is high. Principal side effects are sedation and psychomotor slowing. Patients should be warned about these effects and informed they will subside in 7 to 10 days. Because of their abuse potential, benzodiazepines should be used with caution in patients known to abuse alcohol or other psychoactive substances.

Long-term use of benzodiazepines carries a risk of physical dependence. Withdrawal symptoms include panic, paranoia, and delirium. These can be especially troubling for patients with GAD. Furthermore, they can be confused with a return of pretreatment symptoms. Accordingly, clinicians must differentiate between a withdrawal reaction and relapse. To minimize withdrawal symptoms, benzodiazepines should be tapered gradually—over a period of several months. If relapse occurs, treatment should resume.

Of the 13 benzodiazepines available, 6 are approved for anxiety. The agents prescribed most often are alprazolam [Xanax, Xanax XR, Niravam] and lorazepam [Ativan]. However, there is no proof that any one benzodiazepine is clearly superior to the others. Hence, selection among them is largely a matter of prescriber preference. Dosages for anxiety are summarized in Table 35-3.

The basic pharmacology of the benzodiazepines is discussed in Chapter 34.

Buspirone

Actions and Therapeutic Use. Buspirone [BuSpar] is an anxiolytic drug that differs significantly from the benzodiazepines. Most notably, buspirone is *not* a central nervous system (CNS) depressant. For treatment of anxiety, buspirone is as effective as the benzodiazepines and has three distinct advantages: It does not cause sedation, has no abuse potential, and does not intensify the effects of CNS depressants (benzodiazepines, alcohol, barbiturates, and related drugs). Its major disadvantage is that anxiolytic effects develop *slowly*: Initial responses take a week to appear, and several more weeks must pass before responses peak. Because therapeutic effects are delayed, buspirone is not suitable for PRN use or for patients who need immediate relief. Since buspirone has no abuse potential, it may be especially appropriate for patients known to abuse alcohol and other drugs. Because it lacks depressant properties, buspirone is an attractive alternative to benzodiazepines in patients who require long-term therapy but cannot tolerate benzodiazepine-induced sedation and psychomotor slowing. Buspirone is labeled only for *short-term* treatment of anxiety. However, the drug has been taken for as long as a

year with no reduction in benefit. Buspirone does not display cross-dependence with benzodiazepines. Hence, when patients are switched from a benzodiazepine to buspirone, the benzodiazepine must be tapered slowly. Furthermore, since the effects of buspirone are delayed, buspirone should be initiated 2 to 4 weeks before beginning benzodiazepine withdrawal. In contrast to benzodiazepines, buspirone lacks sedative, muscle relaxant, and anticonvulsant actions—and hence cannot be used for insomnia, muscle spasm, or epilepsy.

The mechanism by which buspirone relieves anxiety has not been established. The drug binds with high affinity to receptors for serotonin and with lower affinity to receptors for dopamine. Buspirone does not bind to receptors for GABA or benzodiazepines.

Pharmacokinetics. Buspirone is well absorbed following oral administration but undergoes extensive metabolism on its first pass through the liver. Administration with food delays absorption but enhances bioavailability (by reducing first-pass metabolism). The drug is excreted in part by the kidneys, primarily as metabolites.

Adverse Effects. Buspirone is generally well tolerated. The most common reactions are *dizziness, nausea, headache, nervousness, lightheadedness, and excitement*. The drug is non-sedating and does not interfere with daytime activities. Furthermore, it poses little or no risk of suicide; huge doses (375 mg/day) have been given to healthy volunteers with only moderate adverse effects (nausea, vomiting, dizziness, drowsiness, miosis).

Drug and Food Interactions. Levels of buspirone can be greatly increased (5- to 13-fold) by *erythromycin* and *ketoconazole*. Levels can also be increased by *grapefruit juice*. Elevated levels may cause drowsiness and subjective effects (dysphoria, feeling “spacey”). Buspirone does not enhance the depressant effects of alcohol, barbiturates, and other general CNS depressants.

Tolerance, Dependence, and Abuse. Buspirone has been used for up to a year without evidence of tolerance, physical dependence, or psychologic dependence. No withdrawal symptoms have been observed upon termination. There is no cross-tolerance or cross-dependence between buspirone and the sedative-hypnotics (eg, benzodiazepines, barbiturates). Buspirone appears to have no potential for abuse, and hence is not regulated under the Controlled Substances Act.

Preparations, Dosage, and Administration. Buspirone tablets [BuSpar] are available in five strengths: 5, 7.5, 10, 15, and 30 mg. The initial dosage is 5 mg 3 times a day. Dosage may be increased to a maximum of 60 mg/day.

Antidepressants: Venlafaxine, Paroxetine, Escitalopram, and Duloxetine

At this time, only four antidepressants—venlafaxine [Effexor XR], duloxetine [Cymbalta], paroxetine [Paxil], and escitalopram [Lexapro, Cipralex[®]][♦]—are approved for GAD. Venlafaxine and duloxetine are serotonin/norepinephrine reuptake inhibitors (SNRIs); paroxetine and escitalopram are SSRIs. All four drugs are especially well suited for patients who have depression in addition to GAD. However, they are also effective even when depression is absent. As with buspirone, anxiolytic effects develop slowly: Initial responses can be seen in a week, but optimal responses require several more weeks to develop. Because relief is delayed, the antidepressants cannot be used PRN. Compared with benzodiazepines, the antidepressants do a better job of decreasing cognitive and psychic symptoms of anxiety, but are not as good at decreasing somatic symptoms. In contrast to the benzodiazepines, antidepressants have no potential for abuse. However, abrupt discontinuation can produce withdrawal symptoms.

Venlafaxine, an SNRI, was the first antidepressant approved for GAD. The drug has been proved effective for both short-term and long-term use. The most common side effect is nausea, which develops in 37% of patients. Fortunately, nausea subsides despite continued treatment. Other common reactions include headache, anorexia, nervousness, sweating, daytime somnolence, and insomnia. In addition, venlafaxine can cause hypertension, although this is unlikely at the doses used in GAD. Combining venlafaxine with a monoamine oxidase inhibitor can result in serious toxicity, and hence must be avoided. Venlafaxine is available in two formulations: standard tablets (generic only) and extended-release capsules [Effexor XR]. Only the extended-release formulation is approved for GAD. The initial dosage is 37.5 mg once a day, and the maintenance range is 75 to 225 mg once a day.

Duloxetine, like venlafaxine, is an SNRI. The usual dosage, both initial and maintenance, is 60 mg once a day.

Paroxetine and *escitalopram* are the only SSRIs approved for GAD. These drugs are as effective as the benzodiazepines, but less well tolerated. For paroxetine, the initial dosage is 20 mg once a day in the morning. Dosage can be gradually increased to a maintenance range of 20 to 50 mg/day. For escitalopram, dosing begins at 10 mg once daily and can be increased to 20 mg once daily after a week. Treatment beyond 8 weeks has not been studied.

The basic pharmacology of venlafaxine, paroxetine, escitalopram, and duloxetine is discussed in Chapter 32.

PANIC DISORDER

Characteristics

Panic disorder is characterized by recurrent, intensely uncomfortable episodes known as *panic attacks*. What's a panic attack? According to the proposed definition in DSM-5, a panic attack is an abrupt surge of intense fear or intense discomfort during which four or more of the following are present:

- Palpitations, pounding heart, racing heartbeat
- Sweating
- Trembling or shaking
- Sensation of shortness of breath or smothering
- Feeling of choking

- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, lightheaded, or faint
- Chills or heat sensations
- Paresthesias (numbness or tingling sensations)
- Derealization (feelings of unreality) or depersonalization (feeling detached from oneself)
- Fear of losing control or going crazy
- Fear of dying

Panic symptoms reach a peak in a few minutes, and then dissipate within 30 minutes. Many patients go to an emergency department because they think they are having a heart attack. Some patients experience panic attacks daily; others have only one or two a month. Panic disorder is a common condition that affects 1.6% of Americans at some time in their lives. The incidence in women is 2 to 3 times the incidence in men. Onset of panic disorder usually occurs in the late teens or early 20s.

Perhaps 50% of patients who get panic disorder also experience *agoraphobia*, a condition characterized by anxiety about being in places or situations from which escape might be difficult or embarrassing, or in which help might be unavailable in the event that a panic attack should occur. Agoraphobia leads to avoidance of certain places (eg, elevators, bridges, tunnels, movie theaters) and situations (eg, being outside the home alone; being in a crowd; standing on line; driving in traffic; traveling by bus, train, or plane). In extreme cases, agoraphobics may never set foot outside the home. Because of avoidance behavior, agoraphobia can severely limit occupational and social options.

What's the underlying cause of panic attacks? We don't know. However, malfunction of the brain's "alarm system" is suspected. This malfunction may result from abnormalities in noradrenergic systems, serotonergic systems, and/or benzodiazepine receptors. Genetic vulnerability also may play a role.

Treatment

Between 70% and 90% of patients with panic disorder respond well to treatment. Two modalities may be employed: drug therapy and CBT. Combining drug therapy with CBT is more effective than either modality alone. As a rule, patients experience rapid and significant improvement. Drug therapy helps suppress panic attacks, while CBT helps patients become more comfortable with situations and places they've been avoiding. Additional benefit can be derived from avoiding caffeine and sympathomimetics (which can trigger panic attacks), avoiding sleep deprivation (which can predispose to panic attacks), and doing regular aerobic exercise (which can reduce anxiety).

Drug therapy should continue at least 6 to 9 months. Stopping sooner is associated with a high rate of relapse.

Antidepressants

Panic disorder responds well to all four classes of antidepressants: SSRIs, SNRIs, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). With all four, full benefits take 6 to 12 weeks to develop. Owing to better tolerability, SSRIs are generally preferred. The basic pharmacology of the antidepressants is discussed in Chapter 32.

Selective Serotonin Reuptake Inhibitors. The SSRIs are first-line drugs for panic disorder. At this time, only three

SSRIs—fluoxetine [Prozac], paroxetine [Paxil], and sertraline [Zoloft]—are approved for this condition. However, the other SSRIs appear just as effective. The SSRIs decrease anticipatory anxiety, avoidance behavior, and the frequency and intensity of attacks. Furthermore, SSRIs decrease panic attacks regardless of whether the patient is actually depressed. However, if the patient does have coexisting depression, antidepressants will benefit the depression and panic disorder simultaneously. Common side effects include nausea, headache, insomnia, and sexual dysfunction. Weight gain is also a problem. In addition, SSRIs can increase anxiety early in treatment. To minimize exacerbation of anxiety, dosage should be low initially and then gradually increased as follows:

- *Paroxetine*—initial, 10 mg/day; target range, 20 to 40 mg/day
- *Fluoxetine*—initial, 10 mg/day; maintenance 20 mg/day
- *Sertraline*—initial, 25 mg/day; target range 50 to 200 mg/day

Venlafaxine. In patients with panic disorder, extended-release venlafaxine [Effexor XR], an SNRI, can induce remission, prevent relapse, and improve quality of life. In clinical trials, efficacy was equal to that of paroxetine, an SSRI. The initial dosage is 37.5 mg/day for 7 days. Daily maintenance doses range between 75 mg and 225 mg. The pharmacology of venlafaxine is presented in chapter 32.

Tricyclic Antidepressants. The TCAs (eg, imipramine [Tofranil], clomipramine [Anafranil]) are second-line drugs for panic disorder. They should be used only after a trial with at least one SSRI has failed. Although TCAs are as effective as SSRIs, they are less well tolerated. The most common side effects are sedation, orthostatic hypotension, and anticholinergic effects: dry mouth, blurred vision, urinary retention, constipation, and tachycardia. Of greater concern, TCAs can cause fatal dysrhythmias if taken in overdose. As with the SSRIs, dosage should be low initially and then gradually increased. For clomipramine, the initial dosage is 25 mg/day, and the target range is 50 to 200 mg/day. For imipramine, the initial dosage is 10 mg/day, and the target range is 100 to 300 mg/day.

Monoamine Oxidase Inhibitors. Although MAOIs (eg, phenelzine) are very effective in panic disorder, they are difficult to use. MAOIs can cause significant side effects, including orthostatic hypotension, weight gain, and sexual dysfunction. In addition, they can cause hypertensive crisis if the patient takes certain drugs or consumes foods rich in tyramine. Because of these drawbacks, MAOIs are considered last-line drugs for panic disorder.

Benzodiazepines. Although benzodiazepines are effective in panic disorder, they are now considered second-line drugs. Why? Because, unlike the SSRIs, benzodiazepines pose a risk of abuse, dependence, and rapid re-emergence of symptoms after discontinuation. Of the available benzodiazepines, the agents used most often are alprazolam [Xanax, Xanax XR, Niravam], clonazepam [Klonopin, Rivotril], and lorazepam [Ativan]. All three provide rapid and effective protection against panic attacks. These drugs also reduce anticipatory anxiety and phobic avoidance. In contrast to antidepressants, which take weeks or even months to work, benzodiazepines often provide relief with the first few doses. Accordingly, benzodiazepines can be especially useful as initial therapy while responses to antidepressants are developing. The principal side effect of the benzodiazepines is sedation, but some tolerance develops in 7 to 10 days. As noted, benzodiazepines can cause physical dependence, which can make withdrawal extremely hard for some patients. The difficulty is that withdrawal produces intense anxiety, which people with panic disorder may find intolerable. To minimize withdrawal symptoms, benzodiazepines should be withdrawn very slowly—over a period of several months. In addition, withdrawal symptoms can be reduced by concurrent treatment with an SSRI. The basic pharmacology of the benzodiazepines is discussed in Chapter 34.

OBSESSIVE-COMPULSIVE DISORDER

Characteristics

Obsessive-compulsive disorder (OCD) is a potentially disabling condition characterized by persistent obsessions and compulsions that cause marked distress, consume at least 1 hour a day, and significantly interfere with daily living. An

obsession is defined as a recurrent, persistent thought, impulse, or mental image that is unwanted and distressing, and comes involuntarily to mind despite attempts to ignore or suppress it. Common obsessions include fear of contamination (eg, acquiring a disease by touching another person), aggressive impulses (eg, harming a family member), a need for orderliness or symmetry (eg, personal bathroom items must be arranged in a precise way), and repeated doubts (eg, did I unplug the iron?). A *compulsion* is a ritualized behavior or mental act that the patient is driven to perform in response to his or her obsessions. In the patient's mind, carrying out the compulsion is essential to prevent some horrible event from occurring (eg, death of a loved one). If performing the compulsion is suppressed or postponed, the patient experiences increased anxiety. Common compulsions include hand washing, mental counting, arranging objects symmetrically, and hoarding. Patients usually understand that their compulsive behavior is excessive and senseless, but nonetheless are unable to stop. Diagnostic criteria for OCD, as proposed for DSM-5, are presented in Table 35-4.

Treatment

Patients with OCD respond to drugs and to behavioral therapy. Optimal treatment consists of both. As a last resort, patients with severe, resistant OCD can be treated with deep brain stimulation.

Behavioral therapy is probably more important in OCD than in any other psychiatric disorder. In the technique employed, patients are exposed to sources of their fears, while being encouraged to refrain from acting out their compulsive rituals. When no dire consequences come to pass, despite the absence of “protective” rituals, patients are able to gradually give up their compulsive behavior. Although this form of therapy causes great anxiety, the success rate is high.

Five drugs are approved for OCD: four SSRIs and one TCA (clomipramine). All five enhance serotonergic transmission. The SSRIs are better tolerated than clomipramine, and hence are preferred.

Selective Serotonin Reuptake Inhibitors

The SSRIs are first-line drugs for OCD. Only four SSRIs—fluoxetine [Prozac], fluvoxamine [Luvox], sertraline [Zoloft], and paroxetine [Paxil]—are approved for OCD. However, the remaining two—citalopram [Celexa] and escitalopram [Lexapro, Cipralex]—are also effective. All six reduce symptoms by enhancing serotonergic transmission. They all are equally effective, although individual patients may respond better to one than to another. With all six, beneficial effects develop slowly, taking several months to become maximal. Common side effects include nausea, headache, insomnia, and sexual dysfunction. Weight gain can also occur. Despite this array of side effects, SSRIs are safer than clomipramine and better tolerated. Dosages are as follows:

- *Citalopram*—20 mg once daily initially, increased to a maximum of 60 mg/day
- *Escitalopram*—10 mg once daily initially; a maximum dosage has not been established
- *Fluoxetine*—20 mg in the morning initially, increased to a maximum of 80 mg/day
- *Fluvoxamine*—50 mg at bedtime initially, increased to a maximum of 300 mg/day

TABLE 35-4 ■ Proposed DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder

- A. Either obsessions or compulsions:
 Obsessions as defined by (1) and (2):
 1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted and that usually cause marked anxiety or distress.*
 2. The person attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).[†]
 Compulsions as defined by (1) and (2):
 1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly.
 2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.
 B. The obsessions or compulsions are time consuming (for example, take more than 1 hour a day), or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.[‡]
 C. (formerly Criterion E.) The obsessive-compulsive symptoms are not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.
 D. The content of the obsessions or compulsions is not restricted to the symptoms of another mental disorder (eg, excessive worries about real life problems in Generalized Anxiety Disorder, preoccupation with food or ritualized eating behavior in an Eating Disorder; hair pulling in Hair Pulling Disorder (Trichotillomania); stereotypies in Stereotypic Movement Disorder; preoccupation with appearance in Body Dysmorphic Disorder; preoccupation with drugs in a Substance Use Disorder; preoccupation with having a serious illness in Hypochondriasis; preoccupation with sexual urges or fantasies in a Paraphilia or Hypersexual Disorder; preoccupation with gambling or other behaviors in behavioral addictions or impulse control disorders; guilty ruminations in Major Depressive Disorder; paranoia or thought insertion in a Psychotic Disorder; or repetitive patterns of behavior in Autism Spectrum Disorder).[§]

Criteria being considered for further modification as of November 11, 2011.

*Rewording the phrase "that usually cause marked anxiety or distress" in Criterion A1 is under consideration.

[†]Adding the concept of avoidance to define obsession is under consideration.

[‡]The wording of this criterion is under consideration.

[§]If Hoarding Disorder or Skin-Picking Disorder are added to DSM-5, they will also need to be mentioned in Criterion D.

Modified from the proposed diagnostic criteria for Obsessive-Compulsive Disorder, to be published in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on November 11, 2011.

- *Paroxetine*—20 mg in the morning initially, increased to a maximum of 60 mg/day
- *Sertraline*—50 mg once a day initially, increased to a maximum of 300 mg/day

How long should treatment last? Therapy of an initial episode should continue for at least 1 year, after which discontinuation can be tried. Withdrawal should be done slowly, reducing the dosage by 25% every 1 to 2 months. Unfortunately, relapse is common; estimates range from 23% to as high as 90%. If relapse continues to occur after three or four attempts at withdrawal, lifelong treatment may be indicated.

Clomipramine

For patients with OCD, clomipramine [Anafranil] is as effective as SSRIs, but less well tolerated. Accordingly, clomipramine is considered a second-line drug for this disorder, and hence should be used only after treatment with one or more SSRIs has failed.

Clomipramine is the only TCA shown effective in OCD. About 70% of patients experience a significant improvement. Initial effects take 4 weeks to develop; maximal effects are seen in 12 weeks.

Clomipramine affects several neurotransmitter systems. As with the SSRIs, benefits in OCD derive from blocking uptake of serotonin. (Among the TCAs, clomipramine is the most effective inhibitor of serotonin uptake.) However, in contrast to SSRIs, which block reuptake of serotonin only, clomipramine blocks reuptake of norepinephrine as well. Like other TCAs, clomipramine also blocks receptors for norepinephrine, acetylcholine, and histamine.

Clomipramine can cause a variety of side effects. Sedation, dry mouth, dizziness, and tremor occur in over 50% of patients. Other common effects include weight gain, constipation, blurred vision, insomnia, headache, and nausea. Of greatest concern, clomipramine can induce seizures. Because of seizure risk, the drug should be avoided in patients with a history of seizures or head injury. Clomipramine greatly increases the risk of hypertensive crisis from MAOIs, and therefore is contraindicated for patients taking these drugs.

Doses should be low initially (20 to 25 mg/day) and then gradually increased. Side effects can be minimized by dividing the early doses and taking them with meals. Maintenance doses of 150 to 250 mg/day are achieved in 2 to 4 weeks.

The basic pharmacology of clomipramine and other TCAs is discussed in Chapter 32.

Deep Brain Stimulation

In 2009, the Food and Drug Administration (FDA) approved the use of an implantable neurostimulator from Medtronic for treating severe, treatment-resistant OCD. The neurostimulator is a small, battery-powered device with

wires connected to electrodes. The device itself is surgically implanted in the abdomen or near the collar bone, and the electrodes are placed deep in the brain. When activated, the device delivers intermittent electrical stimulation that blocks nerve traffic. After 12 months of treatment, symptom reduction, on average, was 40%. Candidates for deep brain stimulation must first fail treatment with psychotherapy and with three or more drugs.

SOCIAL ANXIETY DISORDER (SOCIAL PHOBIA)

Characteristics

Social anxiety disorder, formerly known as social phobia, is characterized by an intense, irrational fear of situations in which one might be scrutinized by others, or might do something that is embarrassing or humiliating. Exposure to the feared situation almost always elicits anxiety. As a result, the person avoids the situation or, if it can't be avoided, endures it with intense anxiety (manifestations include blushing, stuttering, sweating, palpitations, dry throat, and muscle tension and twitches). Diagnostic criteria for social anxiety disorder, as proposed for DSM-5, are listed in Table 35-5.

Social anxiety disorder has two principal forms: generalized and performance only. In the generalized form, the per-

son fears nearly all social and performance situations. In the performance-only form, fear is limited to speaking or performing in public.

Social anxiety disorder can be very debilitating. In younger people, it can retard social development, inhibit participation in social activities, impair acquisition of friends, and make dating difficult or even impossible. It can also preclude pursuit of higher education. In older people, it can severely limit social and occupational options.

Social anxiety disorder is one of the most common psychiatric disorders, and the most common anxiety disorder. In the United States, 13% to 14% of the population is affected at some time in their lives. The disorder typically begins during the teenage years and, left untreated, is likely to continue lifelong.

Treatment

Social anxiety disorder can be treated with psychotherapy, drug therapy, or both. Studies indicate that psychotherapy—both cognitive and behavioral—can be as effective as drugs. However, a combination of psychotherapy *plus* drugs is likely to be more effective than either modality alone.

TABLE 35-5 ■ Proposed DSM-5 Diagnostic Criteria for Social Anxiety Disorder (Social Phobia)

- A. Marked fear or anxiety about one or more social situations in which the person is exposed to possible scrutiny by others. Examples include social interactions (eg, having a conversation), being observed (eg, eating or drinking), or performing in front of others (eg, giving a speech).
- B. The individual fears that he or she will act in a way, or show anxiety symptoms, that will be negatively evaluated (ie, be humiliating, embarrassing, lead to rejection, or offend others).
- C. The social situations consistently provoke fear or anxiety. *Note:* in children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or refusal to speak in social situations.
- D. The social situations are avoided or endured with intense fear or anxiety.
- E. The fear or anxiety is out of proportion to the actual danger posed by the social situation.
- F. The duration is at least 6 months.
- G. The fear, anxiety, and avoidance cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- H. The fear, anxiety, and avoidance are not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.
- I. The fear, anxiety, and avoidance are not restricted to the symptoms of another mental disorder, such as Panic Disorder (eg, anxiety about having a panic attack), Agoraphobia (eg, avoidance of situations in which the individual may become incapacitated), Separation Anxiety Disorder (eg, fear of school), Body Dysmorphic Disorder (eg, fear of public exposure of perceived physical flaws), or Autism Spectrum Disorder.
- J. If a general medical condition (eg, stuttering, Parkinson's disease, obesity, disfigurement from burns or injury) is present, the fear, anxiety, or avoidance is clearly unrelated to it or is excessive.

Specify if:

Performance only: If the fear is restricted to speaking or performing in public.

Generalized: If the fear is of most social situations (and is not restricted to performance situations).

Selective Mutism: Consistent failure to speak in specific social situations (in which there is an expectation for speaking, eg, at school) despite speaking in other situations.

Modified from the proposed diagnostic criteria for Social Anxiety Disorder, to be published in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on November 11, 2011.

TABLE 35-6 ■ Proposed DSM-5 Diagnostic Criteria for Post-Traumatic Stress Disorder*

- A. The person was exposed to one or more of the following event(s): death or threatened death, actual or threatened serious injury, or actual or threatened sexual violation, in one or more of the following ways:¹
1. Experiencing the event(s) him/herself.
 2. Witnessing, in person, the event(s) as they occurred to others.
 3. Learning that the event(s) occurred to a close relative or close friend; in such cases, the actual or threatened death must have been violent or accidental.
 4. Experiencing repeated or extreme exposure to aversive details of the event(s) (eg, first responders collecting body parts; police officers repeatedly exposed to details of child abuse).
- B. Intrusion symptoms that are associated with the traumatic event(s), as evidenced by one or more of the following:
1. Spontaneous or cued recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). *Note:* In children, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
 2. Recurrent distressing dreams in which the content and/or affect of the dream is related to the event(s). *Note:* In children, there may be frightening dreams without recognizable content.²
 3. Dissociative reactions (eg, flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) *Note:* In children, trauma-specific re-enactment may occur in play.
 4. Intense or prolonged psychologic distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
 5. Marked physiologic reactions to reminders of the traumatic event(s).
- C. Persistent avoidance of stimuli associated with the traumatic event(s), as evidenced by efforts to avoid one or more of the following:
1. Avoids internal reminders (thoughts, feelings, or physical sensations) that arouse recollections of the traumatic event(s).
 2. Avoids external reminders (people, places, conversations, activities, objects, situations) that arouse recollections of the traumatic event(s).
- D. Negative alterations in cognition and mood that are associated with the traumatic event(s), as evidenced by three or more of the following: *Note:* In children, as evidenced by two or more of the following:³
1. Inability to remember an important aspect of the traumatic event(s) (typically dissociative amnesia; not due to head injury, alcohol, or drugs).
 2. Persistent and exaggerated negative expectations about one's self, others, or the world (eg, "I am bad," "no one can be trusted," "I've lost my soul forever," "my whole nervous system is permanently ruined," "the world is completely dangerous").
 3. Persistent distorted blame of self or others about the cause or consequences of the traumatic event(s).
 4. Pervasive negative emotional state—for example: fear, horror, anger, guilt, or shame.
 5. Markedly diminished interest or participation in significant activities.
 6. Feeling of detachment or estrangement from others.
 7. Persistent inability to experience positive emotions (eg, unable to have loving feelings, psychic numbing).
- E. Alterations in arousal and reactivity that are associated with the traumatic event(s), as evidenced by three or more of the following: *Note:* In children, as evidenced by two or more of the following:³
1. Irritable or aggressive behavior
 2. Reckless or self-destructive behavior
 3. Hypervigilance
 4. Exaggerated startle response
 5. Problems with concentration
 6. Sleep disturbance—for example, difficulty falling or staying asleep, or restless sleep
- F. Duration of the disturbance (symptoms in Criteria B, C, D and E) is more than 1 month.
- G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- H. The disturbance is not due to the direct physiologic effects of a substance (eg, medication or alcohol) or a general medical condition (eg, traumatic brain injury, coma).

Criteria being considered for further modification as of November 11, 2011:

*Developmental manifestations of PTSD are still being developed. The term "developmental manifestation" in DSM-5 refers to age-specific expressions of one or another criteria that is used to make a diagnosis across age groups.

¹For children, inclusion of loss of a parent or other attachment figure is being considered.

²An alternative is to retain the DSM-IV criterion.

³The optimal number of required symptoms for both adults and children will be further examined with empirical data. Modified from the proposed diagnostic criteria for PTSD, to be published in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on November 11, 2011.

The SSRIs are considered first-line drugs for most patients. These drugs are especially well suited for patients who fear multiple situations and are obliged to face those situations on a regular basis. Currently, only three SSRIs—fluvoxamine [Luvox], paroxetine [Paxil], and sertraline [Zoloft]—are approved for social anxiety disorder. However, available data indicate that the other SSRIs are effective too. Initial effects take about 4 weeks to develop; optimal effects are seen in 8 to 12 weeks. Patients should be informed that benefits will be delayed. For paroxetine, the initial dosage is 20 mg once a day in the morning. The usual maintenance range is 20 to 40 mg/day. Treatment should continue for at least 1 year, after which gradual withdrawal can be tried. Unfortunately, withdrawal frequently results in relapse.

Benzodiazepines (eg, clonazepam [Klonopin, Rivotril[®]], alprazolam [Xanax]) are an option for some patients. These drugs are well tolerated and their benefits are immediate, unlike those of the SSRIs. As a result, benzodiazepines can provide rapid relief and can be used PRN. Accordingly, these drugs are well suited for people whose fear is limited to performance situations, and who must face those situations only occasionally. The usual dosage is 1 to 3 mg/day for clonazepam, and 1 to 6 mg/day for alprazolam.

Propranolol [Inderal] and other beta blockers can benefit patients with performance anxiety. When taken 1 to 2 hours before a scheduled performance, beta blockers can reduce symptoms caused by autonomic hyperactivity (eg, tremors, sweating, tachycardia, palpitations). Doses are relatively small—only 10 to 80 mg for propranolol.

POST-TRAUMATIC STRESS DISORDER

Characteristics

Post-traumatic stress disorder (PTSD) develops following a *traumatic event* that elicited an immediate reaction of *fear*, *helplessness*, or *horror*. PTSD has three core symptoms: *re-experiencing* the event, *avoiding reminders* of the event (coupled with generalized emotional numbing), and a persistent state of *hyperarousal*. According to the proposed criteria for DSM-5, a traumatic event is one that involves a threat of injury or death, or a threat to one's physical integrity. Many events meet this criterion. Among these are physical or sexual assault, rape, torture, combat, industrial explosions, serious accidents, natural disasters, being taken hostage, displacement as a refugee, and terrorist attacks, such as the ones that

took place against the World Trade Center and the Pentagon on September 11, 2001. It should be noted that PTSD can affect persons who were only *witnesses* to a traumatic event—not just those who were directly involved. Proposed DSM-5 diagnostic criteria for PTSD are shown in Table 35-6.

The epidemiology of PTSD is revealing. In the United States, more than 5 million Americans have PTSD in any given year, making PTSD the fourth most common psychiatric disorder. PTSD develops in 5% to 6% of men at some time in their lives, and in 10% to 14% of women. Traumatic events that involve interpersonal violence (eg, assault, rape, torture) are more likely to cause PTSD than are traumatic events that do not (eg, car accidents, natural disasters). For example, among rape victims, the incidence of PTSD is 45.9% for women and 65% for men. In contrast, among natural disaster survivors, the incidence is only 5.4% for women and 3.7% for men. Combat carries a high risk of PTSD: the disorder develops in up to 40% of soldiers who go to war.

Treatment

Post-traumatic stress disorder can be treated with psychotherapy and with drugs, as described in a recent evidence-based guideline—*VA/DoD Clinical Practice Guideline for the Management of Post-Traumatic Stress*—released by the Department of Veterans Affairs and Defense Department in 2010. Two basic types of psychotherapy are recommended: *trauma-focused therapy* and *stress inoculation training*. Trauma-focused therapy uses a variety of cognitive-behavioral techniques, including a very effective one known as *exposure therapy*, in which patients repeatedly reimagine traumatic events as a way to make those events lose their power. Stress inoculation training help patients identify cues that can trigger fear and anxiety, and then teaches them techniques to cope with those disturbing reactions.

Regarding drugs, evidence of efficacy is strongest for three SSRIs (fluoxetine, paroxetine, and sertraline) and one SNRI (venlafaxine). Of these four drugs, only two—paroxetine [Paxil] and sertraline [Zoloft]—are FDA-approved for PTSD. If none of first-line drugs is effective, the guidelines suggest several alternatives: mirtazapine, nefazodone, a TCA (amitriptyline or imipramine), or an MAOI (phenelzine). Current evidence does *not* support the use of monotherapy with either bupropion, buspirone, trazodone, a benzodiazepine, an anti-seizure drug (lamotrigine or gabapentin), or an atypical antipsychotic.

KEY POINTS

- Anxiety is an uncomfortable state that has psychologic manifestations (fear, apprehension, dread, uneasiness) and physical manifestations (tachycardia, palpitations, trembling, dry mouth, sweating, weakness, fatigue, shortness of breath).
- When anxiety is persistent and disabling, intervention is indicated.
- As a rule, optimal therapy of anxiety disorders consists of psychotherapy combined with drug therapy.
- The drugs used most often for anxiety disorders are benzodiazepines and selective serotonin reuptake inhibitors (SSRIs).
- Benzodiazepines are used primarily for panic disorder and generalized anxiety disorder (GAD), whereas SSRIs are used for *all* anxiety disorders.
- GAD is a chronic condition characterized by uncontrollable worrying.

- First-line drugs for GAD are benzodiazepines, buspirone, and four antidepressants: venlafaxine, paroxetine, escitalopram, and duloxetine.
- Benzodiazepines suppress symptoms of GAD immediately. Accordingly, these drugs are preferred agents for rapid stabilization, especially when anxiety is severe.
- With buspirone, venlafaxine, paroxetine, escitalopram, and duloxetine, anxiolytic effects are delayed. Accordingly, these drugs are best suited for long-term management—not rapid relief.
- Benzodiazepines are CNS depressants and hence can cause sedation and psychomotor slowing. In addition, they can intensify CNS depression caused by other drugs.
- Benzodiazepines have some potential for abuse, and hence should be used with caution in patients known to abuse alcohol or other psychoactive drugs.
- When taken long term, benzodiazepines can cause physical dependence. To minimize withdrawal symptoms, dosage should be tapered gradually—over a period of several months.
- Buspirone has three advantages over benzodiazepines: It does not cause CNS depression, has no abuse potential, and does not intensify the effects of CNS depressants.
- Buspirone levels can be increased by erythromycin, ketoconazole, and grapefruit juice.
- Venlafaxine, paroxetine, escitalopram, and duloxetine are especially well suited for treating patients who have depression in addition to GAD. However, they are also effective even when depression is absent.
- Patients with panic disorder experience recurrent panic attacks, characterized by palpitations, pounding heart, chest pain, derealization or depersonalization, and fear of dying or going crazy.
- Many patients with panic disorder also experience agoraphobia, a condition characterized by anxiety about being in places or situations from which escape might be difficult or embarrassing, or in which help might be unavailable if a panic attack should occur.
- SSRIs are first-line drugs for panic disorder.
- SSRIs decrease the frequency and intensity of panic attacks, anticipatory anxiety, and avoidance behavior, and they work regardless of whether the patient has depression.
- Obsessive-compulsive disorder (OCD) is characterized by persistent obsessions and compulsions that cause marked distress, consume at least 1 hour a day, and significantly interfere with daily living.
- SSRIs are first-line drugs for OCD.
- Social anxiety disorder, formerly known as social phobia, is characterized by an intense, irrational fear of being scrutinized by others, or of doing something that could be embarrassing or humiliating.
- The SSRIs are first-line drugs for most patients with social anxiety disorder.
- When social anxiety disorder is limited to fear of speaking or performing in public, and when these situations arise infrequently, PRN treatment with a benzodiazepine may be preferred to long-term treatment with an SSRI.
- Post-traumatic stress disorder (PTSD) develops following a traumatic event that elicited an immediate reaction of fear, helplessness, or horror.
- PTSD has three core symptoms: re-experiencing, avoidance/emotional numbing, and hyperarousal.
- Events that can lead to PTSD include physical or sexual assault, rape, torture, combat, industrial explosions, serious accidents, natural disasters, being taken hostage, displacement as a refugee, and terrorist attacks.
- According to the IOM, exposure therapy is the only treatment for PTSD with good proof of efficacy.
- According to the IOM, there is no good proof that any drugs are effective in PTSD, even though two SSRIs—paroxetine and sertraline—are approved by the FDA for this indication.

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Central Nervous System Stimulants and Attention-Deficit/Hyperactivity Disorder

CENTRAL NERVOUS SYSTEM STIMULANTS

- Amphetamines
- Methylphenidate and Dexmethylphenidate
- Methylxanthines
 - Caffeine
 - Theophylline
 - Theobromine
- Miscellaneous CNS Stimulants
 - Modafinil
 - Armodafinil
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 - Cocaine

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

- Basic Considerations
 - ADHD in Children
 - ADHD in Adults
- Drugs Used for ADHD
 - CNS Stimulants
 - Nonstimulants

SI Box 36-1. Did Kisses Kill Calvin?

CENTRAL NERVOUS SYSTEM STIMULANTS

Central nervous system (CNS) stimulants increase the activity of CNS neurons. Most stimulants act by enhancing neuronal excitation. A few act by suppressing neuronal inhibition. In sufficient doses, all stimulants can cause convulsions.

Clinical applications of the CNS stimulants are limited. Currently these drugs have two principal indications: attention-deficit/hyperactivity disorder (ADHD) and narcolepsy. In the past, stimulants were used to treat obesity and counteract poisoning by CNS depressants, but these uses are no longer recommended.

Please note that CNS stimulants are not the same as antidepressants. The antidepressants act selectively to elevate mood, and hence can relieve depression without affecting other CNS functions. In contrast, CNS stimulants cannot elevate mood without producing generalized excitation. Accordingly, the role of stimulants in treating depression is minor.

Our principal focus is on *amphetamines*, *methylphenidate* [Ritalin, others], and *methylxanthines* (eg, caffeine). These are by far the most widely used stimulant drugs.

AMPHETAMINES

The amphetamine family consists of amphetamine, dextroamphetamine, methamphetamine, and lisdexamfetamine. All are powerful CNS stimulants. In addition to their CNS actions, amphetamines have significant peripheral actions—actions that can cause cardiac stimulation and vasoconstriction. The amphetamines have a high potential for abuse.

Chemistry

Dextroamphetamine and Levamphetamine. Amphetamines are molecules with an asymmetric carbon atom. As a result, amphetamines can exist as mirror images of each other. Such compounds are termed *optical isomers* or *enantiomers*. Dextroamphetamine and levamphetamine, whose structures are shown in Figure 36-1, illustrate the mirror-image concept. As we can see, dextroamphetamine and levamphetamine both contain the same atomic components, but those components are arranged differently around the asymmetric carbon. Because of this structural difference, these compounds have somewhat different properties. For example, dextroamphetamine is more selective than levamphetamine for causing stimulation of the CNS, and hence produces fewer peripheral side effects.

Amphetamine. The term *amphetamine* refers not to a single compound but rather to a 50:50 mixture of dextroamphetamine and levamphetamine. (In chemistry, we refer to such equimolar mixtures of enantiomers as *racemic*.)

Lisdexamfetamine. Lisdexamfetamine [Vyvanse], introduced in 2007, is a prodrug composed of dextroamphetamine covalently linked to L-lysine. Following oral dosing, the drug undergoes rapid hydrolysis by enzymes in the intestine and liver to yield lysine and free dextroamphetamine, the active form of the drug. If lisdexamfetamine is inhaled or injected, hydrolysis will not take place, and hence the drug is not effective by these routes. Accordingly, it may have a lower abuse potential than other forms of amphetamine.

Methamphetamine. Methamphetamine is simply dextroamphetamine with an additional methyl group (see Fig. 36-1).

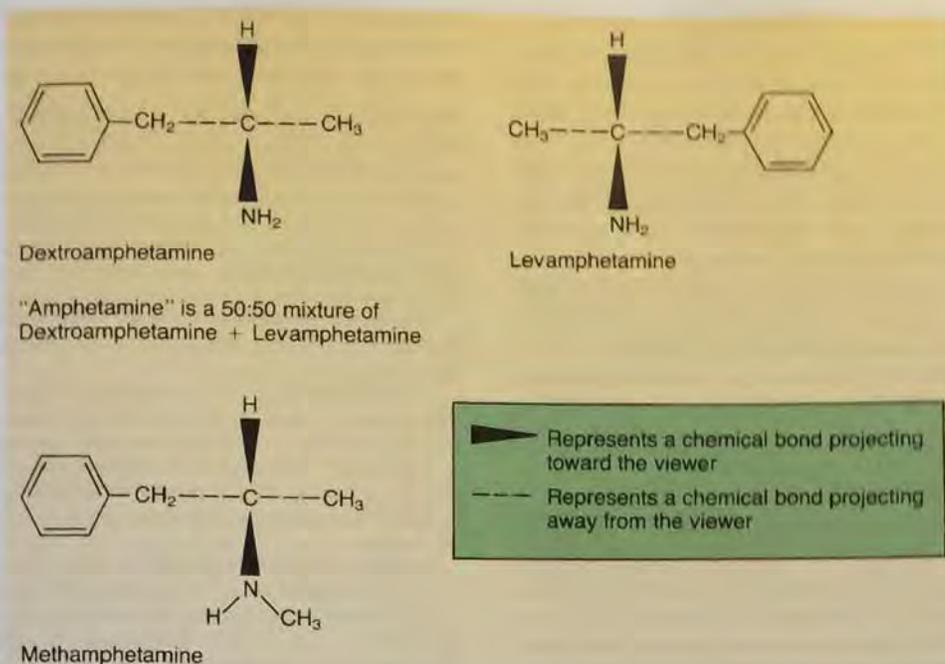


Figure 36-1 ■ Structural formulas of the amphetamines.

"Amphetamine" is a 50:50 mixture of dextroamphetamine and levamphetamine. Note that dextroamphetamine and levamphetamine are simply mirror images of each other. Both compounds contain the same atomic components.

Mechanism of Action

The amphetamines act primarily by causing release of norepinephrine (NE) and dopamine (DA), and partly by inhibiting reuptake of both transmitters. These actions take place in the CNS and in peripheral nerves. Most pharmacologic effects result from release of NE.

Pharmacologic Effects

Central Nervous System. The amphetamines have prominent effects on mood and arousal. At usual doses, they increase wakefulness and alertness, reduce fatigue, elevate mood, and augment self-confidence and initiative. Euphoria, talkativeness, and increased motor activity are likely. Task performance that had been reduced by fatigue or boredom improves.

Amphetamines can stimulate respiration, and suppress appetite and perception of pain. Stimulation of the medullary respiratory center increases respiration. Effects on the hypothalamic feeding center depress appetite. By a mechanism that is not understood, amphetamines can enhance the analgesic effects of morphine and other opioids.

Cardiovascular System. Cardiovascular effects occur secondary to release of NE from sympathetic neurons. Norepinephrine acts in the heart to increase heart rate, atrioventricular (AV) conduction, and force of contraction. Excessive cardiac stimulation can cause dysrhythmias. In blood vessels, NE promotes constriction. Excessive vasoconstriction can cause hypertension.

Tolerance

With regular amphetamine use, tolerance develops to elevation of mood, suppression of appetite, and stimulation of the heart and blood vessels. In highly tolerant users, doses up to

1000 mg (IV) every few hours may be required to maintain euphoric effects. This compares with daily doses of 5 to 30 mg for nontolerant individuals.

Physical Dependence

Chronic amphetamine use produces physical dependence. If amphetamines are abruptly withdrawn from a dependent person, an abstinence syndrome will ensue. Symptoms include exhaustion, depression, prolonged sleep, excessive eating, and a craving for more amphetamine. Sleep patterns may take months to normalize.

Abuse

Because amphetamines can produce euphoria (extreme mood elevation), they have a high potential for abuse. Psychologic dependence can occur. (Users familiar with CNS stimulants find the psychologic effects of amphetamines nearly identical to those of cocaine.) Because of their abuse potential, all amphetamines, including lisdexamfetamine, are classified under Schedule II of the Controlled Substances Act, and must be dispensed accordingly. Whenever amphetamines are used therapeutically, their potential for abuse must be weighed against their potential benefits.

Adverse Effects

CNS Stimulation. Stimulation of the CNS can cause insomnia, restlessness, and extreme loquaciousness. These effects can occur at therapeutic doses.

Weight Loss. By suppressing appetite, amphetamines can cause weight loss. For people who are lean to start with, weight loss is considered an adverse effect. Conversely, for people who are obese, weight loss is desirable.

Cardiovascular Effects. At recommended doses, stimulants produce a small increase in heart rate and blood pressure. For most patients, these increases lack clinical significance. However, for patients with pre-existing cardiovascular disease, dysrhythmias, anginal pain, or hypertension might result. Accordingly, amphetamines must be employed with extreme caution in these people. Any patient who develops cardiovascular symptoms (eg, chest pain, shortness of breath, fainting) while using a stimulant should be evaluated immediately.

Do amphetamines increase the risk of *sudden death*? Probably not. And should children *routinely* receive an electrocardiogram (ECG) before using these drugs? Probably not—despite a 2008 statement from the American Heart Association (AHA) saying it would be reasonable to consider obtaining an ECG in children being evaluated for stimulant therapy of ADHD. Why is the AHA concerned? Because 14 children, 5 with heart defects, died suddenly while using Adderall, a mixture of amphetamine and dextroamphetamine. However, given that millions of children have used the drug, the death rate is no greater than would be expected for a group this size, whether or not Adderall was being used. The bottom line? First, there are no data showing that stimulants increase the risk of sudden death, even in children with heart disease. Second, there are no data showing that limiting the use of stimulants in children with heart defects will protect them from sudden death. And third, there are no data showing that screening for heart disease with an ECG before starting stimulants will be of benefit. Therefore, it would seem that *routine* ECGs are unnecessary before starting a child on stimulant therapy, especially if there is no evidence of heart disease. However, if there *is* evidence of heart disease, an ECG might be appropriate.

Psychosis. Excessive amphetamine use produces a state of paranoid psychosis, characterized by hallucinations and paranoid delusions (suspiciousness, feelings of being watched). Amphetamine-induced psychosis looks very much like schizophrenia. Symptoms are thought to result from release of DA. Consistent with this hypothesis is the observation that symptoms can be alleviated with a DA receptor blocking agent (eg, haloperidol). Following amphetamine withdrawal, psychosis usually resolves spontaneously within a week.

In some individuals, amphetamines can unmask latent schizophrenia. For these people, symptoms of psychosis do not clear spontaneously, and hence psychiatric care is indicated.

Acute Toxicity

Symptoms. Overdose produces dizziness, confusion, hallucinations, paranoid delusions, palpitations, dysrhythmias, and hypertension. Death is rare. Fatal overdose is associated with convulsions, coma, and cerebral hemorrhage.

Treatment. Hallucinations can be controlled with chlorpromazine, an antipsychotic drug. An alpha-adrenergic blocker (eg, phentolamine) can reduce hypertension (by promoting vasodilation). Owing to its ability to block alpha receptors, chlorpromazine helps lower blood pressure. Seizures can be managed with diazepam. Acidifying the urine can accelerate amphetamine excretion.

Therapeutic Uses

Attention-Deficit/Hyperactivity Disorder. The role of amphetamines in ADHD is discussed later.

Narcolepsy. Narcolepsy is a disorder characterized by daytime somnolence and uncontrollable attacks of sleep. By stimulating the CNS, amphetamines can promote arousal and thereby alleviate symptoms.

Obesity. Because they suppress appetite, amphetamines have been employed in programs for weight loss. However,

because of their high potential for abuse, and because they offer no advantages over less dangerous drugs, amphetamines are not recommended for weight reduction.

Preparations, Dosage, and Administration

Four members of the amphetamine family are used clinically: dextroamphetamine, an amphetamine/dextroamphetamine mixture, lisdexamfetamine sulfate, and methamphetamine. In clinical practice, amphetamines are given *orally*. (These drugs are not approved for IV administration. Amphetamines for IV use are available only through illegal sources.) All amphetamines are regulated under Schedule II of the Controlled Substances Act and must be dispensed accordingly.

Dextroamphetamine Sulfate. Dextroamphetamine is available in short-duration (SD) and long-duration (LD) formulations. Both are indicated for ADHD.

Short Duration. SD dextroamphetamine [DextroStat, Dexedrine] is available in 5- and 10-mg tablets. Effects begin rapidly and last 4 to 6 hours. The usual maintenance dosage for ADHD is 5 mg at 8:00 AM, noon, and 4:00 PM.

Long Duration. LD dextroamphetamine [Dexedrine Spansules] is available in 5-, 10-, and 15-mg capsules. Effects begin rapidly and last 6 to 10 hours. The usual maintenance dosage for ADHD is 10 mg once daily in the morning.

Amphetamine/Dextroamphetamine Mixture. Amphetamine mixture is available in SD and LD formulations. Both are used for ADHD.

Short Duration. The SD formulation [Adderall] is available in immediate-release tablets (5, 7.5, 10, 12.5, 15, 20, and 30 mg). Effects begin rapidly and last 4 to 6 hours. The usual maintenance dosage for ADHD is 5 mg twice daily, taken in the morning and 5 hours later.

Long Duration. The LD formulation [Adderall-XR] is available in 5-, 10-, 15-, 20-, 25-, and 30-mg capsules. Half the dose is released immediately, and the remainder 4 hours later. As a result, effects begin rapidly and last 10 to 12 hours. The usual maintenance dosage for ADHD is 20 mg once daily in the morning. This is equivalent to taking 10 mg of SD Adderall at 8:00 AM and again around noon.

Lisdexamfetamine. Lisdexamfetamine [Vyvanse] is available in capsules (20, 30, 40, 50, 60, and 70 mg). Effects begin rapidly and persist about 13 hours. Dosing is done once daily in the morning without regard to meals. The capsules may be swallowed intact, or their contents may be dissolved in water and swallowed immediately. The usual daily maintenance dosage for ADHD is 30 mg.

Methamphetamine. Methamphetamine [Desoxyn] is indicated for ADHD and obesity, although it is not a preferred treatment for either condition. The drug is available in 5-mg SD tablets. The usual regimen for ADHD is 20 to 25 mg/day, administered in two divided doses.

METHYLPHENIDATE AND DEXMETHYLPHENIDATE

Methylphenidate and dexmethylphenidate are nearly identical in structure and pharmacologic actions. Furthermore, the pharmacology of both drugs is nearly identical to that of the amphetamines.

Methylphenidate

Although methylphenidate [Ritalin, Metadate, Methylin, Concerta, Daytrana, Biphentin \clubsuit] is structurally dissimilar from the amphetamines, the pharmacologic actions of these drugs are essentially the same. Consequently, methylphenidate can be considered an amphetamine in all but structure and name. Methylphenidate and amphetamine share the same mechanism of action (promotion of NE and DA release, and inhibition of NE and DA reuptake), adverse effects (insomnia, reduced appetite, emotional lability), and abuse liability (Schedule II). Like amphetamine, methylphenidate is not a single compound, but rather a 50:50 mixture of dextro and levo isomers. The dextro isomer is highly active; the levo isomer is not. Methylphenidate has two indications: ADHD and narcolepsy.

Preparations, Dosage, and Administration

Methylphenidate is available in three types of formulations: short duration (SD), intermediate duration (ID), and long duration (LD). All three are indicated for ADHD. As a rule, the SD and ID formulations must be taken 2 or 3 times a day, whereas the LD formulations can be taken just once a day.

Short Duration. SD methylphenidate [Ritalin, Methylin] is available in standard tablets (5, 10, and 20 mg), chewable tablets (2.5, 5, and 10 mg), and an oral solution (5 and 10 mg/5 mL). Effects begin rapidly and last 3 to 5 hours. Because effects are brief, dosing must be done 2 or 3 times a day. The usual pediatric maintenance dosage for ADHD is 10 mg at 8:00 AM and noon, and 5 mg at 4:00 PM.

Intermediate Duration. ID methylphenidate [Ritalin SR, Metadate ER, Methylin ER] is available in 10- and 20-mg tablets. Effects are delayed and last 6 to 8 hours. Dosing is done once or twice daily. For children with ADHD, the usual maintenance dosage is 20 to 40 mg in the morning, supplemented with 20 mg in the early afternoon if needed.

Long Duration. Five LD products are available. Their trade names are Concerta, Metadate CD, Ritalin LA, Daytrana, and Biphentin. With all five, dosing is done once daily in the morning; no afternoon dose is needed.

Concerta. Concerta tablets—formulated as an osmotic-release oral system (OROS)—consist of an outer coating of immediate-release methylphenidate and a special inner core that releases the remainder of each dose gradually. As a result, effects begin rapidly and last 10 to 12 hours. Because of their special architecture, Concerta tablets must be swallowed whole, not crushed or chewed. The tablet shell may not dissolve fully in the GI tract. Accordingly, patients should be informed they may see tablet “ghosts” in the stool. Concerta tablets are available in four strengths: 18, 27, 36, and 54 mg.

Dosage depends on whether the patient is already taking methylphenidate (SD or ID). For children *not* already taking methylphenidate, the initial dosage is 18 mg once daily in the morning. Dosage can be increased to a maximum of 72 mg once daily. For children who *are* taking methylphenidate (SD or ID), the initial dosage of Concerta is as follows:

- For those taking 5 mg (2 or 3 times a day) of SD methylphenidate or 20 mg once daily of ID methylphenidate, start with 18 mg of Concerta.
- For those taking 10 mg (2 or 3 times a day) of SD or 40 mg once daily of ID, start with 36 mg of Concerta.
- For those taking 15 mg (2 or 3 times a day) of SD or 60 mg once daily of ID, start with 54 mg of Concerta.

Metadate CD. Metadate CD is available in 20-mg capsules that contain immediate-release and delayed-release beads. The beads release 30% of the dose rapidly, and the remaining 70% four hours later. As a result, plasma levels peak twice—at 1.5 and 4.5 hours. This is the same pattern produced by taking SD methylphenidate twice daily. For ADHD patients *not* already taking methylphenidate, the initial dosage is 20 mg once daily in the morning. This can be gradually increased to a maximum of 60 mg once daily. For patients who *are* already taking methylphenidate, start with 20 mg of Metadate once daily (for those taking 10 mg of SD methylphenidate twice daily), or with 40 mg of Metadate once daily (for those taking 20 mg of SD methylphenidate twice daily). If needed, Metadate CD capsules can be opened and sprinkled on a small amount of soft food (eg, applesauce) just prior to ingestion.

Biphentin. Like Metadate CD, Biphentin is formulated in capsules (10, 20, 30, 40, 50, and 60 mg) that contain immediate-release and delayed-release beads. Therapeutic effects begin rapidly and persist for 8 to 10 hours. The capsules may be swallowed intact, or opened to permit sprinkling the beads onto applesauce or some other soft food. Biphentin capsules are approved for treating ADHD in children, adolescents, and adults.

Ritalin LA. Ritalin LA is formulated as extended-release capsules (10, 20, 30, and 40 mg). The product is much like Metadate CD in that some of the dose is released immediately and the rest 4 hours later. Dosing is done *once daily in the morning*. As with Metadate CD and Concerta, dosage depends on whether the patient is already taking methylphenidate (SD or ID). For children *not* already taking methylphenidate, the initial dosage is 20 mg. Dosage can be gradually increased to a maximum of 60 mg. For children who *are* taking methylphenidate (SD or ID), the initial dosage is as follows:

- For those taking 10 mg twice daily of SD methylphenidate or 20 mg once daily of ID methylphenidate, start with 20 mg of Ritalin LA.
- For those taking 15 mg twice daily of SD, start with 30 mg of Ritalin LA.
- For those taking 20 mg twice daily of SD or 40 mg once daily of ID, start with 40 mg of Ritalin LA.
- For those taking 30 mg twice daily of SD or 60 mg once daily of ID, start with 60 mg of Ritalin LA.

Daytrana. Daytrana—a *transdermal methylphenidate patch*—is the first nonoral treatment for ADHD. Following patch application, blood levels of methylphenidate rise slowly and peak in about 9 hours, after which the patch should be removed. Because of the slow rise, effects are delayed about 2 hours. Furthermore, effects will persist for about 3 hours after patch removal. Daytrana patches are available in four sizes—12.5, 18.75, 25, and 37.5 cm²—that deliver 10, 15, 20, and 30 mg/9 hr, respectively. Treatment should begin with the smallest patch, even in patients already taking methylphenidate PO. If needed, larger patches can be tried at weekly intervals. Patients should apply the patch to the hip in the morning—alternating hips each day—and remove it no more than 9 hours later. (They can remove it sooner to terminate effects early.) Application to inflamed skin or application of heat will accelerate drug absorption, and hence should be avoided. Patients should be informed that bathing, showering, and swimming will not dislodge the patch.

Side effects of the patch are like those of oral methylphenidate, with two exceptions. First, users may experience erythema and pruritus at the application site. Second, exposing the skin to methylphenidate can cause a *hypersensitivity reaction*. If hypersensitivity develops, the patient may be unable to use any methylphenidate formulation—transdermal or oral—ever again.

Dexmethylphenidate

Dexmethylphenidate [Focalin, Focalin XR], a drug for ADHD, is simply the dextro isomer of methylphenidate. As noted, the dextro isomer accounts for most of the pharmacologic activity of methylphenidate, a 50:50 mixture of dextro and levo isomers. Accordingly, the pharmacology of dexmethylphenidate is nearly identical to that of methylphenidate. The only difference is that the dosage of dexmethylphenidate is one-half the dosage of methylphenidate. Dexmethylphenidate is available in SD tablets (2.5, 5, and 10 mg) marketed as *Focalin*, and in LD capsules (5, 10, 15, 20, and 30 mg) marketed as *Focalin XR*. Both formulations may be administered with or without food. For children currently treated with methylphenidate, the initial dosage of dexmethylphenidate is one-half the methylphenidate dosage. For children who are *not* currently being treated, the initial dosage is 2.5 mg twice daily (using Focalin), or 5 mg once daily (using Focalin XR). The maximum dosage is 10 mg twice daily (for Focalin) and 20 mg once daily (for Focalin XR). Dexmethylphenidate is a Schedule II drug and must be dispensed accordingly.

METHYLXANTHINES

The methylxanthines are methylated derivatives of xanthine, hence the family name. As shown in Figure 36-2, these compounds consist of a xanthine nucleus with one or more methyl groups attached. Caffeine, the most familiar member of the family, will serve as our prototype.

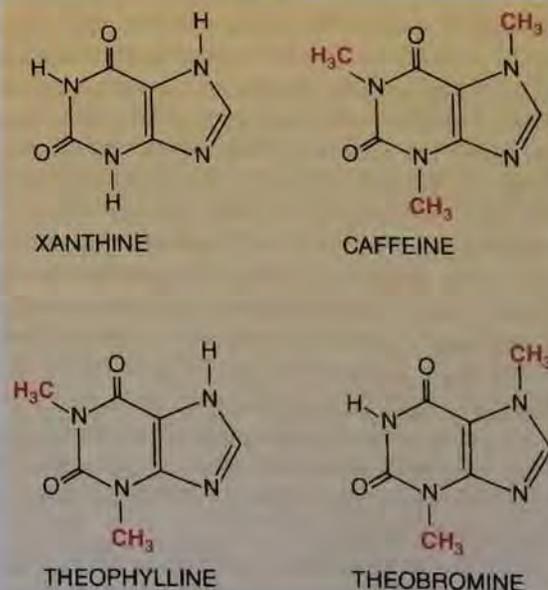


Figure 36-2 • Structural formulas of the methylxanthines.

Caffeine

Caffeine is consumed worldwide for its stimulant effects. In the United States, per capita consumption is about 200 mg/day, mostly in the form of coffee. Although clinical applications of caffeine are few, caffeine remains of interest because of its widespread ingestion for nonmedical purposes.

Dietary Sources

Caffeine can be found in chocolates, desserts, soft drinks, and beverages prepared from various natural products. Common dietary sources are coffee, tea, and cola drinks. The caffeine in cola drinks derives partly from the cola nut and partly from caffeine added by the manufacturer. Caffeine is also present in many noncola soft drinks. The caffeine content of some common foods and beverages is shown in Table 36-1.

Mechanism of Action

Several mechanisms of action have been proposed. These include (1) reversible blockade of adenosine receptors, (2) enhancement of calcium permeability in the sarcoplasmic reticulum, and (3) inhibition of cyclic nucleotide phosphodiesterase, resulting in accumulation of cyclic adenosine monophosphate (cyclic AMP). Blockade of adenosine receptors appears responsible for most effects.

Pharmacologic Effects

Central Nervous System. In low doses, caffeine decreases drowsiness and fatigue and increases the capacity for prolonged intellectual exertion. With increasing dosage, caffeine produces nervousness, insomnia, and tremors. When administered in very large doses, caffeine can cause convulsions. Despite popular belief, there is little evidence that caffeine can restore mental function during intoxication with alcohol, although it might delay passing out.

Heart. High doses of caffeine stimulate the heart. When caffeinated beverages are consumed in excessive amounts, dysrhythmias may result.

Blood Vessels. Caffeine affects blood vessels in the periphery differently from those in the CNS. In the periphery, caffeine promotes *vasodilation*, whereas in the CNS, caffeine promotes *vasoconstriction*. Constriction of cerebral blood vessels is thought to underlie the drug's ability to relieve headache.

Bronchi. Caffeine and other methylxanthines cause relaxation of bronchial smooth muscle, and thereby promote bronchodilation. Theophylline is an especially effective bronchodilator, and hence can be used to treat asthma (see Chapter 76).

Kidney. Caffeine is a diuretic. The mechanism underlying increased urine formation is not fully understood.

Reproduction. Caffeine readily crosses the placenta and may pose a risk of birth defects, although that risk appears low. When applied to cells in culture, caffeine can cause chromosomal damage and mutations. However, the concentrations required are much greater than can be achieved by drinking caffeinated beverages. Also, although there is clear proof that caffeine can cause birth defects in animals, studies have failed to document birth defects in humans. Although caffeine-induced birth defects seem unlikely, caffeine *has* been associated with low birth weight.

According to a meta-analysis reported in 2010, consuming less than 300 mg of caffeine daily does *not* increase the risk of preterm birth. Whether higher doses might increase risk is unclear.

TABLE 36-1 ■ Dietary Caffeine

Product	Amount	Caffeine (mg)
Coffee		
Brewed (typical)	8 oz	60–180
Brewed (Starbucks grande café latte)	16 oz	150
Instant	8 oz	30–120
Espresso	1.5 oz	77
Decaffeinated	8 oz	1–5
Tea		
Brewed (Lipton)	8 oz	35–40
Snapple ice tea	16 oz	48
Celestial Seasonings Herbal Tea, all varieties	8 oz	0
Lipton Natural Brew Iced Tea Mix, decaffeinated	8 oz	<5
Soda		
Jolt Energy Drink	12 oz	71
Mountain Dew	12 oz	55
Diet Coke	12 oz	47
Coca-Cola	12 oz	45
Dr. Pepper	12 oz	41
Orange soda, Sunkist	12 oz	40
Pepsi-Cola	12 oz	37
7-UP	12 oz	0
Sprite	12 oz	0
Concentrated "Energy Drinks"		
Jolt Endurance Shot	2 oz	200
5-Hour Energy	2 oz	138
5150 Juice	1 oz	500
Red Bull Energy Shot	2 oz	80
Spike Double Shot	4.6 oz	350
Caffeinated Water		
Aquafina Alive Energy	16 oz	92
BuzzWater	16.9 oz	200
Krank ₂ O	16.9 oz	100
Water Joe	16.9 oz	60–70
Ice Cream and Yogurt		
Starbucks Coffee Ice Cream	1/2 cup	20–30
Häagen-Dazs Coffee Fudge Ice Cream	1/2 cup	15
Dannon Coffee Yogurt	4 oz	22
Miscellaneous		
Cocoa	8 oz	2–50
Chocolate milk	1.5 oz	3–11
Hershey's Bar (milk chocolate)	1.5 oz	10
Hershey's Special Dark Chocolate Bar	1.5 oz	31
Baker's chocolate	1.5 oz	38–53

Pharmacokinetics

Caffeine is readily absorbed from the GI tract, and achieves peak plasma levels within 1 hour. Plasma half-life ranges from 3 to 7 hours. Elimination is by hepatic metabolism.

Therapeutic Uses

Neonatal Apnea. Premature infants may experience prolonged apnea (lasting 15 seconds or more) along with bradycardia. Hypoxemia and neurologic damage may result. Caf-

feine and other methylxanthines can reduce the number and duration of apnea episodes and can promote a more regular pattern of breathing.

Promoting Wakefulness. Caffeine is used commonly to aid staying awake. The drug is marketed in various over-the-counter preparations [Maximum Strength NoDoz, Vivarin, others] for this purpose. Of course, individuals desiring increased alertness needn't take a pill; they can get just as much caffeine by drinking coffee or some other caffeine-containing beverage.

Other Applications. Intravenous caffeine can help relieve headache induced by spinal puncture. The drug is used orally to enhance analgesia induced by opioids and by nonopioid analgesics (eg, aspirin).

Acute Toxicity

Caffeine poisoning is characterized by intensification of the responses seen at low doses. Stimulation of the CNS results in excitement, restlessness, and insomnia; if the dosage is very high, convulsions may occur. Tachycardia and respiratory stimulation are likely. Sensory phenomena (ringing in the ears, flashing lights) are common. Death from caffeine overdose is rare. When fatalities have occurred, between 5 and 10 gm have been ingested.

Preparations, Dosage, and Administration

For Promoting Wakefulness. Caffeine is available in three formulations for promoting wakefulness: 200-mg tablets, 200-mg capsules, and 75-mg lozenges. The usual dosage is 100 to 200 mg every 3 to 4 hours as needed.

For Neonatal Apnea. Caffeine citrate [Cafcit] is used for neonatal apnea. The drug is available in oral and IV solutions. Both have the same concentration: 20 mg/mL. Treatment consists of an IV loading dose (20 mg/kg) followed every 24 hours by an oral or IV maintenance dose (5 mg/kg). *Note:* The amount of caffeine base in a 20-mg dose of caffeine citrate is only 10 mg (ie, one-half of the total dose on a milligram basis).

Theophylline

Theophylline has pharmacologic actions much like those of caffeine. Like caffeine, theophylline is an effective CNS stimulant. However, in contrast to caffeine, theophylline is not used for its CNS effects. Rather, theophylline is used to treat asthma. Benefits derive from causing bronchodilation. Use in asthma is discussed in Chapter 76.

Theobromine

Theobromine is a methylxanthine that occurs naturally in the seeds of *Theobroma cacao*, from which cocoa and chocolate are made. The caffeine content of these seeds is relatively low. Although there are similarities between theobromine and caffeine, these compounds do differ. The most distinct difference is that caffeine is a more effective CNS stimulant. Accordingly, CNS excitation produced by ingestion of cocoa and chocolate derives primarily from their caffeine content and not from theobromine. Toxicity from theobromine in chocolate is discussed in Box 36-1.

MISCELLANEOUS CNS STIMULANTS

Modafinil

Therapeutic Use. Modafinil [Provigil, Alertec[®]], a unique nonamphetamine stimulant, is approved for promoting wakefulness in patients with excessive sleepiness associated with three disorders: narcolepsy, shift-work sleep disorder (SWSD), and obstructive sleep apnea/hypopnea syndrome (OSAHS). However, although the drug has only three approved uses, most prescriptions (95%) are written for off-label uses, including fatigue, depression, ADHD, jet lag, and sleepiness caused by medications. Investigational uses include ADHD and fatigue associated with multiple sclerosis. The military is studying the drug for use in situations that might require alertness for an extended time. And some people are using it just to stay awake so they can work more or play more.

In clinical trials, modafinil has been moderately effective. In patients with narcolepsy, modafinil increased wakefulness, but only to about 50% of the level seen in normal people. In contrast, methylphenidate and dextroamphetamine increase wakefulness to about 70% of normal. In patients with SWSD and OSAHS, benefits are about the same as those seen in narcolepsy.

Mechanism of Action. How does modafinil ward off sleep? No one knows. The drug does seem to influence hypothalamic areas involved in maintaining the normal sleep-wakefulness cycle. Also, there is evidence that modafinil inhibits the activity of sleep-promoting neurons (in the ventrolateral preoptic nucleus) by blocking reuptake of norepinephrine.

Pharmacokinetics. Modafinil is rapidly absorbed from the GI tract. Plasma levels peak in 2 to 4 hours. Food decreases the rate of absorption but not the extent. Elimination is by hepatic metabolism followed by renal excretion. The half-life is about 15 hours.

Adverse Effects. Modafinil is generally well tolerated. The most common adverse effects are headache, nausea, nervousness, diarrhea, and rhinitis. Modafinil does not disrupt nighttime sleep. In clinical trials, only 5% of patients dropped out because of undesired effects. Initially, the drug was believed devoid of cardiovascular effects. However, we now know it can increase heart rate and blood pressure, apparently by altering autonomic function. Subjective effects—euphoria; altered perception, thinking, and feeling—are like those of other CNS stimulants. However, modafinil has less abuse potential, and hence is regulated as a Schedule IV substance. Physical dependence and withdrawal have not been reported. Modafinil is embryotoxic in laboratory animals, and hence should be avoided during pregnancy.

Postmarketing reports link modafinil to rare cases of serious skin reactions, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis. Patients should be informed about signs of these reactions—swelling or rash, especially in the presence of fever or changes in the oral mucosa—and instructed to discontinue the drug if they develop.

Drug Interactions. Modafinil inhibits some forms of cytochrome P450 (CYP) and induces others. Induction of CYP3A4 may accelerate the metabolism of oral contraceptives, cyclosporine, and certain other drugs, thereby causing their levels to decline. Caution is advised.

Preparations, Dosage, and Administration. Modafinil is available in 100- and 200-mg tablets. For patients with narcolepsy or OSAHS, the usual dosage is 200 mg/day, taken as a single dose in the morning. For patients with SWSD, the usual dosage is 200 mg/day, taken as a single dose 1 hour before the shift starts. For patients with severe hepatic impairment, doses should be decreased by 50%. Dosage reduction may also be needed in the elderly.

Armodafinil

Armodafinil [Nuvigil] is simply the *R*-enantiomer of modafinil, a mixture of *R*- and *S*-enantiomers. Armodafinil differs from modafinil in that the *R*-enantiomer (armodafinil) has a somewhat longer half-life than the *S*-enantiomer component of modafinil. Otherwise, the two drugs are essentially identical, although armodafinil costs more. Armodafinil has the same indications as modafinil—improving wakefulness in people with narcolepsy, SWSD, and OSAHS—and has similar adverse effects, including the potential for rare but severe skin reactions. Like modafinil, armodafinil is classified as a Schedule IV substance. Armodafinil is available in 50-, 150-, and 250-mg tablets. The recommended dosage for narcolepsy and OSAHS is 150 or 250 mg, taken in the morning. The recommended dosage for SWSD is 150 mg, taken 1 hour before the work shift.

Strychnine

Strychnine was introduced in the 16th century as a rat poison. At one time the drug was also employed therapeutically. Although strychnine is no longer used as a medicine, it remains a source of accidental poisoning.

Strychnine is a powerful convulsant that stimulates the CNS at all levels. Stimulation results from blockade of receptors for glycine, an inhibitory neurotransmitter.

Strychnine Poisoning

Causes. A common cause of strychnine poisoning is accidental ingestion of strychnine-based rodenticides. Poisoning also occurs through the use of "street drugs" to which strychnine has been added. (Since strychnine does not enhance the effects of illicit drugs, the practice of mixing this agent with street drugs is not only dangerous, it also lacks any pharmacologic rationale.) The lethal dose is about 15 mg in children, and 50 to 100 mg in adults.

Symptoms. The first manifestation of poisoning is stiffness in the muscles of the face and neck. This is followed by a generalized increase in reflex excitability. During the early stages of poisoning, the victim is fully conscious. As poisoning progresses, convulsions occur. Strychnine-induced convulsions are characterized by tonic contraction of all voluntary muscles; contraction of the diaphragm, abdominal muscles, and thoracic muscles stops respiration. Convulsive episodes alternate with periods of depression until the victim dies or until the poisoning is successfully treated. Few patients survive

DID KISSES KILL CALVIN?

Well ...no. But they might have. Calvin, recently deceased, was a happy little Jack Russell terrier who lived with Nancy, my very significant other, on her horse farm here in central Virginia. Our country squire graciously shared his home with sundry horses and ponies, gaggles of geese, and his dearest friends: Gucci, Hannah, Sandy, and Lucy—Nancy's other four dogs. Calvin enjoyed a rich, tranquil, contented life, until being mortally wounded while defending his home and friends from a canine intruder. We loved our little man. And we miss him.

So, what's the connection between Calvin and lethal kisses? One day, when I tossed Calvin a Hershey's Chocolate Kiss, Nancy became horrified and demanded I stop. "Why?" I asked. "Because," she said, "chocolate is poisonous to dogs. Didn't you know?" Right. Death by chocolate. Needless to say, this pharmacologist was skeptical. So I did some reading. Turns out, Nancy was correct: Chocolate really can kill dogs. What follows is for readers who, like me, didn't know that chocolate could hurt those we love.

Why is chocolate toxic? Because it contains two methylxanthines: *theobromine* and *caffeine*. Both drugs are stimulants that can cause seizures and cardiac dysrhythmias. In the absence of treatment, death can result. Although both compounds are of concern, chocolate contains much more theobromine than caffeine. Accordingly, our discussion focuses on theobromine.

Why is theobromine toxic to dogs but not us? Because dogs eliminate this compound very slowly: In dogs, the half-life of theobromine is 17.5 hours, compared with only 2 hours in humans. Because of delayed elimination, theobromine climbs to higher levels in dogs, and remains at those high levels a long time. If humans took theobromine in big enough doses, it would hurt us too.

What are the symptoms of theobromine/chocolate poisoning? Initial symptoms, which typically develop in 6 to 12 hours, include vomiting, diarrhea, restlessness, and excessive fluid intake. Later symptoms involve the CNS (hyperactivity, incoordination, disturbed balance, tremors, seizures, coma), cardiovascular system (premature ventricular contractions, tachycardia or bradycardia, hypertension or hypotension), oxygenation (rapid breathing, cyanosis), and thermoregulation (hyperthermia). Symptoms may persist for 72 hours. Death, if it occurs, is usually from dysrhythmias, hyperthermia, or respiratory failure.

How is theobromine poisoning treated? There is no specific antidote to theobromine, so treatment is directed at symptom control and poison removal. Tremors and mild seizures can be controlled with diazepam. Severe seizures may require a barbiturate. Tachydysrhythmias can be controlled with a beta blocker (eg, metoprolol), bradydysrhythmias with

atropine, and refractory ventricular dysrhythmias with lidocaine. Once the victim is stabilized—or if symptoms have not yet appeared—decontamination should be implemented. Theobromine can be removed from the stomach by gastric

lavage, or by inducing emesis with apomorphine. Activated charcoal can prevent further absorption from the stomach and intestine. Inducing diuresis with fluids can accelerate excretion of theobromine in the urine.

How much chocolate is lethal? To answer this question, we need to know two things: (1) the average lethal dose (LD_{50}) for theobromine in dogs and (2) the theobromine content of various types of chocolate. In dogs, the LD_{50} for theobromine is about 100 mg/kg body weight (45 mg/lb). Put another way, it takes about 450 mg of theobromine to kill a 10-pound dog. The approximate theobromine content of chocolate types is as follows:

- White chocolate—1 mg/ounce
- Milk chocolate—50 mg/ounce
- Semisweet chocolate—150 mg/ounce
- Unsweetened baker's chocolate—450 mg/ounce

These numbers indicate that, in order to get a lethal dose of theobromine (450 mg), a 10-pound dog would have to ingest the following:

- White chocolate—450 ounces (28 pounds), which is impossible.
- Milk chocolate—9 ounces (0.6 lb), which equals the chocolate in 3 average candy bars. Easy for a dog who likes candy.
- Semisweet chocolate—only 3 ounces.
- Unsweetened baker's chocolate—just one 1-ounce square.

From this information, it's clear that giving Calvin a Chocolate Kiss or two was safe, despite Nancy's alarm. However, it's also clear that it doesn't take a basket of candy to do serious harm. In fact, although the LD_{50} for theobromine is 100 mg/kg, significant reactions can develop at much lower doses. For example, at 20 mg/kg, vomiting and diarrhea can develop; at 40 to 50 mg/kg, cardiotoxicity can develop; and at doses above 60 mg/kg, seizures may develop. Accordingly, it would seem prudent to keep your entire chocolate stash in a doggy-proof place, especially if your little friend is a chocaholic.

So, Dr. Lehne, is chocolate really going to kill my dog—or better yet, my neighbor's little yapper? Probably not. Fact is, fatal chocolate poisoning is rare. Nonetheless, chocolate poisoning is the most common reason for calls to the ASPCA's *Animal Poison Control Center* (APCC), which, for a small fee, can provide professional assistance 24 hours a day, 7 days a week. So, the next time your dog scarf's up an entire pan of brownies, you can call the APCC at 1-888-426-4435 for immediate help.



beyond the fifth convulsive episode; some are killed by the first. Death is from respiratory arrest.

Treatment. Management is directed primarily at controlling convulsions and supporting respiration. Intravenous diazepam is the treatment of choice to suppress convulsions. If poisoning is severe, general anesthesia or neuromuscular blockade may be needed to eliminate convulsions. If anticonvulsant therapy fails to permit adequate breathing, mechanical support of respiration is indicated.

Doxapram

Doxapram [Dopram] stimulates the CNS at all levels. The drug is employed clinically to stimulate respiration. However, since the doses required are close to those that can produce generalized CNS stimulation and convulsions, doxapram must be used with great care. Furthermore, although doxapram is labeled for treatment of general CNS depressant poisoning, its use for this purpose should be discontinued: Experience has shown that respiratory depression from CNS depressant poisoning can be managed more safely and effectively with mechanical support of ventilation than with pharmacologic stimulation of respiration.

Cocaine

Cocaine is a powerful CNS stimulant with a high potential for abuse. The only clinical application of this drug—local anesthesia—is discussed in Chapter 26. The basic pharmacology of cocaine and cocaine abuse are discussed in Chapter 40.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Our discussion of ADHD has two parts. We begin by addressing basic concepts in ADHD—specifically, signs and symptoms, etiology, and treatment strategy. After that, we discuss the pharmacology of the drugs used for treatment.

BASIC CONSIDERATIONS

ADHD in Children

ADHD is the most common neuropsychiatric disorder of childhood, affecting 8% to 9% of school-age children. The incidence in boys is 2 to 3 times the incidence in girls. Symptoms begin between ages 3 and 7, usually persist into the teens, and often persist on into adulthood. The majority (60% to 70%) of children respond well to stimulant drugs. Methylphenidate [Ritalin, Concerta, others] is the agent employed most.

Signs and Symptoms

ADHD is characterized by *inattention*, *hyperactivity*, and *impulsivity*. Affected children are fidgety, unable to concentrate on schoolwork, and unable to wait their turn; switch excessively from one activity to another; call out excessively in class; and never complete tasks. To make a diagnosis, symptoms must appear prior to age 7 and be present for at least 6 months. Since other disorders—especially anxiety and depression—may cause similar symptoms, diagnosis must be done carefully.

Specific diagnostic criteria for ADHD are set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The criteria now in use, published in the fourth edition of the DSM (DSM-IV), were released in 1994. Revised criteria will appear in fifth edition of the DSM (DSM-5), scheduled for release in 2013. The proposed DSM-5 criteria, which are much like those in DSM-IV, are summarized in Table 36-2. In both DSM-IV and DSM-5, ADHD can be subclassified as predominately inattentive type, predominately

hyperactive-impulsive type, or combined type, depending on symptom profile. Former names for ADHD—*hyperkinetic syndrome* and *minimal brain dysfunction*—are misleading and have been abandoned.

Etiology

Although various theories have been proposed, the underlying pathophysiology of ADHD is only partially understood. Neuroimaging studies indicate structural and functional abnormalities in multiple brain areas, including the frontal cortex, basal ganglia, brainstem, and cerebellum—regions involved with regulating attention, impulsive behavior, and motor activity. Several theories implicate dysregulation in neuronal pathways that employ NE, DA, and serotonin as transmitters. These theories would be consistent with the effects of atomoxetine (which blocks NE reuptake), imipramine (which blocks NE and serotonin uptake), and stimulant drugs (which promote release of NE and DA and, to some degree, block their uptake). Genetic factors play a very important role.

Management Overview

Multiple strategies may be employed to manage ADHD. In addition to drugs, which are considered first-line treatment, the management program can include family therapy, parent training, and cognitive therapy for the child. Guidelines issued by the American Academy of Pediatrics emphasize the importance of a comprehensive treatment program, involving collaboration among clinicians, families, and educators. For long-term gains, a combination of cognitive therapy and stimulant drugs appears most effective. Of the drugs employed for ADHD, stimulants are most effective, and hence are considered agents of choice. The nonstimulants (eg, atomoxetine, guanfacine, clonidine) are less effective than stimulants, and hence are considered second-choice drugs.

ADHD in Adults

In about 30% to 60% of cases, childhood ADHD persists into adulthood. In the United States, about 10 million adults are afflicted, although an estimated 90% are undiagnosed and untreated. Symptoms include poor concentration, stress intolerance, antisocial behavior, outbursts of anger, and inability to maintain a routine. Also, adults with ADHD experience more job loss, divorce, and driving accidents. As in childhood ADHD, therapy with a stimulant drug is the foundation of treatment. Methylphenidate is prescribed most often. About 33% of adults fail to respond to stimulants or cannot tolerate their side effects. For these patients, a trial with a nonstimulant may help. Combining behavioral therapy with drug therapy may be more effective than drug therapy alone.

DRUGS USED FOR ADHD

CNS Stimulants

Stimulant drugs are the mainstay of ADHD therapy. Drugs with proven efficacy include *methylphenidate* [Ritalin, Concerta, others], *dexmethylphenidate* [Focalin], *dextroamphetamine* [DextroStat, others], *amphetamine mixture* [Adderall] and *lisdexamfetamine* [Vyvanse]. There are no data to support

TABLE 36-2 ■ Proposed DSM-5 Diagnostic Criteria for ADHD

The disorder consists of a characteristic pattern of behavior and cognitive functioning that is present in different settings where it gives rise to social and educational or work performance difficulties. The manifestations of the disorder and the difficulties that they cause are subject to gradual change, being typically more marked during times when the person is studying or working and lessening during vacation.

Superimposed on these short-term changes are trends that may signal some deterioration or improvement, with many symptoms becoming less common in adolescence. Although irritable outbursts are common, abrupt changes in mood lasting for days or longer are not characteristic of ADHD and will usually be a manifestation of some other distinct disorder.

A. Either (1) and/or (2).

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that impacts directly on social and academic/occupational activities. For older adolescents and adults (age 17 and older), only 4 symptoms are required.

- (a) Often **fails to give close attention to details** or makes careless mistakes in schoolwork, at work, or during other activities.
- (b) Often has **difficulty sustaining attention** in tasks or play activities.
- (c) Often **does not seem to listen** when spoken to directly.
- (d) Often **does not follow through** on instructions (starts tasks but quickly loses focus and is easily sidetracked, fails to finish schoolwork, household chores, or tasks in the workplace).
- (e) Often has **difficulty organizing tasks** and activities. (Has difficulty managing sequential tasks and keeping materials and belongings in order. Work is messy and disorganized. Has poor time management and tends to miss deadlines.)
- (f) Is **reluctant to engage in tasks that require sustained mental effort**.
- (g) Often **loses items** necessary for tasks or activities.
- (h) Is **easily distracted** by extraneous stimuli (for older adolescents and adults may include unrelated thoughts).
- (i) Is often **forgetful** in daily activities, chores, and running errands (for older adolescents and adults, returning calls, paying bills, and keeping appointments).

2. **Hyperactivity and Impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that impacts directly on social and academic/occupational activities. For older adolescents and adults (age 17 and older), only 4 symptoms are required.

- (a) Often **fidgets** or taps hands or feet or squirms in seat.
- (b) Is often **restless** during activities when others are seated (eg, may leave his or her place in the classroom, office, or other workplace).
- (c) Often **runs about** or climbs on furniture and moves excessively in inappropriate situations. In adolescents or adults, may be limited to feeling restless or confined.
- (d) Is often **excessively loud** or noisy during play, leisure, or social activities.
- (e) Is often **"on the go,"** acting as if "driven by a motor." Is uncomfortable being still for an extended time, as in

restaurants, meetings, etc. Seen by others as being restless and difficult to keep up with.

- (f) Often **talks excessively**.
- (g) Often **blurts out an answer** before a question has been completed. Older adolescents or adults may complete people's sentences and "jump the gun" in conversations.
- (h) Has **difficulty waiting his or her turn** or waiting in line.
- (i) Often **interrupts or intrudes** on others (frequently butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; adolescents or adults may intrude into or take over what others are doing).
- (j) Tends to **act without thinking**, such as starting tasks without adequate preparation or avoiding reading or listening to instructions. May speak out without considering consequences. May make important decisions on the spur of the moment, such as impulsively buying items, suddenly quitting a job, or breaking up with a friend.
- (k) Is often **impatient**, as shown by feeling restless when waiting for others and wanting to move faster than others, wanting people to get to the point, speeding while driving, and cutting into traffic to go faster than others.
- (l) Is **uncomfortable doing things slowly and systematically** and often rushes through activities or tasks.
- (m) Finds it **difficult to resist temptations or opportunities**, even if it means taking risks. (A child may grab toys off a store shelf or play with dangerous objects; adults may commit to a relationship after only a brief acquaintance or take a job or enter into a business arrangement without doing due diligence).

- B. Several noticeable inattentive or hyperactive-impulsive symptoms were present by age 12.
- C. The symptoms are apparent in two or more settings (e.g., at home, school, or work, or with friends or relatives).
- D. There must be clear evidence that the symptoms interfere with or reduce the quality of social, academic, or occupational functioning.
- E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

Specify Based on Current Presentation

Combined Presentation: If both Criterion A1 (Inattention) and Criterion A2 (Hyperactivity and Impulsivity) are met for the past 6 months.

Predominately Inattentive Presentation: If Criterion A1 (Inattention) is met but Criterion A2 (Hyperactivity and Impulsivity) is not met and three or more symptoms from Criterion A2 have been present for the past 6 months.

Predominately Hyperactive/Impulsive Presentation: If Criterion A2 (Hyperactivity and Impulsivity) is met and Criterion A1 (Inattention) is not met for the past 6 months.

Inattentive Presentation (Restrictive): If Criterion A1 (Inattention) is met but no more than two symptoms from Criterion A2 (Hyperactivity and Impulsivity) have been present for the past 6 months.

Modified from the proposed diagnostic criteria for ADHD, to be published in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on November 18, 2010.

TABLE 36-3 ■ Major Drugs for Attention-Deficit/Hyperactivity Disorder

Drug	Trade Name	Duration (hr)	Dosing Schedule	Usual Pediatric Maintenance Dosage
STIMULANTS				
Methylphenidate				
Short-duration	Ritalin Methylin	3-5	2 or 3 times daily	10 mg at 8:00 AM and noon, and 5 mg at 4:00 PM
Intermediate-duration	Ritalin SR Metadate ER Methylin ER	6-8	Once or twice daily	20 or 40 mg in AM plus 20 mg in the early PM if needed
Long-duration	Concerta Metadate CD Ritalin LA Daytrana	10-12 8-12 8-12 10-12	Once daily Once daily Once daily Once daily	36 mg in AM 30 mg in AM 30 mg in AM One 15- or 20-mg patch, applied in the AM and removed 9 hr later
Dexmethylphenidate				
Short-duration	Focalin	4-5	Twice daily	10 mg in the AM plus 10 mg in the early PM
Long-duration	Focalin XR	12	Once daily	10 mg in the AM
Dextroamphetamine				
Short-duration	DextroStat	4-6	2 or 3 times daily	5 mg at 8:00 AM, noon, and 4:00 PM
Long-duration	Dexedrine Spansules	6-10	Once or twice daily	10 mg at 8:00 AM
Amphetamine Mixture				
Short-duration	Adderall	4-6	Twice daily	5 mg in AM and 5 hr later
Long-duration	Adderall-XR	10-12	Once daily	20 mg in AM
Lisdexamfetamine				
Long-duration	Vyvanse	10-12	Once daily	30 mg in AM
NONSTIMULANTS				
Atomoxetine	Strattera	24	Once or twice daily	80 mg in AM or 40 mg in AM and early PM
Guanfacine	Intuniv	24	Once daily	1-4 mg in AM
Clonidine	Kapvay	24	Twice daily	0.1-0.2 mg in the AM and PM

use of one stimulant over another. If one stimulant is ineffective, another should be tried before considering a second-line agent.

The response to stimulants can be dramatic. These drugs can increase attention span and goal-oriented behavior while decreasing impulsiveness, distractibility, hyperactivity, and restlessness. Tests of cognitive function (memory, reading, arithmetic) often improve significantly. Unfortunately, although benefits can be dramatic initially, they diminish after 2 to 3 years, as reported in a 2009 paper: *MTA at 8 Years: Prospective Follow-up of Children Treated for Combined-Type ADHD in a Multisite Study*. Nonetheless, stimulant therapy can still buy time to teach youngsters behavioral strategies to help them combat inattention and hyperactivity over the long term.

Although reduction of impulsiveness and hyperactivity with a stimulant may seem paradoxical—it isn't. Stimulants don't suppress rowdy behavior directly. Rather, they improve attention and focus. Impulsiveness and hyperactivity decline because the child is now able to concentrate on the task at hand. It should be noted that stimulants do not create *positive*

behavior; they only reduce *negative* behavior. Accordingly, stimulants cannot give a child good study skills and other appropriate behaviors. Rather, these must be learned once the disruptive behavior is no longer an impediment.

The dosing schedule employed is important, and is determined by the time course of the formulation selected. As discussed above (and shown in Table 36-3), CNS stimulants are available in short-, intermediate-, and long-duration formulations. With the SD and ID formulations, the child usually takes two or three doses a day. In contrast, the LD formulations are taken just once a day (in the morning). Not only is once-daily dosing more convenient, it spares the child any embarrassment or stigma associated with taking medicine at school. Accordingly, LD formulations (eg, Adderall-XR, Concerta, Daytrana) are generally preferred. With all formulations, dosage should be low initially and then gradually increased. Maintenance dosage is determined by monitoring for improvement in symptoms and appearance of side effects.

Principal adverse effects of the stimulants are *insomnia* and *growth suppression*. Insomnia results from CNS stimula-

tion, and can be minimized by reducing the size of the afternoon dose and taking it no later than 4:00 PM. Growth suppression occurs secondary to appetite suppression. Growth reduction can be minimized by administering stimulants during or after meals (which reduces the impact of appetite suppression). In addition, some clinicians recommend taking “drug holidays” on weekends and in the summer (which creates an opportunity for growth to catch up). However, other clinicians argue against this strategy. Why? Because depriving children of medication during these unstructured times can be hard on them. When stimulants are discontinued, a rebound increase in growth will take place; as a result, adult height may not be affected. Other adverse effects include *headache* and *abdominal pain*, which have an incidence of 10%, and *lethargy* and *listlessness*, which can occur when dosage is excessive.

Nonstimulants

Several nonstimulants are used for ADHD, although only three of them—atomoxetine, guanfacine, and clonidine—are FDA approved for this use. The nonstimulants are less effective than the stimulants, and hence are considered second-choice drugs. For treatment of ADHD, the nonstimulants may be employed as monotherapy, or as add-on therapy with a stimulant. Unlike the stimulants, the nonstimulants are not regulated as controlled substances.

Atomoxetine, a Norepinephrine Uptake Inhibitor

Description and Therapeutic Effects. Atomoxetine [Strattera] is a unique drug approved for ADHD in children and adults. It was the first *nonstimulant* approved for ADHD,* and one of only three drugs approved for ADHD in adults (the others are amphetamine mixture [Adderall XR] and lisdexamfetamine [Vyvanse]). In contrast to the CNS stimulants, atomoxetine has no potential for abuse, and hence is not regulated as a controlled substance. As a result, prescriptions can be refilled over the phone, making atomoxetine more convenient than the stimulants. Like the long-acting stimulants, atomoxetine can be administered just once a day.

In clinical trials comparing atomoxetine with placebo in children or adults with ADHD, atomoxetine was clearly superior at reducing symptoms. Benefits were similar whether the drug was given once a day or in two divided doses. It should be noted that responses develop slowly: The initial response takes a few days to develop, and the maximal response is seen in 1 to 3 weeks. This contrasts with the CNS stimulants, whose effects are near maximal with the first dose.

How does atomoxetine compare with stimulants for treating children with ADHD? In two older 3-week randomized trials, comparing atomoxetine with either methylphenidate [Concerta] or an amphetamine [Adderall XR], the stimulants were superior: More children responded to the stimulants, symptom reduction was greater, and benefits developed more quickly. In 2008, these results were reinforced in a large, 6-week, placebo-

controlled trial, in which a stimulant—methylphenidate [Concerta]—was again clearly superior to atomoxetine.

Mechanism of Action. Atomoxetine is a *selective inhibitor of NE reuptake*, and hence causes NE to accumulate at synapses. Although the precise relationship between this neurochemical action and symptom relief is unknown, it would appear that *adaptive changes* that occur following uptake blockade underlie benefits. Why? Because uptake blockade occurs immediately, whereas full therapeutic effects are not seen for at least a week—suggesting that, after uptake blockade occurs, additional processes must take place before benefits can be seen.

Pharmacokinetics. Atomoxetine is rapidly and completely absorbed following oral administration. Plasma levels peak in 1 to 3 hours, depending on whether the drug was taken without or with food. Atomoxetine is metabolized in the liver, primarily by CYP2D6 (the 2D6 isozyme of cytochrome P450). For most patients, the half-life is 5 hours. However, for 5% to 10% of patients, the half-life is much longer: 24 hours. Why? Because they have an atypical form of CYP2D6, which metabolizes atomoxetine slowly. Dosage should be reduced in these people.

Adverse Effects. Like the CNS stimulants, atomoxetine is generally well tolerated. In clinical trials, the most common effects were GI reactions (dyspepsia, nausea, and vomiting), reduced appetite, dizziness, somnolence, mood swings, and trouble sleeping. Sexual dysfunction and urinary retention were seen in adults. Severe allergic reactions, including angioneurotic edema, occurred rarely. If allergy develops, patients should discontinue the drug and contact their prescriber immediately.

Atomoxetine may cause *suicidal thinking* in children and adolescents, but not in adults. Fortunately, the incidence is relatively low: about 4 cases per 1000 patients. Risk is greatest during the first few months of treatment. Young patients should be monitored closely for suicidal thinking and behavior, and for signs of clinical worsening (eg, agitation, irritability).

Appetite suppression may result in *weight loss and growth retardation*. Among children who took atomoxetine for 18 months or longer, mean height and weight percentiles declined. Because experience with the drug is limited, we don't know if expected adult height will be affected. Nor do we know if “drug holidays” would have an impact on growth.

Atomoxetine poses a small risk of *severe liver injury* that may progress to outright liver failure, resulting in death or the need for a liver transplant. Patients should be informed about signs of liver injury—jaundice, dark urine, abdominal tenderness, unexplained flu-like symptoms—and instructed to report these immediately. In the event of jaundice or laboratory evidence of liver injury, atomoxetine should be discontinued.

Atomoxetine may raise or lower blood pressure. During clinical trials, some patients experienced a small increase in blood pressure and heart rate. Accordingly, atomoxetine should be used with caution by patients with hypertension or tachycardia. During postmarketing surveillance, some patients experienced *hypotension and syncope* (fainting). Patients should be informed of this possibility and advised to sit or lie down if they feel faint.

*Some older nonstimulants, such as imipramine and bupropion, although used for ADHD, are not actually approved for ADHD.

Drug Interactions. Combining atomoxetine with a *monoamine oxidase inhibitor* (eg, isocarboxazid [Marplan], phenelzine [Nardil]) can cause hypertensive crisis, owing to accumulation of NE at synapses in the periphery. Accordingly, these drugs must not be used together or within 3 weeks of each other.

Inhibitors of CYP2D6 can increase levels of atomoxetine, and hence must be used with caution. Common examples include paroxetine [Paxil], fluoxetine [Prozac], and quinidine.

Role in ADHD Therapy. Because atomoxetine is a relatively new drug, its role in ADHD has not been firmly established. Yes, atomoxetine appears both safe and effective, and it lacks the potential for abuse. However, we have little information on its long-term dangers, including detrimental effects on growth. Furthermore, stimulants work better. Accordingly, because CNS stimulants are more effective and have a long record of safety and efficacy, it would seem prudent to reserve atomoxetine for patients who are unresponsive to or intolerant of the stimulants. In the absence of a compelling reason, patients doing well on the stimulants shouldn't switch.

Preparations, Dosage, and Administration. Atomoxetine [Strattera] is available in capsules (10, 18, 25, 40, 60, 80, and 100 mg) that should be swallowed whole, with or without food. Dosage is based on body weight as follows:

- Children who weigh *less than 70 kg*—Start with 0.5 mg/kg/day and then, after at least 3 days, increase to the recommended target of 1.2 mg/kg/day. The maximum dosage is 1.4 mg/kg/day or 100 mg, whichever is smaller.
- Children who weigh *more than 70 kg and all adults*—Start with 40 mg/day and then, after at least 3 days, increase to the recommended target of 80 mg/day. Do not exceed 100 mg/day.

Two dosing schedules may be used: Patients may either (1) take the total daily dose all at once in the morning or (2) divide the dosage up, taking half in the morning and half in the late afternoon or early evening. Note that, with either schedule, dosing during school hours is unnecessary.

Dosage should be reduced in patients who are slow metabolizers, either because of hepatic insufficiency or atypical CYP2D6.

Alpha₂-Adrenergic Agonists

Two alpha₂-adrenergic agonists—guanfacine and clonidine—were recently approved for ADHD. Both drugs appear less effective than CNS stimulants. Principal side effects are sedation, hypotension, and fatigue. Unlike the CNS stimulants, guanfacine and clonidine are not controlled substances, and do not cause anorexia or insomnia. The basic pharmacology of these drugs is discussed in Chapter 19 (Indirect-Acting Antiadrenergic Agents).

Guanfacine. Originally approved for hypertension, guanfacine has been used off-label in ADHD for years. In 2009, the FDA approved a new extended-release (ER) formulation, sold as *Intuniv*, for treating children and adolescents with ADHD. In clinical trials, ER guanfacine improved hyperactivity and inattention. Benefits were greater than with placebo, but less than reported with stimulants. How does guanfacine work? We're not sure. We do know that guanfacine activates presynaptic alpha₂-adrenergic receptors in the brain. However, we don't know how this action relates to clinical benefits. Principal side effects are somnolence, fatigue, and reduced blood pressure. Effects on blood pressure are most pronounced during initial therapy, and whenever dosage is increased. Abrupt discontinu-

ation can cause rebound hypertension. In contrast to the stimulants, guanfacine causes weight gain rather than weight loss, causes somnolence rather than insomnia, and is not regulated under the Controlled Substances Act. Who should receive guanfacine? Since the drug does not cause anorexia or insomnia, it might be especially good for children who cannot tolerate these effects of stimulants. Guanfacine can also be combined with a stimulant to treat severe ADHD.

For treatment of ADHD, guanfacine [Intuniv] is available in ER tablets (1, 2, 3, and 4 mg), which should be swallowed intact, without chewing, cutting, or crushing. Dosing with a high-fat meal increases absorption and should be avoided. Dosage starts at 1 mg/day for at least 1 week, and can be increased at intervals of 1 week (or longer) by 1 mg/day. Children switching from immediate-release guanfacine should use the same titration schedule, regardless of the dosage they had been taking. For all children, the maximum dosage is 4 mg/day. When guanfacine is discontinued, dosage should be tapered by 1 mg/day every 3 to 7 days. Abrupt discontinuation should be avoided, owing to a risk of rebound hypertension. The immediate-release formulation used for hypertension, sold as *Tenex*, is discussed in Chapter 19.

Clonidine. Extended-release clonidine [Kapvay], approved for ADHD in 2010, is much like ER guanfacine [Intuniv]. Both drugs are alpha₂ agonists, both were developed for hypertension, and both had been used off-label in ADHD for years. In clinical trials of ADHD, ER clonidine was superior to placebo when used alone, and provided additional symptom relief when combined with a stimulant. As with guanfacine, principal side effects are somnolence, fatigue, and hypotension. Somnolence can be made worse by alcohol and other CNS depressants. Hypotension can be made worse by antihypertensive agents. Because clonidine can lower blood pressure (and slow heart rate too), blood pressure and heart rate should be measured at baseline, following each dose increase, and periodically thereafter. Like guanfacine, clonidine does not cause anorexia or insomnia, and is not a controlled substance. For treatment of ADHD, clonidine [Kapvay] is supplied in 0.1- and 0.2-mg ER tablets, which should be swallowed whole without crushing, cutting, or chewing. Dosing may be done with or without food. The initial dosage is 0.1 mg in the evening, and the maximum dosage is 0.2 mg twice a day. Dosage is titrated, at intervals of 1 week or longer, as follows:

- 0.1 mg in PM
- 0.1 mg in AM and 0.1 mg in PM
- 0.1 mg in AM and 0.2 mg in PM
- 0.2 mg in AM and 0.2 mg in PM

When treatment stops, dosage should be reduced by 0.1 mg every 3 to 7 days to avoid rebound hypertension. Clonidine formulations used for hypertension, marketed as *Catapres*, *Catapres-TTS*, and *Jenloga*, are discussed in Chapter 19.

Antidepressants

Three antidepressants—desipramine, imipramine, and bupropion—can reduce behavioral symptoms in children with ADHD. However, these antidepressants are less effective than CNS stimulants, and are not approved for ADHD. Accordingly, they are generally reserved for children who have not responded to trials with at least two different stimulants.

Tricyclic Antidepressants. Desipramine [Norpramin] and imipramine [Tofranil] can reduce symptoms in children with ADHD. These drugs decrease hyperactivity but have little effect on impulsivity and inattention. Responses develop slowly. Beneficial effects begin in 2 to 3 weeks and reach a maximum at around 6 weeks. Tolerance frequently develops within a few months. In contrast to the stimulants, which can be discontinued on weekends, antidepressants must be taken continuously. Adverse effects include sedation and anticholinergic effects (eg, dry mouth, blurred vision, urinary retention, constipation). More importantly, sudden death (from cardiotoxicity) has occurred in at least three children. Compared with stimulants, antidepressants have their benefits (no insomnia, abuse poten-

tial, or suppression of appetite and growth) as well as their drawbacks (anticholinergic effects, delayed onset, tolerance, less efficacy, risk of sudden death). Because these antidepressants are less effective and more dangerous than the stimulants, they are considered second-line drugs. Dosages for ADHD range from 2 to 5 mg/kg/day, administered in two or three divided doses. The basic pharmacology of the antidepressants is presented in Chapter 32.

Bupropion. Bupropion [Wellbutrin] can reduce behavioral symptoms of ADHD, but is less effective than stimulants. The drug lacks the adverse effects associated with tricyclic antidepressants (eg, cardiotoxicity, anticholinergic effects), but does pose a risk of seizures. Like the tricyclic antidepressants, bupropion is considered a second-line drug for ADHD. Dosage is 100 to 150 mg twice a day. The basic pharmacology of bupropion is presented in Chapter 32.

KEY POINTS

- The amphetamine family consists of dextroamphetamine, amphetamine (a racemic mixture of dextroamphetamine and levamphetamine), methamphetamine, and lisdexamfetamine.
- The amphetamines work primarily by promoting neuronal release of NE and DA, and partly by blocking NE and DA reuptake.
- Through actions in the CNS, the amphetamines can increase wakefulness and alertness, reduce fatigue, elevate mood, stimulate respiration, and suppress appetite.
- By promoting release of norepinephrine from peripheral neurons, amphetamines can cause vasoconstriction and cardiac effects (increased heart rate, increased AV conduction, and increased force of contraction).
- The most common adverse effects of amphetamines are insomnia and weight loss. Amphetamines may also cause psychosis and cardiovascular effects (dysrhythmias, angina, hypertension).
- Amphetamines have a high abuse potential (owing to their ability to elevate mood), and hence are classified as Schedule II drugs.
- The principal indication for amphetamines is ADHD.
- The pharmacology of methylphenidate is nearly identical to that of the amphetamines.
- Methylphenidate and other CNS stimulants are the most effective drugs for ADHD, and hence are considered agents of first choice.
- Methylphenidate and other CNS stimulants reduce symptoms of ADHD by enhancing the patient's ability to focus.
- Only three nonstimulants—atomoxetine, guanfacine, and clonidine—are approved for ADHD.
- In treatment of ADHD, the nonstimulants may be used alone or as add-on therapy with a stimulant.
- Compared with the CNS stimulants, the nonstimulants are less effective in ADHD, but also are safer and have a lower potential for abuse.
- Caffeine and other methylxanthines act primarily by blocking adenosine receptors.
- Responses to caffeine are dose dependent: low doses decrease drowsiness and fatigue; higher doses cause nervousness, insomnia, and tremors; and huge doses cause convulsions.
- Caffeine has two principal uses: treatment of apnea in premature infants and reversal of drowsiness.

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Summary of Major Nursing Implications*

AMPHETAMINES, METHYLPHENIDATE, AND DEXMETHYLPHENIDATE

Preadministration Assessment

Therapeutic Goal

Reduction of symptoms in children and adults with ADHD.
Reduction of sleep attacks in patients with narcolepsy.

Baseline Data

Children with ADHD. Document the degree of inattention, impulsivity, hyperactivity, and other symptoms of ADHD. Symptoms must be present for at least 6 months to allow a diagnosis of ADHD. Obtain baseline values of height and weight.

Narcolepsy. Document the degree of daytime sleepiness and the frequency and circumstances of sleep attacks.

Identifying High-Risk Patients

All amphetamines are *contraindicated* for patients with symptomatic cardiovascular disease, advanced atherosclerosis,

hypertension, hyperthyroidism, agitated states, and a history of drug abuse, and in those who have taken monoamine oxidase inhibitors within the previous 2 weeks. *Amphetamine mixture* [Adderall XR] is *generally contraindicated* for patients with structural cardiac defects.

Implementation: Administration

Routes

Oral. Amphetamines, methylphenidate, and dexamethylphenidate.

Transdermal. Methylphenidate only.

Administration

Oral. Instruct patients to swallow long-acting formulations intact, without crushing or chewing.

Advise parents that children with ADHD should take the morning dose after breakfast and the last daily dose by 4:00 PM.

Transdermal. Instruct patients using transdermal methylphenidate [Daytrana] to apply one patch to alternating

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

hips each morning, and to remove each patch not more than 9 hours after applying it. Instruct patients to avoid application to skin that is inflamed.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Children with ADHD. Monitor for reductions in symptoms (impulsiveness, hyperactivity, inattention) and for improvement in cognitive function.

Minimizing Adverse Effects

Excessive CNS Stimulation. CNS stimulants can cause restlessness and insomnia. Advise patients to use the smallest dose required and to avoid dosing late in the day. Advise patients to minimize or eliminate dietary caffeine (eg, coffee, tea, caffeinated soft drinks).

Weight Loss. Appetite suppression can cause weight loss. Advise patients to take the morning dose after breakfast and the last daily dose early in the afternoon to minimize interference with eating.

Cardiovascular Effects. Warn patients about cardiovascular responses (palpitations, hypertension, angina, dysrhythmias) and instruct them to notify the prescriber if these develop.

Very rarely, children using stimulants for ADHD have experienced sudden cardiac death. In response, the AHA says it is reasonable to consider giving a child an ECG before starting stimulant therapy. However, there is no proof that stimulants actually cause sudden death, or that withholding stimulants will protect from sudden death, or that screening for cardiac defects with an ECG will be of any benefit. Therefore, it would seem that routine ECG screening is unnecessary, especially in children with no signs or symptoms of heart defects.

Psychosis. If amphetamine-induced psychosis develops, therapy should be discontinued. For most individuals,

symptoms resolve within a week. For some patients, drug-induced psychosis may represent unmasking of latent schizophrenia, indicating a need for psychiatric care.

Withdrawal Reactions. Abrupt discontinuation can produce extreme fatigue and depression. Minimize by withdrawing amphetamines and methylphenidate gradually.

Hypersensitivity Reactions. Transdermal methylphenidate [Daytrana] can cause hypersensitivity reactions, which may necessitate discontinuing all methylphenidate products, oral as well as transdermal. Inform patients about signs of hypersensitivity—erythema, edema, papules, vesicles—and instruct them to inform the prescriber if these develop.

Minimizing Abuse

If the medical history reveals the patient is prone to drug abuse, monitor use of these drugs closely.

Avoid routine use of amphetamines for weight loss.

CAFFEINE

General Considerations

Caffeine is usually administered to promote wakefulness. Warn patients against habitual caffeine use to compensate for chronic lack of sleep. Advise patients to consult the prescriber if fatigue is persistent or recurrent.

Minimizing Adverse Effects

Cardiovascular Effects. Inform patients about cardiovascular responses to caffeine (palpitations, rapid pulse, dizziness) and instruct them to discontinue caffeine if these occur.

Excessive CNS Stimulation. Warn patients that overdose can cause convulsions. Advise them to ingest no more caffeine than needed.

*Patient education information is highlighted as blue text.

Definitions

APA Diagnostic Criteria Regarding Drugs of Abuse

Factors That Contribute to Drug Abuse

Neurobiology of Addiction

Principles of Addiction Treatment

The Controlled Substances Act

Mind-altering drugs have intrigued human beings since the dawn of civilization. Throughout history, people have taken drugs to elevate mood, release inhibitions, distort perceptions, induce hallucinations, and modify thinking. Many of those who take mind-altering drugs restrict usage to socially approved patterns. However, many others self-administer drugs to excess. Excessive drug use is our focus in this chapter and the three that follow.

Drug abuse extracts a huge toll on the individual and on society. Tobacco alone kills about 440,000 Americans each year. Alcohol and illicit drugs kill another 100,000. In addition to putting people at risk of death, drug abuse puts them at risk of long-term illness, and impairs their ability to fulfill role obligations at home, school, and work. The economic burden of drug abuse is staggering: The combined direct and indirect costs from abusing nicotine, alcohol, and illicit substances are estimated at over \$500 billion each year.

Drug abuse confronts clinicians in a variety of ways, making knowledge of abuse a necessity. Important areas in which expertise on drug abuse may be applied include (1) diagnosis and treatment of acute toxicity, (2) diagnosis and treatment of secondary medical complications of drug abuse, (3) facilitating drug withdrawal, and (4) providing education and counseling to maintain long-term abstinence.

Our discussion of drug abuse occurs in two stages. In this chapter, we discuss basic concepts in drug abuse. In Chapters 38, 39, and 40, we focus on the pharmacology of specific abused agents and methods of treatment.

DEFINITIONS**Drug Abuse**

Drug abuse can be defined as *using a drug in a fashion inconsistent with medical or social norms*. Traditionally, the term also implies drug usage that is harmful to the individual or society. As we shall see, although we can give abuse a general definition, deciding whether a particular instance of drug use constitutes "abuse" is often difficult.

Whether or not drug use is considered abuse depends, in part, on the purpose for which a drug is taken. Not everyone who takes large doses of psychoactive agents is an abuser. For example, we do not consider it abuse to take opioids in large doses long term to relieve pain caused by cancer. However, we do consider it abusive for an otherwise healthy individual to take those same opioids in the same doses to produce euphoria.

Abuse can have different degrees of severity. Some people, for example, use heroin only occasionally, whereas others use it habitually and compulsively. Although both patterns of drug use are socially condemned, and therefore constitute abuse, there is an obvious quantitative difference between taking heroin once or twice and taking it routinely and compulsively.

Note that, by the definition above, *drug abuse is culturally defined*. Because abuse is culturally defined, and because societies differ from one another and are changeable, there can be wide variations in what is labeled abuse. *What is defined as abuse can vary from one culture to another*. For example, in the United States, moderate consumption of alcohol is not usually considered abuse. In contrast, *any ingestion of alcohol would be considered abuse in some Muslim societies*. Furthermore, *what is defined as abuse can vary from one time to another within the same culture*. For example, when a few Americans first experimented with lysergic acid diethylamide (LSD) and other psychedelic drugs, these agents were legal and their use was not generally disapproved. However, when use of psychedelics became widespread, our societal posture changed and legislation was passed to make the manufacture, sale, and use of these drugs illegal.

Within the United States, there is divergence of opinion about what constitutes drug abuse. For example, some people would consider any use of marijuana to be abuse, whereas others would call smoking marijuana abusive only if it were done *habitually*. Similarly, although many Americans do not consider cigarette smoking abuse (even though the practice is compulsive and clearly harmful to the individual and society), others believe very firmly that cigarette smoking is a blatant form of abuse.

As we can see, distinguishing between culturally acceptable drug use and drug use that is to be called abuse is more in the realm of social science than pharmacology. Accordingly, since this is a pharmacology text and not a sociology text, we will not attempt to define just what patterns of drug use do or do not constitute abuse. Instead, we will focus on the pharmacologic properties of abused drugs—leaving distinctions about what is and is not abuse to sociologists and legislators. Fortunately, we can identify the drugs that tend to be abused and discuss their pharmacology without having to resolve all arguments about what patterns of use should or should not be considered abusive.

Addiction

According to the National Institute on Drug Abuse, addiction is defined as a *chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences*. Please note that nowhere in this definition is addiction equated with physical dependence. As discussed below, although physical dependence can contribute to addictive behavior, it is neither necessary nor sufficient for addiction to occur.

Other Definitions

Tolerance results from regular drug use and can be defined as a state in which a particular dose elicits a smaller response than it did with initial use. As tolerance increases, higher and higher doses are needed to elicit desired effects.

Cross-tolerance is a state in which tolerance to one drug confers tolerance to another. Cross-tolerance generally develops among drugs within a particular class, and not between drugs in different classes. For example, tolerance to one opioid (eg, heroin) confers cross-tolerance to other opioids (eg, morphine), but not to central nervous system (CNS) depressants, psychostimulants, psychedelics, or nicotine.

Psychologic dependence can be defined as an intense subjective need for a particular psychoactive drug.

Physical dependence can be defined as a state in which an abstinence syndrome will occur if drug use is discontinued. Physical dependence is the result of neuroadaptive processes that take place in response to prolonged drug exposure.

Cross-dependence refers to the ability of one drug to support physical dependence on another drug. When cross-dependence exists between drug A and drug B, taking drug A will prevent withdrawal in a patient physically dependent on drug B, and vice versa. As with cross-tolerance, cross-dependence generally exists among drugs in the same pharmacologic family, but not between drugs in different families.

A **withdrawal syndrome** is a constellation of signs and symptoms that occurs in physically dependent individuals when they discontinue drug use. Quite often, the symptoms seen during withdrawal are opposite to effects the drug produced before it was withdrawn. For example, discontinuation of a CNS depressant can cause CNS excitation.

APA DIAGNOSTIC CRITERIA REGARDING DRUGS OF ABUSE

The American Psychiatric Association (APA) has established diagnostic criteria for disorders relating to drugs of abuse. The criteria now in use, published in the fourth edition of the APA's *Diagnostics and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), were released in 1994. Revised criteria will be published in the fifth edition (DSM-5), scheduled for release in 2013. The new criteria, viewable online at www.DSM5.org, differ significantly from the criteria in DSM-IV. Both sets of criteria are summarized in Table 37-1. As the table shows, DSM-IV divides substance use disorders into two major groups: *substance abuse* and *substance dependence*. Substance dependence, which can be equated with our definition of addiction, is a more severe disorder than substance abuse. Accordingly, individuals whose drug problem is not bad enough to meet

the criteria for substance dependence might nonetheless meet the criteria for substance abuse. In DSM-5, the criteria for substance abuse and substance dependence will be merged into a single, new diagnostic category—*substance use disorder*—which will replace the two older categories. This change is welcome in that the distinction between substance abuse and substance dependence is somewhat vague, and hence has been a source of confusion.

As indicated in Table 37-1, tolerance and withdrawal are among the criteria for having a substance use disorder. Please note, however, that tolerance and withdrawal, by themselves, are neither necessary nor sufficient for a substance use disorder to exist. Put another way, the pattern of drug use that constitutes substance dependence (under DSM-IV) or a substance use disorder (under DSM-5) can exist in persons who are not physically dependent on drugs and who have not developed tolerance. Because this distinction is extremely important, I will express it another way: *Being physically dependent on a drug is not the same as being addicted!* Many people are physically dependent but do not meet the criteria for a substance use disorder. These people are not considered addicts because they do not demonstrate the behavior pattern that constitutes substance dependence. Patients with terminal cancer, for example, are often physically dependent on opioids. However, since their lives are not disrupted by their medication (quite the contrary), their drug use does not meet the criteria for a substance use disorder. Similarly, some degree of physical dependence occurs in all patients who take phenobarbital to control epilepsy. However, despite their physical dependence, epileptics do not carry out stereotypic addictive behavior, and therefore are not substance dependent (as defined in DSM-IV), and do not have a substance use disorder (as defined in DSM-5).

Having stressed that physical dependence and addiction are different from each other, we must note that the two states are not entirely unrelated. As discussed below, although physical dependence is not the same as addiction, physical dependence often contributes to addictive behavior.

FACTORS THAT CONTRIBUTE TO DRUG ABUSE

Drug abuse is the end result of a progressive involvement with drugs. Taking psychoactive drugs is usually initiated out of curiosity. From this initial involvement, the user can progress to occasional use. Occasional use can then evolve into compulsive use. Factors that play a role in the progression from experimental use to compulsive use are discussed below.

Reinforcing Properties of Drugs

Although there are several reasons for initiating drug use (eg, curiosity, peer pressure), individuals would not continue drug use unless drugs produced desirable feelings or experiences. By making people feel "good," drugs reinforce the reasons for their use. Conversely, if drugs did not give people experiences that they found desirable, the reasons for initiating drug use would not be reinforced, and drug use would stop.

Reinforcement by drugs can occur in two ways. First, drugs can give the individual an experience that is pleasurable. Cocaine, for example, produces a state of euphoria.

TABLE 37-1 • American Psychiatric Association Diagnostic Criteria Pertaining to Drugs of Abuse

Diagnostic Criteria from DSM-IV-TR*

Substance Abuse

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one or more of the following within a 12-month period:

1. Recurrent substance use that results in a failure to fulfill major role obligations at work, school, or home
2. Recurrent substance use in situations in which it is physically hazardous
3. Recurrent substance-related legal problems
4. Continued substance use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the substance

Individuals who display tolerance, withdrawal, and other symptoms of substance dependence would be diagnosed under Substance Dependence, a more severe disorder, rather than under Substance Abuse.

Substance Dependence

A. A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring at any time in the same 12-month period:

1. Tolerance, as manifested by either:
 - a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect *or*
 - b. Markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifested by either:
 - a. The characteristic withdrawal syndrome for the substance *or*
 - b. The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer time than intended
4. Substance use continues despite a persistent desire or repeated efforts to cut down or control consumption
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
6. Important social, occupational, or recreational activities are given up or reduced because of substance use
7. Substance use continues despite knowledge of a persistent or recurrent physical or psychologic problem that substance use probably caused or exacerbated (eg, drinking despite knowing that alcohol made an ulcer worse)

Proposed Diagnostic Criteria for DSM-5[†]

Substance Use Disorder

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by two or more of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home
2. Recurrent substance use in situations in which it is physically hazardous
3. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance
4. Tolerance, as defined by either:[‡]
 - a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect *or*
 - b. Markedly diminished effect with continued use of the same amount of the substance
5. Withdrawal, as manifested by either:[‡]
 - a. The characteristic withdrawal syndrome for the substance *or*
 - b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
6. The substance is often taken in larger amounts or over a longer period than was intended
7. There is a persistent desire or unsuccessful efforts to cut down or control substance use
8. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
9. Important social, occupational, or recreational activities are given up or reduced because of substance use
10. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychologic problem that is likely to have been caused or exacerbated by the substance
11. Craving or a strong desire or urge to use a specific substance

Severity Specifiers

Moderate: 2–3 criteria positive

Severe: 4 or more criteria positive

Specify If

With Physiologic Dependence: evidence of tolerance or withdrawal (ie, either Item 4 or 5 is present)

Without Physiological Dependence: no evidence of tolerance or withdrawal (ie, neither Item 4 nor 5 is present)

*Modified from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association, 2000, with permission. Copyright © 2000 American Psychiatric Association.

[†]Modified from the proposed diagnostic criteria for a Substance Use Disorder, to be published in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on November 12, 2010.

[‡]Tolerance and withdrawal are not counted if they develop for medications (eg, analgesics, anxiolytics) taken under medical supervision.

Second, drugs can reduce the intensity of unpleasant experiences. For example, drugs can reduce anxiety and stress.

The reinforcing properties of drugs can be clearly demonstrated in experiments with animals. In the laboratory, animals will self-administer most of the drugs that are abused by humans (eg, opioids, barbiturates, alcohol, cocaine, amphetamines, phencyclidine, nicotine, caffeine). When these drugs

are made freely available, animals develop patterns of drug use that are similar to those of humans. Animals will self-administer these drugs (except for nicotine and caffeine) in preference to eating, drinking, and sex. When permitted, they often die from lack of food and fluid. These observations strongly suggest that pre-existing psychopathology is not necessary for drug abuse to develop. Rather, these studies suggest

that drug abuse results, in large part, from the reinforcing properties of drugs themselves.

Physical Dependence

As defined above, physical dependence is a state in which an abstinence syndrome will occur if drug use is discontinued. The degree of physical dependence is determined largely by dosage and duration of drug use. Physical dependence is greatest in people who take large doses for a long time. The more physically dependent a person is, the more intense the withdrawal syndrome. Substantial physical dependence develops to the opioids (eg, morphine, heroin) and CNS depressants (eg, barbiturates, alcohol). Physical dependence tends to be less prominent with other abused drugs (eg, psychostimulants, psychedelics, marijuana).

Physical dependence can contribute to compulsive drug use. Once dependence has developed, the desire to avoid withdrawal becomes a motivator for continued dosing. Furthermore, if the drug is administered after the onset of withdrawal, its ability to alleviate the discomfort of withdrawal can reinforce its desirability. Please note, however, that although physical dependence plays a role in the abuse of drugs, physical dependence should not be viewed as the primary cause of addictive behavior. Rather, physical dependence is just one of several factors that can contribute to the development and continuation of compulsive use.

Psychologic Dependence

Psychologic dependence is defined as *an intense subjective need for a drug*. Individuals who are psychologically dependent feel very strongly that their sense of well-being is dependent upon continued drug use; a sense of "craving" is felt when the drug is unavailable. There is no question that psychologic dependence can be a major factor in addictive behavior. For example, it is psychologic dependence—and not physical dependence—that plays the principal role in causing renewed use of opioids by addicts who had previously gone through withdrawal.

Social Factors

Social factors can play an important role in the development of abuse. The desire for social status and approval is a common reason for initiating drug use. Also, since initial drug experiences are frequently unpleasant, the desire for social approval can be one of the most compelling reasons for repeating drug use after the initial exposure. For example, most people do not especially enjoy their first cigarette; were it not for peer pressure, many would quit before they smoked enough for it to become pleasurable. Similarly, initial use of heroin, with its associated nausea and vomiting, is often deemed unpleasant; peer pressure is a common reason for continuing heroin use long enough to develop tolerance to these undesirable effects.

Drug Availability

Drug availability is clearly a factor in the development and maintenance of abuse. Abuse can flourish only in environments where drugs can be readily obtained. In contrast, where procurement is difficult, abuse is minimal. The ready availability of drugs in hospitals and clinics is a major reason for the unusually high rate of addiction among pharmacists, nurses, and physicians.

Vulnerability of the Individual

Some individuals are more prone to becoming drug abusers than others. By way of illustration, let's consider three individuals from the same social setting who have equal access to the same psychoactive drug. The first person experiments with the drug briefly and never uses it again. The second person progresses from experimentation to occasional use. The third goes on to take the drug compulsively. Since social factors, drug availability, and the properties of the drug itself are the same for all three people, these factors cannot explain the three different patterns of drug use. We must conclude, therefore, that the differences must lie in the people: one individual was not prone to drug abuse, one had only moderate tendencies toward abuse, and the third was highly vulnerable to becoming an abuser.

Several psychologic factors have been associated with tendencies toward drug abuse. Drug abusers are frequently individuals who are impulsive, have a low tolerance for frustration, and are rebellious against social norms. Other psychologic factors that seem to predispose individuals to abusing drugs include depressive disorders, anxiety disorders, and antisocial personality. It is also clear that individuals who abuse one type of drug are likely to abuse other drugs.

There is speculation that some instances of drug abuse may actually represent self-medication to relieve emotional discomfort. For example, some people may use alcohol and other depressants to control severe anxiety. Although their drug use may appear excessive, it may be no more than they need to neutralize intolerable feelings.

Genetics also contribute to drug abuse. Vulnerability to alcoholism, for example, may result from an inherited predisposition.

NEUROBIOLOGY OF ADDICTION

How does repeated use of an addictive drug contribute to the transition from voluntary drug use to compulsive use? The answer: By causing molecular changes in the brain. Each time the drug is taken, it causes changes that promote further drug use. With repeated drug exposure, these changes are reinforced, making drug use increasingly more difficult to control.

Where do these molecular changes occur? The most important site is the so-called *reward circuit*—a system that normally serves to reinforce behaviors essential for survival, such as eating and reproductive activities. Neurons of the reward circuit originate in the ventral tegmental area of the midbrain, and project to the nucleus accumbens. Their major transmitter is *dopamine*. Under normal circumstances, biologically critical behavior, such as sexual intercourse, activates the circuit. The resultant release of dopamine rewards and reinforces the behavior. Like natural positive stimuli, addictive drugs can also activate the circuit, and thereby cause dopamine release. In fact, drugs are so effective at activating the circuit that the amount of dopamine released may be 2 to 10 times the amount released by natural stimuli. Ultimately, whether the system is activated by use of drugs or by behavior essential for survival, the outcome is the same: a tendency to repeat the behavior that turned the system on. With repeated activation over time, the system undergoes synaptic remodeling, thereby consolidating changes in brain function. This neural remodeling persists after drug use has ceased.

An important aspect of drug-induced remodeling is a phenomenon known as *down-regulation*, which serves to *reduce* the response to drugs. Because drugs release abnormally large amounts of dopamine, the reward circuit is put in a state of excessive activation. In response, the brain (1) produces less dopamine and (2) reduces the number of dopamine receptors. As a result, responses to drugs are reduced. Unfortunately, the ability of natural stimuli to activate the circuit is reduced as well. In the absence of pleasurable feelings from natural stimuli, the abuser is left feeling flat, lifeless, and depressed. The good news is that, when drug use stops, neural remodeling tends to gradually reverse.

PRINCIPLES OF ADDICTION TREATMENT

Drug addiction is a treatable disease of the brain. With therapy, between 40% and 60% of addicts can reduce drug use. The first science-based guide on addiction therapy—*Principles of Drug Addiction Treatment*—was published by the National Institute on Drug Abuse in 1999, and later revised in 2009. The guide centers on 13 principles of effective treatment, summarized in Table 37-2.

Ideally, the goal of treatment is *complete cessation* of drug use. However, total abstinence is not the only outcome that can be considered successful. Treatment that changes drug use from compulsive to moderate will permit increased productivity, better health, and a decrease in socially unacceptable behavior. Clearly, this outcome is beneficial both to the individual and to society—even though some degree of drug use continues. It must be noted, however, that in the treatment of some forms of abuse, nothing short of total abstinence can be considered a true success. Experience has shown that abusers of *cigarettes*, *alcohol*, and *opioids* are rarely capable of sustained moderation. Hence, for many of these individuals, abstinence must be complete if there is to be any hope of avoiding a return to compulsive use.

Recovery from addiction is a prolonged process that typically requires multiple treatment episodes. Why? Because addiction is a *chronic, relapsing* illness. As such, periods of treatment-induced abstinence will very likely be followed by relapse. This does not mean that treatment has failed. Rather, it simply means that at least one more treatment episode is needed. Eventually, many patients achieve stable, long-term abstinence, along with a more productive and rewarding life.

Because addiction is a complex illness that affects all aspects of life, the treatment program must be comprehensive and multifaceted. In addition to addressing drug use itself, the program should address any related medical, psychological, social, vocational, and legal problems. Obviously, treatment must be tailored to the individual; no single approach works for all people. Multiple techniques are employed. Techniques with proven success include (1) group and individual therapy directed at resolving emotional problems that underlie drug use, (2) substituting alternative rewards for the rewards of drug use, (3) threats and external pressure to discourage drug use, and (4) use of pharmacologic agents to modify the effects of abused drugs. The most effective treatment programs incorporate two or more of these methods.

THE CONTROLLED SUBSTANCES ACT

The *Comprehensive Drug Abuse Prevention and Control Act* of 1970, known informally as the *Controlled Substances Act* (CSA), is the principal federal legislation addressing drug abuse. One objective of the CSA is to reduce the chances that drugs originating from legitimate sources will be diverted to abusers. To accomplish this goal, the CSA sets forth regulations for the handling of controlled substances by manufacturers, distributors, pharmacists, nurses, and physicians. Enforcement of the CSA is the responsibility of the *Drug Enforcement Agency* (DEA), an arm of the U.S. Department of Justice.

Record Keeping

In order to keep track of controlled substances that originate from legitimate sources, a written record must be made of all transactions involving these agents. Every time a controlled substance is purchased or dispensed, the transfer must be recorded. Physicians, pharmacists, and hospitals must keep an inventory of all controlled substances in stock. This inventory must be reported to the DEA every 2 years. Although not specifically obliged to do so by the CSA, many hospitals require that floor stocks of controlled substances be counted at the beginning and end of each nursing shift.

DEA Schedules

Each drug preparation regulated under the Controlled Substances Act has been assigned to one of five categories: Schedule I, II, III, IV, or V. Drugs in Schedule I have a high potential for abuse and no approved medical use in the United States. In contrast, drugs in Schedules II through V all have approved applications. Assignment to Schedules II through V is based on abuse potential and potential for causing physical or psychological dependence. Of the drugs that have medical applications, those in Schedule II have the highest potential for abuse and dependence. Drugs in the remaining schedules have decreasing abuse and dependence liabilities. Table 37-3 lists the primary drugs that come under the five DEA Schedules.

Scheduling of drugs under the Controlled Substances Act undergoes periodic re-evaluation. With increased understanding of the abuse and dependence liabilities of a drug, the DEA may choose to reassign it to a different Schedule. For example, glutethimide (a general CNS depressant) was recently switched from Schedule III to Schedule II.

Prescriptions

The Controlled Substances Act places restrictions on prescribing drugs in Schedules II through V. (Drugs in Schedule I have no approved uses, and hence are not prescribed.) Only prescribers registered with the DEA are authorized to prescribe controlled drugs. Regulations on prescribing controlled substances are summarized below.

Schedule II. All prescriptions for Schedule II drugs must be typed or filled out in ink or indelible pencil and signed by the prescriber. Alternatively, prescribers may submit prescriptions using a new electronic prescribing procedure, established by the DEA in 2010. Oral prescriptions may be made, but only in emergencies, and a written prescription must follow within 72 hours. Prescriptions for Schedule II drugs cannot be refilled. However, a DEA rule issued in 2007 now al-

TABLE 37-2 • Principles of Drug-Addiction Treatment

1. **Addiction is a complex but treatable disease that affects brain function and behavior.** Drugs of abuse alter brain structure and function, resulting in changes that persist long after drug use has stopped. These persistent changes may explain why former abusers are at the risk of relapse after prolonged abstinence.
2. **No single treatment is appropriate for everyone.** It is critical to match treatment settings, interventions, and services to each patient's problems and needs.
3. **Treatment must be readily available.** Treatment applicants can be lost if treatment is not immediately available or readily accessible. As with other chronic diseases, the earlier treatment is offered in the disease process, the greater the likelihood of positive outcomes.
4. **Effective treatment must attend to multiple needs of the individual, not drug use.** In addition to addressing drug use, treatment must address the individual's medical, psychologic, social, vocational, and legal problems.
5. **Remaining in treatment for an adequate time is critical.** Treatment duration is based on individual need. Most patients require at least 3 months of treatment to significantly reduce or stop drug use. Additional treatment can produce further progress. As with other chronic illnesses, relapses can occur, signaling a need for treatment to be reinstated or adjusted. Programs should include strategies to prevent patients from leaving prematurely.
6. **Individual and/or group counseling and other behavioral therapies are the most common forms of drug abuse treatment.** In therapy, patients address motivation, build skills to resist drug use, replace drug-using activities with constructive and rewarding activities, and improve problem-solving abilities. Behavioral therapy also addresses incentives for abstinence and facilitates interpersonal relationships. Ongoing group therapy and other peer support programs can help maintain abstinence.
7. **Medication can be an important element of treatment, especially when combined with counseling and other behavioral therapies.** Methadone, buprenorphine, and naltrexone can help persons addicted to opioids. Nicotine replacement therapy (eg, patches, gum), bupropion, and varenicline can help persons addicted to nicotine. Disulfiram, naltrexone, topiramate, and acamprosate can help persons addicted to alcohol.
8. **Because needs of the individual can change, the plan for treatment and services must be reassessed continually and modified as indicated.** At different times during treatment, a patient may develop a need for medications, medical services, family therapy, parenting instruction, vocational rehabilitation, and social and legal services.
9. **Many drug-addicted individuals also have other mental disorders, which must be addressed.** Because drug addiction often co-occurs with other mental illnesses, patients presenting with one condition should be assessed for other conditions and treated as indicated.
10. **Medically assisted detoxification is only the first stage of addiction treatment and, by itself, does little to change long-term drug use.** Medical detoxification manages the acute physical symptoms of withdrawal—and can serve as a precursor to effective long-term treatment.
11. **Treatment needn't be voluntary to be effective.** Sanctions or enticements coming from the family, employer, or criminal justice system can significantly increase treatment entry, retention, and success.
12. **Drug use during treatment must be monitored continuously, as relapses during treatment do occur.** Knowing that drug use is being monitored (eg, through urinalysis) can help the patient withstand urges to use drugs. Monitoring also can provide early evidence of drug use, thereby allowing timely adjustment of the treatment program.
13. **Treatment programs should provide assessment for HIV/AIDS, hepatitis B and C, tuberculosis, and other infectious diseases, along with counseling to help patients modify behaviors that place them or others at risk.**

HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome.

Adapted from National Institute on Drug Abuse: Principles of Drug Addiction Treatment: A Research-Based Guide, 2nd ed. (Publication No. 09-4180). Bethesda, MD: National Institutes of Health, 2009.

allows a prescriber to write multiple prescriptions on the same day—for the same patient and same drug—to be filled sequentially for up to a 90-day supply.

Schedules III and IV. Prescriptions for drugs in Schedules III and IV may be oral, written, or electronic. If authorized by the prescriber, these prescriptions may be refilled up to 5 times. Refills must be made within 6 months of the

original order. If additional medication is needed beyond the amount provided for in the original prescription, a new prescription must be written.

Schedule V. The same regulations for prescribing drugs in Schedules III and IV apply to drugs in Schedule V. In addition, Schedule V drugs may be dispensed without a prescription provided the following conditions are met: (1) the drug is

TABLE 37-3 ■ Drug Enforcement Agency Classification of Controlled Substances

Schedule I Drugs	Schedule II Drugs	Schedule III Drugs	Schedule IV Drugs	Schedule V Drugs
Opioids	Opioids	Opioids	Opioids	Opioids
Acetylmethadol	Alfentanil	Buprenorphine	Butorphanol	Diphenoxylate plus atropine
Heroin	Codeine	Hydrocodone	Pentazocine	
Normethadone	Fentanyl	Paregoric	Propoxyphene	
Many others	Hydromorphone	Cannabinoids	Stimulants	
Psychedelics	Levorphanol	Dronabinol (THC)	Diethylpropion	
Bufotenin	Meperidine	Stimulants	Fenfluramine	
Diethyltryptamine	Methadone	Benzphetamine	Mazindol	
Dimethyltryptamine	Morphine	Phendimetrazine	Pemoline	
Ibogaine	Opium tincture	Barbiturates	Phentermine	
<i>d</i> -Lysergic acid	Oxycodone	Aprobarbital	Barbiturates	
diethylamide (LSD)	Oxymorphone	Butabarbital	Mephobarbital	
Mescaline	Remifentanil	Metharbital	Methohexital	
3,4-Methylenedioxy-	Sufentanil	Talbutal	Phenobarbital	
methamphetamine	Psychostimulants	Thiamylal	Benzodiazepines	
(MDMA)	Amphetamine	Thiopental	Alprazolam	
Psilocin	Cocaine	Miscellaneous	Chlordiazepoxide	
Psilocybin	Dextroamphetamine	Depressants	Clonazepam	
Cannabis Derivatives	Methamphetamine	Methypylon	Clorazepate	
Hashish	Methylphenidate	Anabolic Steroids	Diazepam	
Marijuana	Phenmetrazine	Fluoxymesterone	Estazolam	
Others	Barbiturates	Methyltestosterone	Flurazepam	
Flunitrazepam	Amobarbital	Nandrolone	Halazepam	
Gamma-hydroxybutyrate	Pentobarbital	Oxandrolone	Lorazepam	
Methaqualone	Secobarbital	Stanozolol	Midazolam	
Phencyclidine	Miscellaneous	Testosterone	Oxazepam	
	Depressants	Many others	Prazepam	
	Glutethimide	Others	Quazepam	
		Ketamine	Temazepam	
			Triazolam	
			Benzodiazepine-like	
			Drugs	
			Eszopiclone	
			Zaleplon	
			Zolpidem	
			Miscellaneous	
			Depressants	
			Chloral hydrate	
			Dichloralphenazone	
			Ethchlorvynol	
			Ethinamate	
			Meprobamate	
			Paraldehyde	

dispensed by a pharmacist; (2) the amount dispensed is very limited; (3) the recipient is at least 18 years old and can prove it; (4) the pharmacist writes and initials a record indicating the date, the name and amount of the drug, and the name and address of the recipient; and (5) state and local laws do not prohibit dispensing Schedule V drugs without a prescription.

Labeling

When drugs in Schedules II, III, and IV are dispensed, their containers must bear this label: *Caution—Federal law prohibits the transfer of this drug to any person other than the*

patient for whom it was prescribed. The label must also indicate whether the drug belongs to Schedule II, III, or IV. The symbols C-II, C-III, and C-IV are used to indicate the Schedule.

State Laws

All states have their own laws regulating drugs of abuse. In many cases, state laws are more stringent than federal laws. As a rule, whenever there is a difference between state and federal laws, the more restrictive of the two takes precedence.

KEY POINTS

- Drug abuse can be defined as drug use that is inconsistent with medical or social norms.
- Drug abuse is a culturally defined term. Hence, what is considered abuse can vary from one culture to another and from one time to another within the same culture.
- Addiction can be defined as a chronic, relapsing brain disease characterized by compulsive drug seeking and use, despite harmful consequences. Note that physical dependence is not required for addiction to exist.
- Tolerance is a state in which a particular drug dose elicits a smaller response than it formerly did.
- Cross-tolerance is a state in which tolerance to one drug confers tolerance to another drug.
- Psychologic dependence is defined as an intense subjective need for a particular psychoactive drug.
- Physical dependence is a state in which an abstinence syndrome will occur if drug use is discontinued. Physical dependence is *not* the same as addiction.
- Cross-dependence refers to the ability of one drug to support physical dependence on another drug.
- A withdrawal syndrome is a group of signs and symptoms that occur in physically dependent individuals when they discontinue drug use.
- Although tolerance and withdrawal are among the diagnostic criteria for substance dependence, they are neither necessary nor sufficient for a diagnosis.
- Although physical dependence is not the same as addiction, physical dependence can certainly contribute to addictive behavior.
- Drugs can reinforce their own use by providing pleasurable experiences, reducing the intensity of unpleasant experiences, and warding off a withdrawal syndrome.
- All addictive drugs activate the brain's dopamine reward circuit. Over time, they cause adaptive changes in the circuit that make it more and more difficult to control use.
- Some individuals, because of psychologic or genetic factors, are more prone to drug abuse than others.
- Because addiction is a chronic, relapsing illness, recovery is a prolonged process that typically requires multiple episodes of treatment.
- The ideal goal of treatment is complete abstinence. However, treatment that substantially reduces drug use can still be considered a success.
- Under the Controlled Substances Act, drugs in Schedule I have a high potential for abuse and no medically approved use in the United States. Drugs in Schedules II through V have progressively less abuse potential and are all medically approved.

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Basic Pharmacology of Alcohol**Alcohol Use Disorder****Drugs for Alcohol Use Disorder****Drugs Used to Facilitate Withdrawal****Drugs Used to Maintain Abstinence****Nutritional Support, Fluid Replacement,
and Antibiotics**

Alcohol (ethyl alcohol, ethanol) is the most commonly used and abused psychoactive agent in the United States. Although alcohol does have some therapeutic applications, the drug is of interest primarily for its nonmedical use. When consumed in moderation, alcohol prolongs life; reduces the risk of dementia and cardiovascular disorders; and, many would argue, contributes to the joy of living. Conversely, when consumed in excess, alcohol does nothing but diminish life in both quality and quantity. These dose-related contrasts between the detrimental and beneficial effects of alcohol were aptly summed up by our 16th president, Abraham Lincoln, when he noted:

"None seemed to think the injury arose from use of a bad thing, but from the abuse of a very good thing."

In approaching our study of alcohol, we begin by discussing the basic pharmacology of alcohol, and then we discuss alcohol use disorder and the drugs employed for treatment.

BASIC PHARMACOLOGY OF ALCOHOL**Central Nervous System Effects**

Acute Effects. Alcohol has two acute effects on the brain: (1) general depression of central nervous system (CNS) function and (2) activation of the reward circuit.

How does alcohol affect CNS activity? For many years, we believed that alcohol simply dissolved into the neuronal membrane, thereby disrupting the ordered arrangement of membrane phospholipids. However, we now know that alcohol interacts with specific proteins—certain receptors, ion channels, and enzymes—that regulate neuronal excitability. Three target proteins are of particular importance, namely (1) receptors for gamma-aminobutyric acid (GABA), (2) receptors for glutamate, and (3) the 5-HT₃ subset of receptors for serotonin (5-hydroxytryptamine, 5-HT). The *depressant* effects of alcohol result from binding with receptors for GABA (the principal inhibitory transmitter in the CNS) and receptors for glutamate (a major excitatory transmitter in the CNS). When alcohol binds with GABA receptors, it enhances GABA-mediated inhibition, and thereby causes widespread depres-

TABLE 38-1 ■ Central Nervous System Responses at Various Blood Alcohol Levels

Blood Alcohol Level (%)	Pharmacologic Response	Brain Area Affected
-0.50	Peripheral collapse	Medulla
-0.45	Respiratory depression	
-0.40	Stupor, coma	Diencephalon
-0.35	Apathy, inertia	
-0.30	Altered equilibrium	Cerebellum
-0.25	Double vision	
-0.25	Altered perception	Occipital lobe
-0.20	↓ Motor skills	
-0.20	Slurred speech	Parietal lobe
-0.15	Tremors	
-0.15	Ataxia	Frontal lobe
-0.10	↓ Attention	
-0.10	Loquaciousness	
-0.10	Altered judgment	
-0.05	Increased confidence	
-0.05	Euphoria, ↓ inhibitions	

sion of CNS activity. When alcohol binds with glutamate receptors, it blocks glutamate-mediated excitation, and thereby reduces overall CNS activity. The *rewarding* effects of alcohol result from binding with 5-HT₃ receptors in the brain's reward circuit. When these receptors are activated (by serotonin), they promote release of dopamine, the major transmitter of the reward system. When alcohol binds with these receptors, it enhances serotonin-mediated release of dopamine, and thereby intensifies the reward process.

The depressant effects of alcohol are dose dependent. When dosage is low, higher brain centers (cortical areas) are primarily affected. As dosage increases, more primitive brain areas (eg, medulla) become depressed. With depression of cortical function, thought processes and learned behaviors are altered, inhibitions are released, and self-restraint is replaced by increased sociability and expansiveness. Cortical depression also impairs motor function. As CNS depression deepens, reflexes diminish greatly and consciousness becomes impaired. At very high doses, alcohol produces a state of general anesthesia. (Alcohol can't be used for anesthesia because the doses required are close to lethal.) Table 38-1 summarizes

the effects of alcohol as a function of blood alcohol level and indicates the brain areas involved.

Chronic Effects. When consumed chronically and in excess, alcohol can produce severe neurologic and psychiatric disorders. Injury to the CNS is caused by the direct actions of alcohol and by the nutritional deficiencies often seen in chronic heavy drinkers.

Two neuropsychiatric syndromes are common in alcoholics: *Wernicke's encephalopathy* and *Korsakoff's psychosis*. Both disorders are caused by thiamin deficiency, which results from poor diet and alcohol-induced suppression of thiamin absorption. Wernicke's encephalopathy is characterized by confusion, nystagmus, and abnormal ocular movements. This syndrome is readily reversible with thiamin. Korsakoff's psychosis is characterized by polyneuropathy, inability to convert short-term memory into long-term memory, and confabulation (unconscious filling of gaps in memory with fabricated facts and experiences). Korsakoff's psychosis is not reversible.

Perhaps the most dramatic effect of long-term excessive alcohol consumption is enlargement of the cerebral ventricles, presumably in response to atrophy of the cerebrum itself. These gross anatomic changes are associated with impairment of memory and intellectual function. With cessation of drinking, ventricular enlargement and cognitive deficits partially reverse, but only in some individuals.

Impact on Cognitive Function. Low to moderate drinking helps preserve cognitive function in older people and may protect against development of dementia.

Effect on Sleep. Although alcohol is commonly used as a sleep aid, it actually disrupts sleep. Drinking can alter sleep cycles, decrease total sleeping time, and reduce the quality of sleep. In addition, alcohol can intensify snoring and exacerbate obstructive sleep apnea. Having a drink with dinner won't affect sleep—but drinking late in the evening will.

Other Pharmacologic Effects

Cardiovascular System. When alcohol is consumed acutely and in moderate doses, cardiovascular effects are minor. The most prominent effect is *dilation of cutaneous blood vessels*, causing increased blood flow to the skin. By doing so, alcohol imparts a sensation of warmth—but at the same time promotes loss of heat. Hence, despite images of Saint Bernards with little barrels of whiskey about their necks, alcohol may do more harm than good for the individual stranded in the snow with hypothermia.

Although the cardiovascular effects of moderate alcohol consumption are unremarkable, chronic and excessive consumption is clearly harmful. Abuse of alcohol results in *direct damage to the myocardium*, thereby increasing the risk of heart failure. Some investigators believe that alcohol may be the major cause of cardiomyopathy in the Western world.

In addition to damaging the heart, alcohol produces a dose-dependent *elevation of blood pressure*. The cause is vasoconstriction in vascular beds of skeletal muscle brought on by increased activity of the sympathetic nervous system. Estimates suggest that heavy drinking may be responsible for 10% of all cases of hypertension.

Not all of the cardiovascular effects of alcohol are deleterious: There is clear evidence that people who drink *moderately* (2 drinks a day or less for men, 1 drink a day or less for women) experience less ischemic stroke, coronary artery disease (CAD),

myocardial infarction (MI), and heart failure than do abstainers. It is important to note, however, that *heavy drinking* (5 or more drinks/day) *increases* the risk of heart disease and stroke. How does moderate drinking protect against heart disease? Primarily by raising levels of high-density lipoprotein (HDL) cholesterol. As discussed in Chapter 50, HDL cholesterol protects against CAD, whereas low-density lipoprotein (LDL) cholesterol promotes CAD. Of all the agents that can raise HDL cholesterol, alcohol is the most effective known. In addition to raising HDL cholesterol, alcohol may confer protection through four other mechanisms: decreasing platelet aggregation, decreasing levels of fibrinogen (the precursor of fibrin, which reinforces clots), increasing levels of tissue plasminogen activator (a clot-dissolving enzyme), and suppressing the inflammatory component of atherosclerosis. The degree of cardiovascular protection is nearly equal for beer, wine, and distilled spirits. That is, protection is determined primarily by the *amount* of alcohol consumed—not by the particular beverage the alcohol is in. Also, the *pattern* of drinking matters: protection is greater for people who drink moderately 3 or 4 days a week than for people who drink just 1 or 2 days a week. Finally, cardioprotection is greatest for those with an *unhealthy* lifestyle: Among people who exercise, eat fruits and vegetables, and do not smoke, alcohol has little or no effect on the incidence of coronary events; conversely, among people who lack these health-promoting behaviors, moderate alcohol intake is associated with a 50% reduction in coronary risk.

Glucose Metabolism. Alcohol has several effects on glucose metabolism that may decrease the risk for type 2 diabetes. For example, alcohol raises levels of adiponectin, a compound that enhances insulin sensitivity. In addition, alcohol suppresses gluconeogenesis, blunts the postprandial rise in blood glucose, and lowers fasting levels of both glucose and insulin.

Bone Health. Alcohol increases bone mineral density. How? Probably by increasing levels of sex hormones.

Respiration. Like all other CNS depressants, alcohol depresses respiration. Respiratory depression from moderate drinking is negligible. However, when consumed in excess, alcohol can cause death by respiratory arrest. The respiratory depressant effects of alcohol are potentiated by other CNS depressants (eg, benzodiazepines, opioids, barbiturates).

Liver. Alcohol-induced liver damage can progress from fatty liver to hepatitis to cirrhosis, depending on the amount consumed. Acute drinking causes reversible accumulation of fat and protein in the liver. With more chronic drinking, *hepatitis* develops in about 90% of heavy users. In 8% to 20% of chronic alcoholics, hepatitis evolves into cirrhosis—a condition characterized by proliferation of fibrous tissue and destruction of liver parenchymal cells. Although various factors other than alcohol can cause cirrhosis, alcohol abuse is unquestionably the major cause of *fatal* cirrhosis.

Stomach. Immoderate use of alcohol can cause *erosive gastritis*. About one-third of alcoholics have this disorder. Two mechanisms are involved. First, alcohol stimulates secretion of gastric acid. Second, when present in high concentrations, alcohol can injure the gastric mucosa directly.

Kidney. Alcohol is a diuretic. It promotes urine formation by inhibiting the release of antidiuretic hormone (ADH) from the pituitary. Since ADH acts on the kidney to promote water reabsorption, thereby decreasing urine formation, a reduction in circulating ADH will increase urine production.

Pancreas. Approximately 35% of cases of acute pancreatitis can be attributed to alcohol, making alcohol the second most common cause of the disorder. Flare-ups typically occur after a bout of heavy drinking. Only 5% of alcoholics develop pancreatitis, and then only after years of overindulgence.

Sexual Function. Alcohol has both psychologic and physiologic effects related to human sexual behavior. Although alcohol is not exactly an aphrodisiac, its ability to release inhibitions has been known to motivate sexual activity. Ironically, the physiologic effects of alcohol may frustrate attempts at consummating the activity that alcohol inspired: Objective measurements in males and females show that alcohol significantly decreases our physiologic capacity for sexual responsiveness. The opposing psychologic and physiologic effects of alcohol on sexual function were aptly described long ago by no less an authority than William Shakespeare. In *Macbeth* (Act II, Scene 1), Macduff inquires of a porter "What . . . does drink especially provoke?" To which the porter replies,

"Lechery, sir, it provokes, and unprovokes; it provokes the desire, but it takes away the performance."

In males, long-term use of alcohol may induce *feminization*. Symptoms include testicular atrophy, impotence, sterility, and breast enlargement.

Cancer. Alcohol—even in moderate amounts—is associated with an increased risk of several common cancers. Among these are cancers of the breast, liver, rectum, and aerodigestive tract, which includes the lips, tongue, mouth, nose, throat, vocal cords, and portions of the esophagus and trachea. How much cancer does alcohol cause? According to a 2011 study, alcohol causes 10% of all cancers in men and 3% of all cancers in women. The fraction attributable to alcohol is highest of aerodigestive tract cancers (44% in men and 25% in women), somewhat lower for liver cancer (33% and 18%), even lower for colorectal cancer (17% and 4%), and lowest for breast cancer in women (5%). The bottom line? Current data suggest that, regarding cancer risk, no amount of alcohol can be considered safe—although risk is lowest with moderate drinking (2 drinks or less a day for men and 1 drink or less a day for women).

Pregnancy. Effects of alcohol on the developing fetus are dose dependent. Risk of fetal injury is greatest with heavy drinking, and much lower with light drinking. Is there some low level of drinking that is *completely* safe? We don't know.

Fetal alcohol exposure can cause structural and functional abnormalities, ranging from mild neurobehavioral deficits to facial malformation and mental retardation. The term *fetal alcohol spectrum disorder* (FASD) is used in reference to the *full range* of outcomes—from mild to severe—that drinking during pregnancy can cause. In contrast, the term *fetal alcohol syndrome* (FAS) is reserved for the most severe cases of FASD, characterized by craniofacial malformations, growth restriction (including microcephaly), and neurodevelopmental abnormalities, manifesting during childhood as cognitive and social dysfunction. In addition to causing FASD and FAS, heavy drinking during pregnancy can result in stillbirth, spontaneous abortion, and giving birth to an alcohol-dependent infant.

Is *light* drinking safe during pregnancy? The data are unclear. Two studies published in 2010 suggest that light drinking may

carry little risk. One study, conducted in the United Kingdom, found no clinically relevant behavioral or cognitive problems in 5-year-olds whose mothers consumed 1 to 2 drinks a week during pregnancy. The other study, conducted in Australia, found no link between *low to moderate* alcohol consumption during pregnancy and alcohol-related birth defects (ARBDs), although the same study did show that *heavy* drinking was associated with a fourfold increased risk of an ARBD. These results are consistent with other recent studies, which have failed to show a relationship between occasional or light drinking during pregnancy and abnormalities in newborns or older children. However, since all of these studies were observational, rather than randomized controlled trials, the negative results might be explained by confounding factors, especially educational level, income, or access to prenatal care. Furthermore, since the follow-up time for these studies was relatively short (only 5 years), the long-term effects of light drinking remain unknown.

What's the bottom line? If there *is* some amount of alcohol that is safe during pregnancy, that amount is very low. Accordingly, despite the studies noted above, the American College of Obstetricians and Gynecologists (ACOG) continues to maintain its long-held position that no amount of alcohol can be considered safe during pregnancy. Therefore, in the interests of fetal health, all women should be advised to avoid alcohol *entirely* while pregnant or trying to conceive. Having said that, it is important to appreciate that a few drinks early in pregnancy are not likely to harm the fetus. Consequently, if a woman consumed a little alcohol before realizing she was pregnant, she should be reassured that the risk to her baby—if any—is extremely low.

Lactation. The concentration of alcohol in breast milk parallels the concentration in blood. Recent data indicate that drinking while breast-feeding can adversely affect the infant's feeding and behavior.

Impact on Longevity

The effects of alcohol on life span depend on the amount consumed. *Heavy* drinkers have a higher mortality rate than the population at large. Causes of death include cirrhosis, respiratory disease, cancer, and fatal accidents. The risk of mortality associated with alcohol abuse increases markedly in individuals who consume 6 or more drinks a day.

Interestingly, people who consume *moderate* amounts of alcohol live *longer* than those who abstain—and combining regular exercise with moderate drinking prolongs life even more. Compared with nondrinkers, moderate drinkers have a 30% lower mortality rate, a 50% lower incidence of MI, and a 59% lower incidence of heart failure. According to a study by the American Medical Association, if all Americans were to give up drinking, deaths from heart disease would *increase* by 81,000 a year. Hence, for people who already *are* moderate drinkers, continued moderate drinking would seem beneficial. Conversely, despite the apparent benefits of drinking—and the apparent health disadvantage of abstinence—no one is recommending that abstainers take up drinking. Furthermore, when the risks of alcohol outweigh any possible benefits—as in the examples listed in Table 38-2—then alcohol consumption should be avoided entirely.

How does alcohol prolong life? In large part by reducing cardiovascular disease. For people who drink red wine, a small benefit may come from *resveratrol*, although the amount present appears too small to have a significant effect (see Chapter 108).

TABLE 38-2 ■ People Who Should Avoid Alcohol*

- Women who are pregnant or trying to conceive.
- People who plan to drive or perform other activities that require unimpaired attention or muscular coordination.
- People taking antihistamines, sedatives, or other drugs that can intensify alcohol's effects.
- Recovering alcoholics.
- People under age 21.

Caution is indicated for people with a strong family history of alcoholism and for those with diabetes, peptic ulcer disease, and other medical conditions that can be exacerbated by alcohol.

*According to the National Institute on Alcohol Abuse and Alcoholism.

Pharmacokinetics

Absorption. Alcohol is absorbed from the stomach and small intestine. About 20% of ingested alcohol is absorbed from the stomach. Gastric absorption is relatively slow and is delayed even further by the presence of food. Milk is especially effective at retarding absorption. Absorption from the small intestine is rapid and largely independent of food; about 80% of ingested alcohol is absorbed from this site. Because most alcohol is absorbed from the small intestine, gastric emptying time is a major determinant of individual variation in alcohol absorption.

Distribution. Because alcohol is both nonionic and water soluble, it distributes well to all tissues and body fluids. The drug crosses the blood-brain barrier with ease, allowing alcohol in the brain to equilibrate rapidly with alcohol in the blood. Alcohol also crosses the placenta and hence can affect the developing fetus.

Distribution in body water partly explains why women are more sensitive to alcohol than men. As a rule, women have a lower percentage of body water than men. Hence, when a woman drinks, the alcohol is diluted in a smaller volume of water, causing the concentration of alcohol in tissues and fluids to be relatively high, which causes the effects of alcohol to be more intense.

Metabolism. Alcohol is metabolized in both the liver and stomach. The liver is the primary site. The pathway for alcohol metabolism is shown in Figure 38-1. As depicted, the process begins with conversion of alcohol to acetaldehyde, a reaction catalyzed by *alcohol dehydrogenase*. This reaction is slow and puts a limit on the rate at which alcohol can be inactivated. Once formed, acetaldehyde undergoes *rapid* conver-

sion to acetic acid. Through a series of reactions, acetic acid is then used to synthesize cholesterol, fatty acids, and other compounds.

The kinetics of alcohol metabolism differ from those of most other drugs. With most drugs, as plasma drug levels rise, the amount of drug metabolized per unit time increases too. This is not true for alcohol: As the alcohol content of blood increases, there is almost no change in the speed of alcohol breakdown. That is, alcohol is metabolized at a relatively *constant rate*—regardless of how much alcohol is present. The average rate at which individuals can metabolize alcohol is about *15 mL (0.5 oz) per hour*.

Because alcohol is metabolized at a slow and constant rate, there is a limit to how much alcohol one can consume without having the drug accumulate. For practical purposes, that limit is about *1 drink per hour*. Consumption of more than 1 drink per hour—be that drink beer, wine, straight whiskey, or a cocktail—will result in alcohol buildup.

The information in Table 38-3 helps explain why we can't metabolize more than 1 drink's worth of alcohol per hour. As the table indicates, beer, wine, and whiskey differ from one another with respect to alcohol concentration and usual serving size. However, despite these differences, it turns out that *the average can of beer, the average glass of wine, and the average shot of whiskey all contain the same amount of alcohol—namely, 18 mL (0.6 oz)*. Since the liver can metabolize about 15 mL of alcohol per hour, and since the average alcoholic drink contains 18 mL of alcohol, 1 drink contains just about the amount of alcohol that the liver can comfortably process each hour. Consumption of more than 1 drink per hour will overwhelm the capacity of the liver for alcohol metabolism, and therefore alcohol will accumulate.

When used on a regular basis, alcohol induces hepatic drug-metabolizing enzymes, thereby increasing the rate of its own metabolism and that of other drugs. As a result, individuals who consume alcohol routinely in high amounts can metabolize the drug faster than people who drink occasionally and moderately.

Males and females differ with respect to activity of alcohol dehydrogenase in the stomach. Specifically, women have lower activity than men. As a result, gastric metabolism of alcohol is significantly less in women. This difference partly explains why women achieve higher blood alcohol levels than men after consuming the same number of drinks.

Blood Levels of Alcohol. Since alcohol in the brain rapidly equilibrates with alcohol in the blood, blood levels of alco-

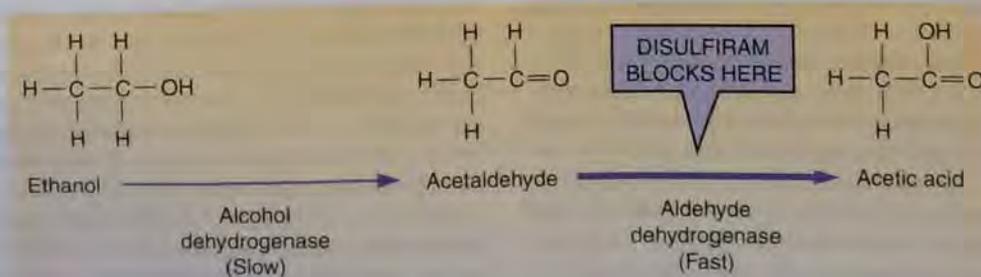


Figure 38-1 ■ Ethanol metabolism and the effect of disulfiram.

Conversion of ethanol into acetaldehyde takes place slowly (about 15 mL/hr). Consumption of more than 15 mL/hr will cause ethanol to accumulate. Effects of disulfiram result from accumulation of acetaldehyde secondary to inhibition of aldehyde dehydrogenase.

TABLE 38-3 ■ Alcohol Content of Beer, Wine, and Whiskey

	Wine	Beer	Whiskey
Usual serving	1 glass	1 can or bottle	1 shot
Serving size	150 mL (5 oz)	360 mL (12 oz)	45 mL (1.5 oz)
Alcohol concentration	12% ^a	5% ^b	40% ^c
Alcohol per serving	18 mL ^d (0.6 oz)	18 mL ^e (0.6 oz)	18 mL ^f (0.6 oz)

^aThe alcohol content of wine varies from 8% to 20%; typical table wines contain 12%.

^bThe alcohol content of beer varies; 5% alcohol is typical of American premium beers; cheaper American beers and light beers have less alcohol (2.4% to 5%); and imported beers may have more alcohol (6%). Beer sold in Europe may have 7% to 8% alcohol.

^cWhiskeys and other distilled spirits (eg, rum, vodka, gin) are usually 80 proof (40% alcohol) but may also be 100 proof (50% alcohol).

^dThe alcohol in a 5-ounce glass of wine varies from 12 to 30 mL, depending on the alcohol concentration in the wine. Wine with 12% alcohol has 18 mL of alcohol per 5-ounce glass.

^eThe alcohol in a 12-ounce can of beer varies from 9 to 29 mL, depending on the alcohol concentration in the beer. Beer with 5% alcohol has 18 mL per 12-ounce can.

^fThe alcohol in a 1.5-ounce shot of whiskey can be either 18 or 22.5 mL, depending on the proof of the whiskey. Eighty-proof whiskey has 18 mL of alcohol per 1.5-ounce serving.

hol are predictive of CNS effects. The behavioral effects associated with specific blood levels are summarized in Table 38-1. The earliest effects (euphoria, reduced inhibitions, increased confidence) are seen when blood alcohol content is about 0.05%. As blood alcohol rises, intoxication becomes more intense. When blood alcohol exceeds 0.4%, there is a substantial risk of respiratory depression, peripheral collapse, and death. In all states of the Union, a level of 0.08% defines intoxication.

Tolerance

Chronic consumption of alcohol produces tolerance. As a result, in order to alter consciousness, people who drink on a regular basis require larger amounts of alcohol than people who drink occasionally. Tolerance to alcohol confers cross-tolerance to general anesthetics, barbiturates, and other general CNS depressants. However, no cross-tolerance develops to opioids. Tolerance subsides within a few weeks following drinking cessation.

Although tolerance develops to many of the effects of alcohol, *very little tolerance develops to respiratory depression*. Consequently, the lethal dose of alcohol for chronic, heavy drinkers is not much bigger than the lethal dose for nondrinkers. Alcoholics may tolerate blood alcohol levels as high as 0.4% (5 times the amount defined by law as intoxicating) with no marked reduction in consciousness. However, if blood levels rise only slightly above this level, death may ensue.

Physical Dependence

Chronic use of alcohol produces physical dependence. If alcohol is withdrawn abruptly, an abstinence syndrome will result. The intensity of the abstinence syndrome is proportional

to the degree of physical dependence. Individuals who are physically dependent on alcohol show cross-dependence with other general CNS depressants (eg, barbiturates, chloral hydrate, benzodiazepines) but not with opioids. The alcohol withdrawal syndrome and its management are discussed in detail below.

Drug Interactions

CNS Depressants. The CNS effects of alcohol are additive with those of other CNS depressants (eg, barbiturates, benzodiazepines, opioids). Consumption of alcohol with other CNS depressants intensifies the psychologic and physiologic manifestations of CNS depression, and greatly increases the risk of death from respiratory depression.

Nonsteroidal Anti-inflammatory Drugs. Like alcohol, aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs) can injure the GI mucosa. The combined effects of alcohol and NSAIDs can result in significant gastric bleeding.

Acetaminophen. The combination of acetaminophen [Tylenol, others] with alcohol poses a risk of potentially fatal liver injury. There is evidence that relatively modest alcohol consumption (2 to 4 drinks a day) can cause fatal liver damage when combined with acetaminophen taken in normal therapeutic doses. Accordingly, some authorities recommend that people who drink take no more than 2 gm of acetaminophen a day (ie, half the normal dosage). The interaction between alcohol and acetaminophen is discussed further in Chapter 71.

Disulfiram. The combination of alcohol with disulfiram [Antabuse] can cause a variety of adverse effects, some of which are dangerous. These effects, and the use of disulfiram to maintain abstinence, are discussed later.

Antihypertensive Drugs. Since alcohol raises blood pressure, it tends to counteract the effects of antihypertensive medications. However, elevation of blood pressure is significant only when alcohol dosage is high. Conversely, when the dosage is low, alcohol may actually help: Among hypertensive men, light to moderate alcohol consumption is associated with reduced risk for both cardiovascular mortality and all-cause mortality.

Acute Overdose

Acute overdose produces vomiting, coma, pronounced hypotension, and respiratory depression. The combination of vomiting and unconsciousness can result in aspiration, which in turn can result in pulmonary obstruction and pneumonia. Alcohol-induced hypotension results from a direct effect on peripheral blood vessels, and cannot be corrected with vasoconstrictors (eg, epinephrine). Hypotension can lead to renal failure (secondary to compromised renal blood flow) and cardiovascular shock, a common cause of alcohol-related death. Although death can also result from respiratory depression, this is not the usual cause.

Because symptoms of acute alcohol poisoning can mimic symptoms of other pathologies (eg, diabetic coma, skull fracture), a definitive diagnosis may not be possible without measuring alcohol in the blood, urine, or expired air. The smell of "alcohol" on the breath is not a reliable means of diagnosis, since the breath odors we associate with alcohol are due to impurities in alcoholic beverages—and not to alcohol itself. Hence, these odors may or may not be present.

Alcohol poisoning is treated like poisoning with all other general CNS depressants. Details of management are discussed in Chapter 34. Alcohol can be removed from the body by gastric lavage and dialysis. Stimulants (eg, caffeine, pentylentetrazol) should not be given.

Summary of Precautions and Contraindications

Alcohol can injure the GI mucosa and should not be consumed by persons with *peptic ulcer disease*. Alcohol is harmful to the liver and should not be used by individuals with *liver disease*. Alcohol should be avoided during *pregnancy* owing to the risk of FASD (including FAS), stillbirth, spontaneous abortion, and neurodevelopmental abnormalities.

Alcohol must be used with caution by patients with *epilepsy*. During alcohol use, the CNS is depressed. When alcohol consumption ceases, the CNS undergoes rebound excitation; seizures can result.

Alcohol causes a dose-related increase in the risk of *breast cancer*. All women—and especially those at high risk—should minimize alcohol consumption. Alcohol also increases the risk of cancer of the liver, rectum, and aerodigestive tract.

Alcohol can cause serious adverse effects if combined with *CNS depressants*, *NSAIDs*, *acetaminophen*, *vasodilators*, and *disulfiram*. These combinations should be avoided.

Therapeutic Uses

Although our emphasis has been on the nonmedical use of alcohol, it should be remembered that alcohol does have therapeutic applications.

Topical. Alcohol applied to the skin can promote cooling in febrile patients. Topical alcohol is also an effective skin disinfectant. In addition, alcohol application can help prevent decubitus ulcers.

Oral. Because of its ability to promote gastric secretion, alcohol can serve as an aid to digestion in bedridden patients. Oral alcohol is frequently used as self-medication for insomnia—although it can actually disrupt sleep.

Intravenous. Solutions of alcohol (5% or 10%) in 5% dextrose are administered by slow IV infusion to provide calories and fluid replacement. Intravenous alcohol is also used to treat poisoning by methanol and ethylene glycol. Intravenous alcohol should not be used to manage alcohol withdrawal symptoms.

Local Injection. Injection of alcohol in the vicinity of nerves produces nerve block. This technique can relieve pain of trigeminal neuralgia, inoperable carcinoma, and other causes.

ALCOHOL USE DISORDER

Alcohol use disorder, commonly known as *alcoholism* or *alcohol dependence*, is a chronic, relapsing disorder characterized by impaired control over drinking, preoccupation with alcohol consumption, use of alcohol despite awareness of adverse consequences, and distortions in thinking, especially as evidenced by denial of a drinking problem. The development and manifestations of alcoholism are influenced by genetic, psychosocial, and environmental factors. The disease is progressive and often fatal. In the United States, about 8 million adults are alcoholics.

Diagnostic criteria regarding unhealthy alcohol use are set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The criteria now in use, published in the fourth edition of the DSM (DSM-IV), were released in 1994. Revised criteria will appear in fifth edition of the DSM (DSM-5), scheduled for release in 2013. The new criteria, viewable online at www.DSM5.org, differ significantly from the criteria in DSM-IV. Both sets of criteria are summarized in Table 38-4. As the table shows, DSM-IV

divides alcohol use disorders into two major groups: *alcohol abuse* (if tolerance and dependence are absent) and *alcohol dependence* (if tolerance and dependence are present). In DSM-5, the criteria for alcohol abuse and alcohol dependence will be merged into a single, new diagnostic category—*alcohol use disorder*—which will replace the two older categories.

In the United States, misuse of alcohol is responsible for 6 million nonfatal injuries each year, and 85,000 deaths. Causes of death range from liver disease to automobile wrecks. Fully 45% of all fatal highway crashes are alcohol related. Among teens, alcohol-related crashes are the leading cause of death. Alcohol also causes industrial accidents, and is responsible for 40% of industrial fatalities.

Alcohol abuse is a major public health problem, and its consequences are numerous. Alcoholism produces psychologic derangements, including anxiety, depression, and suicidal ideation. Malnutrition, secondary to inadequate diet and malabsorption, is common. Poor work performance and disruption of family life reflect the social deterioration suffered by alcoholics. Alcohol abuse during pregnancy can result in FASD (including FAS), stillbirth, and spontaneous abortion. Lastly, chronic alcohol abuse is harmful to the body; consequences include liver disease, cardiomyopathy, and brain damage—not to mention injury and death from accidents.

Chronic alcohol consumption produces substantial tolerance. Tolerance is both pharmacokinetic (accelerated alcohol metabolism) and pharmacodynamic. Pharmacodynamic tolerance is evidenced by an increase in the blood alcohol level required to produce intoxication. Alcoholics may tolerate blood alcohol levels of 200 to 400 mg/dL—2.5 to 5 times the level that defines legal intoxication—with no marked reduction in consciousness. It should be noted, however, that very little tolerance develops to respiratory depression. Hence, as the alcoholic consumes increasing amounts in an effort to feel good, the risk of death from respiratory arrest gets increasingly high. Cross-tolerance exists with general anesthetics and other CNS depressants, but not with opioids.

Chronic use of alcohol produces physical dependence, and abrupt withdrawal produces an abstinence syndrome. When the degree of physical dependence is low, withdrawal symptoms are mild (disturbed sleep, weakness, nausea, anxiety, mild tremors) and last less than a day. In contrast, when the degree of dependence is high, withdrawal symptoms can be severe. Initial symptoms appear 12 to 72 hours after the last drink and continue 5 to 7 days. Early manifestations include cramps, vomiting, hallucinations, and intense tremors; heart rate, blood pressure, and temperature may rise, and tonic-clonic seizures may develop. As the syndrome progresses, disorientation and loss of insight occur. A few alcoholics (less than 1%) experience *delirium tremens* (severe persecutory hallucinations). Hallucinations can be so vivid and lifelike that alcoholics often can't distinguish them from reality. In extreme cases, alcohol withdrawal can result in cardiovascular collapse and death. Drugs used to ease withdrawal are discussed below.

In 2005, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) issued a document—*Helping Patients Who Drink Too Much: A Clinician's Guide*—that contains clear, concise information on screening, counseling, and treatment

TABLE 38-4 ■ American Psychiatric Association Diagnostic Criteria Pertaining to Alcohol Use

Diagnostic Criteria from DSM-IV-TR*	Proposed Diagnostic Criteria for DSM-5†
<p>Alcohol Dependence</p> <p>A. A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring within a 12-month period:</p> <ol style="list-style-type: none"> 1. Tolerance to alcohol 2. Withdrawal from alcohol 3. Consumption of alcohol in larger amounts or over longer periods than intended 4. Continued alcohol use despite a persistent desire or repeated efforts to cut down or control consumption 5. A great deal of time is spent drinking alcohol or recovering from its effects 6. Important social, occupational, or recreational activities are given up or reduced because of alcohol 7. Alcohol use continues despite knowledge of a persistent or recurrent physical or psychologic problem that alcohol probably caused or exacerbated (eg, drinking despite knowing that alcohol made an ulcer worse) <p>Alcohol Abuse</p> <p>A. A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by one (or more) of the following within a 12-month period:</p> <ol style="list-style-type: none"> 1. Recurrent alcohol use that results in a failure to fulfill major role obligations at work, school, or home 2. Recurrent alcohol use in situations in which it is physically hazardous 3. Recurrent alcohol-related legal problems 4. Continued alcohol use despite persistent or recurrent social or interpersonal problems caused or exacerbated by alcohol <p>Individuals who display tolerance, withdrawal, and other symptoms of alcohol dependence would be diagnosed under Alcohol Dependence rather than Alcohol Abuse.</p>	<p>Alcohol Use Disorder</p> <p>A. A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by two (or more) of the following, occurring within a 12-month period:</p> <ol style="list-style-type: none"> 1. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home 2. Recurrent alcohol use in situations in which it is physically hazardous 3. Continued alcohol use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the alcohol 4. Tolerance, as defined by either: <ol style="list-style-type: none"> a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect b. Markedly diminished effect with continued use of the same amount of alcohol 5. Withdrawal, as manifested by either <ol style="list-style-type: none"> a. The characteristic withdrawal syndrome for alcohol b. Alcohol (or a closely related) substance is taken to relieve or avoid withdrawal symptoms 6. Alcohol is often taken in larger amounts or over a longer period than was intended 7. Continued alcohol use despite a persistent desire or repeated efforts to cut down or control consumption 8. A great deal of time is spent in activities necessary to obtain or use alcohol, or to recover from its effects 9. Important social, occupational, or recreational activities are given up or reduced because of alcohol use 10. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol 11. Craving or a strong desire or urge to use alcohol <p>Severity Specifiers</p> <p><i>Moderate:</i> 2–3 criteria positive <i>Severe:</i> 4 or more criteria positive</p> <p>Specify If</p> <p><i>With Physiologic Dependence:</i> evidence of tolerance or withdrawal <i>Without Physiologic Dependence:</i> no evidence of tolerance or withdrawal</p>

*Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association, 2000, with permission. Copyright © 2000 American Psychiatric Association.

†Adapted from the proposed diagnostic criteria for alcohol disorder, to be published in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. Expected publication date: May 2013. Copyright © American Psychiatric Association. The proposed criteria are from the DSM-5 web site—www.DSM5.org—accessed on December 7, 2010.

of alcohol use disorders. By following this guide, clinicians can help reduce morbidity and mortality among people who drink more than is safe, defined as more than 4 drinks in a day (or 14/week) for men, or more than 3 drinks in a day (or 7/week) for women. Helping patients involves four simple steps:

- Ask about alcohol use.
- Assess for alcohol use disorders, using the Alcohol Use Disorders Identification Test (AUDIT).
- Advise and assist (brief intervention).
- At follow-up: continue support.

This process is founded in part on two lines of evidence. First, we can identify people who misuse alcohol with an easily administered questionnaire, such as AUDIT (Table 38-5).^{*} Second, for many people, alcohol consumption can be reduced through brief interventions, such as offering feedback and advice about drinking and about setting goals. Long-term follow-up studies have shown that these simple interventions

^{*}Rapid screening can be accomplished with a single question: How many times in the past year have you had x or more drinks in a day? ($x = 5$ for men and 4 for women). A positive response is defined as 1 or more. If this simple screen is positive, a more detailed diagnostic interview is indicated.

TABLE 38-5 ■ Screening Instrument: The Alcohol Use Disorders Identification Test (AUDIT)

	0	1	2	3	4	Score
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other healthcare worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
Total Score						

Instructions to patient: Place an X in the box that best describes your answer to each question.

Scoring: Record the score (0, 1, 2, 3, or 4) for each response in the blank box at the end of each line, and then add up the total score. The maximum possible is 40. A total score of 8 or more (for men up to age 60), or 4 or more (for women, adolescents, and men over 60) is considered a positive screen. For patients with totals near the cut-points, clinicians may wish to examine individual responses to questions and clarify them during the clinical examination.

Reprinted with permission from the World Health Organization. To reflect standard drink sizes in the United States, the number of drinks in question 3 was changed from 6 to 5.

can decrease hospitalization and lower mortality rates. The guide is available online at www.niaaa.nih.gov/guide.

To help individuals who drink too much, the NIAAA created an interactive web site, located at rethinkingdrinking.niaaa.nih.gov. Content includes tools to identify and manage problem drinking, plus a calculator for determining the alcohol content of various beverages.

DRUGS FOR ALCOHOL USE DISORDER

In the United States, about 1 million alcoholics seek treatment every year. Although the success rate is discouraging—nearly 50% relapse during the first few months—treatment should nonetheless be tried. The objective is to modify drinking patterns (ie, to reduce or completely eliminate alcohol consumption). Drugs can help in two ways. First, they can facilitate

withdrawal. Second, they can help maintain abstinence once withdrawal has been accomplished.

Drugs Used to Facilitate Withdrawal

Management of withdrawal depends on the degree of dependence. When dependence is mild, withdrawal can be accomplished on an outpatient basis without drugs. However, when dependence is great, withdrawal carries a risk of death. Accordingly, hospitalization and drug therapy are indicated. The goals of management are to minimize symptoms of withdrawal, prevent seizures and delirium tremens, and facilitate transition to a program for maintaining abstinence. In theory, any drug that has cross-dependence with alcohol (ie, any of the general CNS depressants) should be effective. However, in actual practice, benzodiazepines are the drugs of choice. The benefits of benzodiazepines and other drugs used during withdrawal are summarized in Table 38-6.

Benzodiazepines

Of the drugs used to facilitate alcohol withdrawal, benzodiazepines are the most effective. Furthermore, they are safe. In patients with severe alcohol dependence, benzodiazepines can stabilize vital signs, reduce symptom intensity, and decrease the risk of seizures and delirium tremens. Although all benzodiazepines are effective, agents with longer half-lives are generally preferred. Why? Because they provide the greatest protection against seizures and breakthrough symptoms. The benzodiazepines employed most often are chlordiazepoxide [Librium, others], diazepam [Valium], oxazepam (generic only), and lorazepam [Ativan]. Traditionally, benzodiazepines have been administered around-the-clock on a fixed schedule. However, PRN administration (in response to symptoms) is just as effective and permits speedier withdrawal.

Adjuncts to Benzodiazepines

Combining a benzodiazepine with another drug may improve withdrawal outcome. Agents that have been tried include carbamazepine (an antiepileptic drug), clonidine (an α_2 -adrenergic agonist), and atenolol and propranolol (beta-adrenergic blockers). Carbamazepine may reduce withdrawal symptoms and the risk of seizures. Clonidine and the beta blockers reduce the autonomic component of withdrawal symptoms. In addition, the beta blockers may improve vital signs and decrease craving. It should be stressed, however, that these drugs are not very effective as monotherapy. Hence, they should be viewed only as adjuncts to benzodiazepines—not as substitutes.

Drugs Used to Maintain Abstinence

Once detoxification has been accomplished, the goal is to prevent—or at least minimize—future drinking. The ideal goal is complete abstinence. However, if drinking must resume, keeping it to a minimum is still beneficial, since doing so will reduce alcohol-related morbidity.

In trials of drugs used to maintain abstinence, several parameters are used to measure efficacy. These include

- Proportion of patients who maintain complete abstinence
- Days to relapse
- Number of drinking days
- Number of drinks per drinking day

TABLE 38-6 ■ Drugs Used to Facilitate Alcohol Withdrawal

Drug	Benefit During Withdrawal
Benzodiazepines	
Chlordiazepoxide	Decrease withdrawal symptoms; stabilize vital signs; prevent seizures and delirium tremens
Diazepam	
Oxazepam	
Lorazepam	
Beta-Adrenergic Blockers	
Atenolol	Improve vital signs; decrease craving; decrease autonomic component of withdrawal symptoms
Propranolol	
Central α_2-Adrenergic Agonist	
Clonidine	Decreases autonomic component of withdrawal symptoms
Antiepileptic Drug	
Carbamazepine	Decreases withdrawal symptoms; prevents seizures

In the United States, only three drugs—disulfiram, naltrexone, and acamprosate—are approved for maintaining abstinence. Disulfiram works by causing an unpleasant reaction if alcohol is consumed. Naltrexone blocks the pleasurable effects of alcohol and decreases craving. Acamprosate reduces some of the unpleasant feelings (eg, tension, dysphoria, anxiety) brought on by alcohol abstinence. Of the three drugs, naltrexone appears most effective. However, even with this agent, benefits are modest.

Owing to the risk of relapse, prolonged treatment is needed. The minimum duration is 3 months. However, continuing for a year or more is not unreasonable. If the first drug fails, clinicians often try a different one.

Disulfiram Aversion Therapy

Therapeutic Effects. Disulfiram [Antabuse] helps alcoholics avoid drinking. How? By causing unpleasant effects if alcohol is ingested. Disulfiram has no applications outside the treatment of alcoholism.

Although disulfiram has been employed for over 50 years, its efficacy is only moderate. In clinical trials, the drug is no better than placebo at maintaining abstinence: The proportion of patients who relapse and the time to relapse are the same as with placebo. However, although disulfiram doesn't prevent drinking, it does decrease the frequency of drinking after relapse has occurred—presumably because of the unpleasant reaction that the patient is now familiar with. Supervised administration of disulfiram may be more effective than when patients self-administer the drug.

Mechanism of Action. As indicated in Figure 38-1, disulfiram disrupts alcohol metabolism. Specifically, disulfiram causes *irreversible inhibition of aldehyde dehydrogenase*, the enzyme that converts acetaldehyde to acetic acid. As a result, if alcohol is ingested, *acetaldehyde* will accumulate to toxic levels, producing unpleasant and potentially harmful effects.

Pharmacologic Effects. The constellation of effects caused by alcohol plus disulfiram is referred to as the *acetaldehyde syndrome*, a potentially dangerous event. In its "mild"

form, the syndrome manifests as nausea, copious vomiting, flushing, palpitations, headache, sweating, thirst, chest pain, weakness, blurred vision, and hypotension; blood pressure may ultimately decline to shock levels. This reaction, which may last from 30 minutes to several hours, can be brought on by consuming as little as 7 mL of alcohol.

In its most severe manifestation, the acetaldehyde syndrome is life threatening. Possible reactions include marked respiratory depression, cardiovascular collapse, cardiac dysrhythmias, myocardial infarction, acute congestive heart failure, convulsions, and death. Clearly, the acetaldehyde syndrome is not simply unpleasant; this syndrome can be extremely hazardous and must be avoided.

In the absence of alcohol, disulfiram rarely causes significant effects. Drowsiness and skin eruptions may occur during initial use, but they diminish with time.

Patient Selection. Owing to the severity of the acetaldehyde syndrome, candidates must be carefully chosen. Alcoholics who lack the determination to stop drinking should not receive disulfiram. In other words, disulfiram must not be administered to alcoholics who are likely to attempt drinking while undergoing treatment.

Patient Education. Patient education is an extremely important component of therapy. Patients must be thoroughly informed about the potential hazards of treatment. That is, they must be made aware that consuming any alcohol while taking disulfiram may produce a severe, potentially fatal, reaction. Patients must be warned to avoid all forms of alcohol, including alcohol found in sauces and cough syrups, and alcohol applied to the skin in aftershave lotions, colognes, and liniments. Patients should be made aware that the effects of disulfiram will persist about 2 weeks after the last dose, and hence continued abstinence is necessary. Individuals using disulfiram should be encouraged to carry identification indicating their status.

Preparations, Dosage, and Administration. Disulfiram [Antabuse] is supplied in 250- and 500-mg tablets. At least 12 hours must elapse between the patient's last drink and starting treatment. The initial dosage is 500 mg once daily for 1 to 2 weeks. Maintenance dosages range from 125 to 500 mg/day, usually taken as a single dose in the morning. Therapy may last months or even years.

Naltrexone

Naltrexone [ReVia, Vivitrol] is a pure opioid antagonist that decreases craving for alcohol and blocks alcohol's reinforcing (pleasurable) effects. Alcoholics report that naltrexone decreases their "high." Although the mechanism underlying these effects is uncertain, one possibility is blockade of dopamine release secondary to blockade of opioid receptors. Naltrexone is generally well tolerated. Nausea is the most common adverse effect (10%), followed by headache (7%), anxiety (2%), and sedation (2%). Since naltrexone is an opioid antagonist, the drug will precipitate withdrawal if given to a patient who is opioid dependent. Conversely, if a patient taking naltrexone needs emergency treatment with an opioid analgesic, high doses of the opioid will be required.

Naltrexone was approved for alcoholism on the basis of randomized clinical trials that combined extensive counseling along with the drug. In these trials, naltrexone cut the relapse rate by 50%. Compared with patients taking placebo, those taking naltrexone reported less craving for alcohol, fewer days drinking, fewer drinks per occasion, and reduced severity of

alcohol-related problems. In contrast to the original trials, a more recent trial, conducted by the U.S. Department of Veterans Affairs, failed to show any benefit of naltrexone in maintaining abstinence. Why did naltrexone work in the original trials but not in the more recent one? The most likely reason is that the subjects in the two trials were very different: The alcoholic veterans suffered from long-term alcoholism, had little or no social support, and received minimal counseling during the trial, whereas subjects in the earlier studies were younger, had good support systems, and received extensive counseling along with naltrexone. Hence, the new study does not prove that naltrexone doesn't work. Rather, it only proves that naltrexone doesn't work for all drinkers, and doesn't work in the absence of adequate counseling.

Naltrexone is available in two formulations: 50-mg tablets [ReVia] for oral use, and a 380-mg depot formulation [Vivitrol] for IM injection. The oral dosage is 50 mg once a day. The IM dosage is 380 mg once a month. Depot naltrexone is especially good when patient adherence is a concern. As with disulfiram, patients must stop drinking before starting naltrexone.

The basic pharmacology of naltrexone is discussed in Chapter 28.

Acamprosate

Therapeutic Use. Acamprosate [Campral] is approved for maintaining abstinence in patients with alcohol dependence following detoxification. Benefits derive from reducing unpleasant feelings (eg, tension, dysphoria, anxiety) brought on by abstinence. This effect contrasts with the effects of disulfiram (which makes drinking unpleasant) and naltrexone (which blocks the pleasant feelings that alcohol can cause). Acamprosate should be used only as part of a comprehensive management program that includes psychosocial support.

In clinical trials, acamprosate was moderately effective. Compared with patients taking placebo, those taking acamprosate abstained from their first drink longer, had greater rates of complete abstinence, and were abstinent for more total days. Benefits may be related to the degree of alcohol dependence: The greater the dependence, the more likely that acamprosate will help. Among patients who lack psychosocial support, little or no benefit is seen.

Acamprosate is somewhat less effective than naltrexone: Patients taking naltrexone abstain from their first drink longer and accumulate more days of abstinence. Combining acamprosate with naltrexone is more effective than acamprosate alone, but no better than naltrexone alone.

Mechanism of Action. Just how acamprosate works is unknown. One theory suggests that acamprosate enhances inhibitory neurotransmission (mediated by GABA) and suppresses excitatory neurotransmission (mediated by glutamate), and thereby restores a balance between these transmitter systems. When given to alcohol-dependent animals, the drug reduces voluntary alcohol intake. Acamprosate is devoid of direct anxiolytic, anticonvulsant, and antidepressant activity, and does not cause alcohol aversion.

Pharmacokinetics. Acamprosate is administered orally, and bioavailability is low (11%). Food reduces absorption even further. The drug has a long half-life (20 to 33 hours), and hence about 5 days are required for plasma levels to reach a plateau. Acamprosate does not undergo metabolism, and is excreted unchanged in the urine.

Adverse Effects and Drug Interactions. Acamprosate is generally well tolerated. With most adverse effects, the incidence is no greater than with placebo. The principal exception is diarrhea, which occurs in 17% of acamprosate users compared with 10% of those taking placebo. Reports of suicide-related events (suicidal ideation, suicide attempts, completed suicide) are rare, but more common than with placebo. Acamprosate can cause fetal malformations in animals (at doses close to those used by humans). Accordingly, it would seem prudent to avoid this drug during pregnancy, especially since alternatives are available. Acamprosate has no potential for dependence or abuse, and appears devoid of significant drug interactions.

Preparations, Dosage, and Administration. Acamprosate [Campral] is available in 333-mg delayed-release tablets. The recommended dosage is 2 tablets (666 mg) 3 times a day, taken with meals. (The reason for administration with meals is to promote compliance—not to influence absorption or GI effects.) Dosing should start immediately after detoxification is over, and should continue even if relapse occurs. For patients with *mild* renal impairment, the recommended initial dosage is 333 mg 3 times a day. If the patient has *severe* renal impairment, acamprosate should not be used.

Topiramate

Preliminary evidence suggests that topiramate [Topamax], a drug currently approved for epilepsy and migraine, can reduce craving for alcohol, and hence may reduce alcohol consumption in problem drinkers. In a double-blind, placebo-controlled study, subjects taking topiramate had fewer drinks per day (compared with subjects taking placebo), a lower percentage of drinking days, and a higher percentage of days with no drinking. Benefits took about 6 weeks to develop. As with acamprosate, benefits are believed to result from reducing neuronal excitation by glutamate and boosting neuronal inhibition by GABA. In addition, topiramate may normalize the activity of calcium channels, which can be disrupted by chronic alcohol exposure. To minimize adverse effects (tingling or numbness, altered taste, anorexia, difficulty concentrating, memory problems), dosages should be low initially (25 mg daily at bedtime) and then gradually increased (by 25 to 50 mg daily each week) to a target dose of 200 mg/day. Compared with other drugs for maintaining abstinence, topiramate has one distinct advantage: *Patients can start topiramate without first giving up drinking for several days.* Despite its use in epilepsy, topiramate should not be given to manage convulsions trig-

gered by alcohol withdrawal. The basic pharmacology of topiramate is discussed in Chapter 24.

Ondansetron

Ondansetron [Zofran], a selective 5-HT₃ receptor antagonist, is under study as an aid to maintaining sobriety. The drug was originally developed to suppress nausea and vomiting caused by anticancer drugs (see Chapter 80). Why give ondansetron to alcoholics? Because, by blocking 5-HT₃ receptors, the drug could, in theory, prevent alcohol from activating the brain's reward system, and hence could decrease motivation for drinking. In two studies, ondansetron did help suppress alcohol ingestion—but only among certain alcoholics. In one study, ondansetron reduced drinking among people with *early-onset* alcoholism (alcoholism that began before age 25) but had no effect on people with *late-onset* alcoholism (alcoholism that began after age 25). In the other study, benefits were limited to subjects with a specific genetic variant, known as the *LL* genotype of the 5-HTTLPR polymorphism. In both studies, ondansetron significantly increased the proportion of days spent without drinking and decreased the number of drinks consumed on drinking days. The most effective dosage was 4 mg/kg twice a day. These studies are important in that they suggest that dysfunction of serotonergic transmission differs in early-onset alcoholism compared with late-onset alcoholism, and that dysfunction of the serotonergic system may be linked to a specific genetic variation. For clinical practice, these studies indicate that ondansetron therapy should be tailored to either (1) the patient's clinical subtype (early-onset alcoholism rather than late-onset alcoholism) or (2) the presence of the *LL* genotype, as determined by genetic testing.

Nutritional Support, Fluid Replacement, and Antibiotics

Malnutrition is a common problem in the chronic alcoholic. The underlying causes are poor diet and malabsorption of nutrients and vitamins. Malabsorption results from alcohol-induced damage to the GI mucosa. Poor diet occurs in part because alcoholics meet up to 50% of their caloric needs with alcohol, and therefore consume subnormal amounts of foods with high nutritional value. Because of their poor nutritional state, alcoholics are in need of fat, protein, and vitamins. The B vitamins (thiamin, folic acid, cyanocobalamin) are especially needed. To correct nutritional deficiencies, a program of dietary modification and vitamin supplements should be implemented.

Alcoholics frequently require fluid replacement therapy and antibiotics. Fluids are needed to replace fluids lost because of gastritis, or because of vomiting associated with withdrawal. Antibiotics may be needed to manage pneumonitis, a common complication of alcoholism.

KEY POINTS

- Alcohol is generally beneficial when consumed in moderation and always detrimental when consumed in excess.
- Alcohol causes CNS depression by enhancing the depressant effects of GABA and reducing the excitatory effects of glutamate.
- As blood levels of alcohol rise, CNS depression progresses from cortical areas to more primitive brain areas (eg, medulla).
- Long-term, excessive drinking reduces the size of the cerebrum.
- Alcohol produces a dose-dependent increase in blood pressure.
- Moderate drinking is defined as 2 drinks per day or less for men, and 1 drink per day or less for women.
- Moderate drinking significantly reduces the risk of CAD, MI, ischemic stroke, and heart failure—primarily by raising HDL cholesterol, and partly by suppressing platelet aggregation, reducing fibrin formation, enhancing fibrinolysis, and suppressing the inflammatory component of atherosclerosis.
- Excessive drinking causes direct damage to the myocardium.
- Like all other CNS depressants, alcohol depresses respiration.
- Chronic, heavy drinking can cause hepatitis and cirrhosis. People with liver disease should avoid alcohol.
- Heavy drinking can cause erosive gastritis.
- Alcohol is a diuretic.
- Alcohol, even in low doses, increases the risk of breast cancer, as well as cancers of the liver, rectum, and aerodigestive tract.
- Excessive drinkers die younger than the population at large.
- Because of the cardioprotective effects of alcohol, moderate drinkers live longer than those who abstain.
- Alcohol dehydrogenase is the rate-limiting enzyme in alcohol metabolism.
- Alcohol is metabolized at a constant rate, regardless of how high blood levels rise. In contrast, the rate of me-

metabolism of most drugs increases as their blood levels rise.

- Most people can metabolize about 1 drink per hour—be it beer, wine, straight whiskey, or a cocktail. Consuming more than 1 drink per hour causes alcohol to accumulate.
- Chronic drinking produces tolerance to many of alcohol's effects—but not to respiratory depression.
- Tolerance to alcohol confers cross-tolerance to general anesthetics, barbiturates, and other general CNS depressants—but not to opioids.
- The CNS-depressant effects of alcohol are additive with those of other CNS depressants.
- The combined effects of alcohol and NSAIDs can cause significant gastric bleeding. People with peptic ulcer disease should avoid alcohol.
- The combination of alcohol and acetaminophen can cause fatal hepatic failure.
- Alcohol use during pregnancy can result in FASD (including FAS), stillbirth, and spontaneous abortion. Women who are pregnant or trying to conceive should not drink.

- Benzodiazepines (eg, chlordiazepoxide, diazepam, lorazepam) are drugs of choice for facilitating withdrawal in alcohol-dependent individuals. Benzodiazepines suppress symptoms because of cross-dependence with alcohol.
- Three drugs are approved for maintaining alcohol abstinence: disulfiram, naltrexone, and acamprosate.
- Disulfiram blocks aldehyde dehydrogenase. As a result, if alcohol is consumed, acetaldehyde will accumulate, thereby causing a host of unpleasant and potentially dangerous symptoms.
- Naltrexone blocks opioid receptors, and thereby decreases craving for alcohol and blocks alcohol's reinforcing effects.
- Acamprosate decreases tension, anxiety, and other unpleasant feelings caused by the absence of alcohol. The underlying mechanism is unclear.

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Summary of Major Nursing Implications*

DISULFIRAM

Preadministration Assessment

Therapeutic Goal

Maintaining alcohol abstinence.

Patient Selection

Candidates for therapy must be chosen carefully. Disulfiram must not be given to alcoholics who are likely to attempt drinking while taking this drug.

Identifying High-Risk Patients

Disulfiram is *contraindicated* for patients suspected of being incapable of abstinence from alcohol; for patients with myocardial disease, coronary occlusion, or psychosis; and for patients who have recently received alcohol, metronidazole, or alcohol-containing medications (eg, cough syrups, tonics).

Implementation: Administration

Route

Oral.

Administration

Instruct the patient not to administer the first dose until at least 12 hours after his or her last drink.

Dosing is done once daily and may continue for months or even years.

Inform patients that tablets may be crushed or mixed with liquid.

Implementation: Measures to Enhance Therapeutic Effects

Patient education is essential for safety. **Inform patients about the potential hazards of treatment, and warn them to avoid all forms of alcohol, including alcohol in vinegar, sauces, and cough syrups, and alcohol applied to the skin in aftershave lotions, colognes, and liniments. Inform patients that the effects of disulfiram will persist about 2 weeks after the last dose and that alcohol must not be consumed during this time. Encourage patients to carry identification to alert emergency healthcare personnel to their condition.**

*Patient education information is highlighted as **blue text**.

Basic Pharmacology of Nicotine Pharmacologic Aids to Smoking Cessation

Nicotine Replacement Therapy

Bupropion SR

Varenicline

Nortriptyline and Clonidine

Nicotine Conjugate Vaccine

Products That Are Not Recommended

SI Box 39-1. Smoking Cessation During Pregnancy

Cigarette smoking remains the greatest single cause of preventable illness and premature death. In the United States, smoking kills more than 443,000 adults each year—about 1 of every 5 deaths. Around the world, tobacco kills over 5 million people each year. On average, male smokers die 13.2 years prematurely, and females die 14.5 years prematurely. As shown in Table 39-1, most deaths result from lung cancer (125,522), heart disease (101,009), and chronic airway obstruction (79,898). Not only do cigarettes kill people who smoke, every year, through secondhand smoke, cigarettes kill about 50,000 nonsmoking Americans, and about 600,000 nonsmokers worldwide. The direct medical costs of smoking exceed \$95 billion a year. Indirect costs, including lost time from work and disability, add up to an additional \$97 billion. In the United States, the prevalence of smoking among adults fell steadily from 1965 (42%) through the 1980s and 1990s, but has now leveled off, remaining constant between 2004 (20.9%) and 2008 (20.6%).

Although tobacco smoke contains many dangerous compounds, nicotine is of greatest concern. Other hazardous components in tobacco smoke include carbon monoxide, hydrogen cyanide, ammonia, nitrosamines, and tar. Tar is composed of various polycyclic hydrocarbons, some of which are proven carcinogens.

What is the regulatory status of cigarettes? Good question, given that cigarettes are the single most dangerous product available to U.S. consumers. Until recently, cigarettes had avoided virtually all federal regulation. However, strong regulations are now in place. Under the *Family Smoking Prevention and Tobacco Control Act*, passed in June 2009, the Food and Drug Administration (FDA) now has the authority to

- Strengthen advertising restrictions, including the prohibition on marketing to youth.
- Require revised and more prominent warning labels.
- Require disclosure of all ingredients in tobacco products and restrict harmful additives.
- Monitor nicotine yields, and mandate gradual nicotine reduction to nonaddictive levels.

TABLE 39-1 ■ Average Annual Smoking-Attributable Mortality (United States, 2000–2004)*

Disease Category	Smoking-Related Deaths	
	Male	Female
Malignant Neoplasms		
Lip, oral cavity, pharynx	3,749	1,144
Esophagus	6,961	1,631
Stomach	1,900	584
Pancreas	3,147	3,536
Larynx	2,446	563
Trachea, lung, bronchus	78,680	46,842
Cervix, uteri	0	447
Kidney and renal pelvis	2,827	216
Urinary bladder	3,907	1,076
Acute myeloid leukemia	855	337
Subtotal	104,472	56,376
Cardiovascular Diseases		
Ischemic heart disease	50,884	29,121
Other heart disease	12,944	8,060
Cerebrovascular disease	7,896	8,026
Atherosclerosis	1,282	611
Aortic aneurysm	5,628	2,791
Other circulatory diseases	505	749
Subtotal	79,139	49,358
Respiratory Diseases		
Pneumonia, influenza	6,042	4,381
Bronchitis, emphysema	7,536	6,391
Chronic airway obstruction	40,217	38,771
Subtotal	53,795	49,543
AVERAGE ANNUAL TOTAL	237,406	155,277

*Data are for adults ages 35 and older, and do not include deaths caused by burns or secondhand smoke.

Data were obtained online at apps.nccd.cdc.gov/sammecl/—the web site of the Centers for Disease Control and Prevention: Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC).

BASIC PHARMACOLOGY OF NICOTINE

Mechanism of Action

The effects of nicotine result from actions at nicotinic receptors. Whether these receptors are activated or inhibited depends on nicotine dosage. *Low* doses activate nicotinic receptors; *high* doses block them. The amount of nicotine received from cigarettes is relatively low. Accordingly, cigarette smoking causes receptor activation.

Nicotine can activate nicotinic receptors at several locations. Most effects result from activating nicotinic receptors in autonomic ganglia and the adrenal medulla. In addition, nicotine can activate nicotinic receptors in the carotid body, aortic

arch, and CNS. As discussed below, actions in the CNS mimic those of cocaine and other highly addictive substances. When present at the levels produced by smoking, nicotine has no significant effect on nicotinic receptors of the neuromuscular junction.

Pharmacokinetics

Absorption of nicotine depends on whether the delivery system is a cigarette, a cigar, or smokeless tobacco. Nicotine in cigarette smoke is absorbed primarily from the lungs. When cigarette smoke is inhaled, between 90% and 98% of nicotine in the lungs enters the blood. Unlike nicotine in cigarette smoke, nicotine in cigar smoke is absorbed primarily from the mouth, as is nicotine in smokeless tobacco.

Nicotine can cross membranes easily and is widely distributed throughout the body. The drug readily enters breast milk, reaching levels that can be toxic to the nursing infant. Nicotine also crosses the placental barrier and can cause fetal harm. When inhaled in cigarette smoke, nicotine reaches the brain in just 10 seconds.

Nicotine is rapidly metabolized to inactive products. Nicotine and its metabolites are excreted by the kidney. The drug's half-life is 1 to 2 hours.

Pharmacologic Effects

The pharmacologic effects discussed in this section are associated with *low* doses of nicotine. These are the effects caused by smoking cigarettes. Responses to *high* doses are discussed under *Acute Poisoning*.

Cardiovascular Effects. The cardiovascular effects of nicotine result primarily from activating nicotinic receptors in *sympathetic ganglia* and the *adrenal medulla*. Activation of these receptors promotes release of norepinephrine from sympathetic nerves and release of epinephrine (and some norepinephrine) from the adrenals. Norepinephrine and epinephrine act on the cardiovascular system to constrict blood vessels, accelerate the heart, and increase the force of ventricular contraction. The net result is elevation of blood pressure and increased cardiac work. These effects underlie cardiovascular deaths.

GI Effects. Nicotine influences GI function primarily by activating nicotinic receptors in *parasympathetic* ganglia, thereby increasing secretion of gastric acid and augmenting tone and motility of GI smooth muscle. In addition, nicotine can promote vomiting. Nicotine-induced vomiting results from a complex process that involves nicotinic receptors in the aortic arch, carotid sinus, and CNS.

CNS Effects. Nicotine is a CNS stimulant. The drug stimulates respiration and produces an arousal pattern on an electroencephalograph. Moderate doses can cause tremors, and high doses can cause convulsions.

Nicotine has multiple psychologic effects. The drug increases alertness, facilitates memory, improves cognition, reduces aggression, and suppresses appetite. In addition, by promoting release of dopamine, nicotine activates the brain's "pleasure system" located in the mesolimbic area. The effects of nicotine on the pleasure system are identical to those of other highly addictive drugs, including cocaine, amphetamines, and opioids.

Effects During Pregnancy and Lactation. Nicotine exposure during gestation can harm the fetus, and nicotine in breast milk can harm the nursing infant. Nonetheless, as dis-

cussed in Box 39-1, since pharmaceutical nicotine is safer than tobacco smoke, it is reasonable to consider using nicotine therapy during pregnancy to help a woman quit smoking.

Tolerance and Dependence

Tolerance. Tolerance develops to some effects of nicotine but not to others. Tolerance does develop to nausea and dizziness, which are common in the unseasoned smoker. In contrast, *very little tolerance develops to the cardiovascular effects*: Veteran smokers continue to experience increased blood pressure and increased cardiac work whenever they smoke.

Dependence. Chronic cigarette smoking results in dependence. By definition, this means that individuals who discontinue smoking will experience an abstinence syndrome. Prominent symptoms are craving, nervousness, restlessness, irritability, impatience, increased hostility, insomnia, impaired concentration, increased appetite, and weight gain. Symptoms begin about 24 hours after smoking has ceased, and can last for weeks to months. Women report more discomfort than men. Experience has shown that abrupt discontinuation may be preferable to gradual reduction. (All that gradual reduction seems to do is prolong suffering.)

Acute Poisoning

Nicotine is highly toxic. Doses as low as 40 mg can be fatal. Toxicity is underscored by the use of nicotine as an insecticide. Common causes of nicotine poisoning include ingestion of tobacco by children and exposure to nicotine-containing insecticides.

Symptoms. The most prominent symptoms involve the cardiovascular, GI, and central nervous systems. Specific symptoms include nausea, salivation, vomiting, diarrhea, cold sweat, disturbed hearing and vision, confusion, and faintness; pulses may be rapid, weak, and irregular. Death results from respiratory paralysis, which is caused by direct effects of nicotine on the muscles of respiration, as well as by effects in the CNS.

Treatment. Management centers on reducing nicotine absorption and supporting respiration; there is no specific antidote to nicotine poisoning. Absorption of ingested nicotine can be reduced by giving activated charcoal. If respiration is depressed, ventilatory assistance is indicated. Since nicotine undergoes rapid metabolic inactivation, recovery from the acute phase of poisoning can occur within hours.

Chronic Toxicity from Smoking

According to a 2004 report from the U.S. Surgeon General, the adverse consequences of smoking are more extensive than previously understood. It is now clear that chronic smoking can injure nearly every organ of the body. We already knew that smoking could cause cardiovascular disease, chronic lung disease, and cancers of the larynx, lung, esophagus, oral cavity, and bladder. New additions to the list include leukemia, cataracts, pneumonia, periodontal disease, type 2 diabetes, abdominal aortic aneurysm, and cancers of the cervix, kidney, pancreas, and stomach. Smoking during pregnancy increases the risk of low birth weight, preterm labor, stillbirth, miscarriage, spontaneous abortion, perinatal mortality, and sudden infant death. As shown in Table 39-1, the leading causes of smoking-related death are lung cancer, ischemic heart disease, and chronic airway obstruction.

SMOKING CESSATION DURING PREGNANCY

Smoking is the largest modifiable risk factor for pregnancy-related morbidity and mortality. Smoking increases the risk of ectopic pregnancy, placenta previa, placental abruption, chorioamnionitis, stillbirth, preterm birth, and spontaneous abortion. In addition, fetal exposure increases the risk of low birth weight, perinatal mortality, sudden infant death syndrome (SIDS), and cognitive, behavioral, and emotional deficits in childhood.

Of the many harmful chemicals in tobacco smoke, reproductive toxicity is due in large part to just three: *nicotine*, *carbon monoxide*, and *oxidizing agents*. Nicotine reduces placental blood flow (by promoting vasoconstriction), delays or impairs fetal brain development (by direct neurotoxic effects), inhibits maturation of fetal pulmonary cells, and increases the risk of SIDS. Carbon monoxide reduces the oxygen-carrying capacity of blood and, in high levels, is neuroteratogenic. Oxidizing agents increase the risk of thrombotic events and, by decreasing the availability of nitrous oxide (a smooth muscle relaxant), they contribute to placental vasoconstriction and preterm labor.

Clearly, smoking during pregnancy is dangerous and should be stopped. Ideally, women should quit prior to conception or early in pregnancy. However, quitting later is still beneficial. To aid smoking cessation, the authors of *Treating Tobacco Use and Dependence: 2008 Update* recommend that clinicians offer effective interventions at the first prenatal visit, and throughout the course of pregnancy as needed. Intensive, person-to-person psychosocial intervention should be offered to all pregnant smokers. Pharmacologic intervention—mainly *nicotine replacement therapy* (NRT)—may also be offered, but only if psychosocial intervention alone has failed. Of note, quit rates with a combination of psychosocial intervention plus NRT are higher than with psychosocial intervention alone.

What do we know about NRT during pregnancy? Not as much as we would like. Studies on the efficacy of NRT in pregnant smokers have been inconclusive—probably because the nicotine dosage was too low. (During the later stages of pregnancy, nicotine is metabolized at a high rate. Hence, if conventional NRT doses are used, nicotine blood levels may be too low to be effective.) Nonetheless, even if we are uncertain about NRT efficacy, it seems likely that NRT is much *safer* than smoking. After all, cigarette smoke contains thousands of harmful chemicals (in addition to nicotine), whereas NRT contains nicotine only. In fact, among women who switched from smoking to NRT, there was no evidence of serious adverse effects, and there was an important benefit: birth weight was increased.

Who should use NRT? According to a 2009 review,* use of NRT should be based on the number of cigarettes smoked. Pregnant woman who smoke no more than 5 cigarettes a day should be offered psychosocial support, but not NRT. Conversely, pregnant woman who smoke a lot should be offered NRT, along with psychosocial support.

What about bupropion and varenicline? Compared with NRT, bupropion has two advantages: (1) it lacks the potential adverse effects of nicotine and (2) it can counteract weight gain and cravings brought on by smoking cessation. One prominent voice—the American College of Obstetricians and Gynecologists (ACOG)—says that bupropion may be considered when behavioral interventions have failed. However, another prominent voice—the Motherisk Program—says that bupropion should be avoided until we know more about its safety and efficacy. As for varenicline, we have no human data on safety in pregnancy, but we do have animal data showing fetal harm. Accordingly, varenicline should not be used.

*Osadchy A, Kazmn A, Koren G: Nicotine replacement therapy during pregnancy: recommended or not recommended? *J Obstet Gynaecol Can* 31:744–747, 2009.

PHARMACOLOGIC AIDS TO SMOKING CESSATION

Cigarettes are highly addictive, which makes giving them up very hard. Nonetheless, abstinence *can* be achieved. Every year, about 41% of Americans who smoke make one or more attempts to quit. Of those who try to quit without formal help, only 3% to 5% achieve long-term success. In contrast, when a combination of counseling and drugs is employed, the 1-year abstinence rate approaches 30%. However, even with the aid of counseling and drugs, the first attempt usually fails. In fact, most people try quitting 5 to 7 times before they ultimately succeed. As time without a cigarette increases, the chances of relapse get progressively smaller: Of those who quit for a year, only 15% smoke again; and of those who quit for 5 years, only 3% smoke again.

Long-term smokers should be assured that quitting offers important health benefits. Regardless of how long you have smoked, quitting can reduce the risk of developing a tobacco-related disease, slow the progression of an established tobacco-related disease, and increase life expectancy. These

benefits apply not only to people who quit while they are young and healthy, but also to people who quit after age 65 and to those with established tobacco-related disease. Data from the Nurses' Health Study indicate that former smokers eventually achieve the same disease-risk status as never smokers, even with respect to lung cancer. The risk of chronic obstructive pulmonary disease or death from a heart attack declines to that of never smokers in 20 years, and the risk of lung cancer reaches that of never smokers in 30 years.

Nine drug products have been shown to aid smoking cessation (Table 39-2). Of these, seven are specifically approved by the FDA for this use, and are considered first-line treatments. The other two drugs—nortriptyline and clonidine—are considered second-line treatments. Of the seven first-line products, five contain nicotine and two don't. The nicotine-based products—nicotine gum, nicotine lozenge, nicotine patch, nicotine inhaler, and nicotine nasal spray—are employed as nicotine replacement therapy (NRT). The nicotine-free products—sustained-release bupropion (bupropion SR) [Zyban, Buproban] and varenicline [Chantix, Champix♣]—are taken to decrease nico-

TABLE 39-2 ■ Pharmacologic Aids for Smoking Cessation

Product	Common Side Effects	Advantages	Disadvantages
FIRST-LINE AGENTS			
Nicotine-Based Products			
Nicotine patch [Nicotrol, NicoDerm CQ]	Transient itching, burning, and redness under the patch; insomnia	Nonprescription; provides a steady level of nicotine; easy to use; unobtrusive	User cannot adjust dose if craving occurs; nicotine released more slowly than in other products
Nicotine gum [Nicorette, others]	Mouth and throat irritation, aching jaw muscles, dyspepsia	Nonprescription; user controls dose	Unpleasant taste; requires proper chewing technique; cannot eat or drink while chewing the gum; can damage dental work and is difficult for denture wearers to use
Nicotine lozenge [Commit, Thrive♣]	Hiccups, dyspepsia, mouth irritation, nausea	Nonprescription; user controls dose; easier to use than nicotine gum	Cannot eat or drink while the lozenge is in the mouth
Nicotine nasal spray [Nicotrol NS]	During 1st week: mouth and throat irritation, rhinitis, sneezing, coughing, teary eyes	User controls dose; fastest nicotine delivery and highest nicotine levels of all nicotine-based products	Prescription required; most irritating nicotine-based product; device visible when used
Nicotine inhaler [Nicotrol Inhaler, Nicorette Inhaler♣]	Mouth and throat irritation, cough	User controls dose; mimics hand-to-mouth motion of smoking	Prescription required; slow onset and low nicotine levels; frequent puffing needed; device visible when used
Nicotine-Free Products			
Varenicline [Chantix, Champix♣]	Nausea, sleep disturbances, headaches, abnormal dreams	Easy to use (pill); no nicotine; most effective pharmacologic aid to smoking cessation	Prescription required; does not counter weight gain associated with smoking cessation; may cause neuropsychiatric disturbances, including suicidal thoughts and actions
Bupropion [Zyban, Buproban]	Insomnia, dry mouth, agitation	Easy to use (pill); no nicotine; promotes weight loss, which may limit cessation-related weight gain; first-choice drug for smokers with depression	Prescription required; carries a small risk of seizures
SECOND-LINE AGENTS			
Nortriptyline* [Aventyl, Pamelor]	Dry mouth, sedation, dizziness	Easy to use (pill); no nicotine	Prescription required; side effects are common; caution required in patients with heart disease
Clonidine* [Catapres]	Dry mouth, sedation, dizziness	Easy to use (pill); no nicotine	Prescription required; side effects limit use

*Not FDA-approved for use as a smoking cessation aid.

tine craving and to suppress symptoms of withdrawal. The most effective drug therapies for smoking cessation are varenicline alone and the nicotine patch combined with a short-acting nicotine product (ie, nasal spray or gum).

At this time, we cannot predict who will respond best to a particular product. Accordingly, selection among the first-line drugs should be based on patient preference, success with a particular product in the past, and side effects. The second-line drugs should be reserved for patients who can't use the first-line drugs or who failed to quit while using them.

Interventions for smoking cessation can be found in *Treating Tobacco Use and Dependence: 2008 Update*, a clinical practice guideline issued by the U.S. Public Health Service. As stated in the guideline, tobacco dependence is a chronic condition that warrants repeated intervention until long-term abstinence is achieved. This is the same philosophy that guides treatment of dependence on other highly addictive substances, including cocaine and heroin. Tobacco dependence can be treated with two methods: drugs and counseling. Both methods are effective, but a combination of both is more

TABLE 39-3 • Internet-Based Resources for Smoking Cessation**United States**

- U.S. Department of Health and Human Services: <http://www.surgeongeneral.gov/tobacco/>
- Centers for Disease Control and Prevention: http://www.cdc.gov/tobacco/quit_smoking/
- American Lung Association: <http://www.lungusa.org/stop-smoking/>

Canada

- Canadian Council for Tobacco Control: <http://www.cctc.ca/>
- Health Canada: <http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/index-eng.php>
- Quit4Life: http://www.quit4life.com/index_e.asp
- The Lung Association: http://www.lung.ca/home-accueil_e.php

effective than either one alone. Accordingly, the guidelines recommend that all patients who want to quit be offered (1) at least one first-line drug (bupropion, varenicline, or a nicotine-based product) along with (2) counseling, be it one-on-one, in a group, or over the phone (dial 1-800-QUITNOW in the United States or 1-877-513-5333 in Canada). The overall intervention strategy is summarized in the “5 A’s” model for treating tobacco use and dependence:

- Ask (screen all patients for tobacco use).
- Advise tobacco users to quit.
- Assess willingness to make a quit attempt.
- Assist with quitting (offer medication and provide or refer to counseling).
- Arrange follow-up contacts, beginning within the first week after the quit date.

For additional information on smoking cessation, visit the internet sites for Canada and the United States listed in Table 39-3.

Nicotine Replacement Therapy

NRT allows smokers to substitute a pharmaceutical source of nicotine for the nicotine in cigarettes—and then gradually withdraw the replacement nicotine. This is analogous to using methadone to wean addicts from heroin.

Five FDA-approved formulations are available: chewing gum, lozenges, transdermal patches, a nasal spray, and an inhaler (see Table 39-2). With the gum, lozenges, patches, and inhaler, blood levels of nicotine rise slowly and remain relatively steady. Because nicotine levels rise slowly, these delivery systems produce less pleasure than cigarettes, but nonetheless do relieve symptoms of withdrawal. With the nasal spray, blood levels of nicotine rise rapidly, much as they do with smoking. Hence the nasal spray provides some of the subjective pleasure that smoking does.

Long-term quit rates are significantly greater with NRT than with placebo—although absolute success rates remain low. For example, the 1-year success with nicotine patches is about 25%, compared with 9% for placebo. Success rates are highest when replacement therapy is combined with counseling.

Nicotine products are classified in FDA Pregnancy Risk Category C (chewing gum, lozenge) or Category D (patch, inhaler, nasal spray). Accordingly, they should generally be

avoided during pregnancy. However, since smoking is probably more harmful than NRT, use of NRT during pregnancy is worth consideration (see Box 39-1).

Nicotine Chewing Gum (Nicotine Polacrilex)

Nicotine chewing gum [Nicorette, others] is composed of a gum base plus nicotine polacrilex, an ion exchange resin to which nicotine is bound. The gum must be chewed to release the nicotine. Following release, nicotine is absorbed across the oral mucosa into the systemic circulation. Like other forms of NRT, nicotine gum doubles the cessation success rate.

The most common adverse effects are mouth and throat soreness, jaw muscle ache, eructation (belching), and hiccups. Using optimal chewing technique minimizes these problems.

Patients should be advised to chew the gum slowly and intermittently for about 30 minutes. Rapid chewing can release too much nicotine at one time, resulting in effects similar to those of excessive smoking (eg, nausea, throat irritation, hiccups). Since foods and beverages can reduce nicotine absorption, patients should not eat or drink while chewing or for 15 minutes before chewing.

Nicotine gum is available in two strengths: 2 mg/piece and 4 mg/piece. Dosing is individualized and based on the degree of nicotine dependence. For initial therapy, patients with low to moderate nicotine dependence should use the 2-mg strength; highly dependent patients (those who smoke more than 25 cigarettes a day) should use the 4-mg strength. The average adult dosage is 9 to 12 pieces a day. The maximum daily dosage is 30 pieces of the 2-mg strength or 20 pieces of the 4-mg strength. Experience indicates that dosing on a fixed schedule (one piece every 2 to 3 hours) is more effective than PRN dosing for achieving abstinence.

After 3 months without cigarettes, patients should discontinue nicotine use. Withdrawal should be done gradually. Use of nicotine gum beyond 6 months is not recommended.

Nicotine Lozenges (Nicotine Polacrilex)

The pharmacology of nicotine lozenges [Commit, Thrive♦] is very similar to that of nicotine gum. Both products contain nicotine bound to polacrilex. Sucking on the lozenge releases nicotine, which is then absorbed across the oral mucosa into the systemic circulation. Like nicotine gum and other forms of NRT, nicotine lozenges double the cessation success rate.

The most common adverse effects are mouth irritation, dyspepsia, nausea, and hiccups—all of which can be made worse by taking two lozenges at once or by taking several lozenges in immediate succession.

Administration consists of placing the lozenge in the mouth and allowing it to dissolve, which takes 20 to 30 minutes. Users should not eat or drink for 15 minutes before dosing and while the lozenge is in the mouth. Also, they should not chew or swallow the lozenge.

Like nicotine gum, nicotine lozenges are available in two strengths: 2 mg and 4 mg. However, in contrast to nicotine gum, which is dosed on the basis of total cigarettes smoked per day, dosing with the lozenges is based on when the first cigarette of the day is smoked: The 2-mg strength is indicated for people who start smoking 30 minutes or more after waking; the 4-mg strength is indicated for those who smoke sooner. Users should consume no more than 5 lozenges every 6 hours, and no more than 20 lozenges per day. The recommended dosing schedule is 1 lozenge every 1 to 2 hours for

TABLE 39-4 ■ Nicotine Transdermal Systems (Patches)

Trade Name	Surface Area (cm ²)	Hours/Day in Place	Dose Absorbed	Duration of Use	
				Per Patch Size	Total
Nicoderm CQ Step 1	30	24	21 mg over 24 hr	First 4-6 wk	8-10 wk
Nicoderm CQ Step 2	20	24	14 mg over 24 hr	Next 2 wk	
Nicoderm CQ Step 3	10	24	7 mg over 24 hr	Next 2 wk	
Nicotrol Step 1	30	16	15 mg over 16 hr	First 6 wk	10 wk
Nicotrol Step 2	20	16	10 mg over 16 hr	Next 2 wk	
Nicotrol Step 3	10	16	5 mg over 16 hr	Next 2 wk	

the first 6 weeks; 1 every 2 to 4 hours for the next 3 weeks; and 1 every 4 to 8 hours for the next 3 weeks, after which dosing should stop.

Nicotine Transdermal Systems (Patches)

Nicotine transdermal systems are nicotine-containing adhesive patches that, after application to the skin, slowly release their nicotine content. The nicotine is absorbed into the skin and then into the blood, producing steady blood levels. Use of the patch about doubles the cessation success rate.

Two systems are available: NicoDerm CQ and Nicotrol. Both can be purchased without a prescription. As indicated in Table 39-4, the patches come in different sizes. The larger patches release more nicotine.

Nicotine patches are applied once a day to clean, dry, non-hairy skin of the upper body or upper arm. The site should be changed daily and not reused for at least 1 week. NicoDerm CQ patches are left in place for 24 hours and then immediately replaced with a fresh one. In contrast, Nicotrol patches are applied in the morning and removed 16 hours later at bedtime. This pattern is intended to simulate nicotine dosing produced by smoking.

Most patients begin with a large patch and then use progressively smaller patches over several weeks (see Table 39-4). Certain patients (those with cardiovascular disease, those who weigh less than 100 pounds, or those who smoke less than one-half pack of cigarettes a day) should begin with a smaller patch.

Adverse effects are generally mild. Short-lived erythema, itching, and burning occur under the patch in 35% to 50% of users. In 14% to 17% of users, persistent erythema occurs, lasting up to 24 hours after patch removal. Patients who experience severe, persistent local reactions (eg, severe erythema, itching, edema) should discontinue the patch and contact a physician or nurse practitioner.

Nicotine Inhaler

The nicotine inhaler [Nicotrol Inhaler, Nicorette Inhaler[®]] differs from other NRT products in that it looks much like a cigarette. Puffing on it delivers the nicotine. Because of this delivery method, using the inhaler can substitute for the hand-to-mouth behavior of smoking. In addition to nicotine, the inhaler contains menthol, whose purpose is to create a sensation in the back of the throat reminiscent of that caused by smoke. Like other forms of NRT, the inhaler doubles cessation success rates.

The nicotine inhaler consists of a mouthpiece and a sealed, tubular cartridge. Inside the cartridge is a porous plug containing 10 mg of nicotine. Inserting the cartridge into the mouthpiece breaks the seal. Puffing on the mouthpiece draws

air over the plug, and thereby draws nicotine vapor into the mouth. Most of the nicotine is absorbed through the *oral mucosa*—not in the lungs. As a result, blood levels rise slowly, and peak 10 to 15 minutes after puffing stops. Blood levels are less than half those achieved with cigarettes. Each cartridge can deliver 300 to 400 puffs. Benefits are greatest with frequent puffing over 20 minutes, after which the cartridge is discarded. Patients generally use 6 to 16 cartridges a day for 3 months, and then taper off over 2 to 3 months.

Adverse effects are mild. The most frequent are dyspepsia, coughing, throat irritation, oral burning, and rhinitis. The inhaler should not be used by patients with asthma. Because the cartridges contain dangerous amounts of nicotine, they should be kept away from children and pets.

Nicotine Nasal Spray

Nicotine nasal spray [Nicotrol NS] differs from other NRT formulations in that blood levels of nicotine rise *rapidly* after each administration, thereby closely simulating smoking. Because nicotine levels rise rapidly, the spray provides some of the subjective pleasure associated with cigarettes. As with other forms of NRT, the spray doubles smoking cessation rates.

The spray device delivers 0.5 mg of nicotine per activation. Two sprays (one in each nostril) constitute one dose and are equivalent to the amount of nicotine absorbed from one cigarette. Treatment should be started with 1 or 2 doses per hour—and never more than 5 doses per hour, or 40 doses a day. After 4 to 6 weeks, dosing should be gradually reduced and then stopped.

Quitting success with the spray has been good news and bad news. The good news, as reported in one study, is that 27% of users avoided smoking for 1 year—about twice the abstinence rate achieved with placebo. The bad news is that many patients continued to use the spray, being unwilling or unable to give it up. Nonetheless, since the spray delivers nicotine without the additional hazards in cigarettes, using the spray is clearly preferable to smoking.

Adverse effects are mild and temporary. At first, most users experience rhinitis, sneezing, coughing, watering eyes, and nasal and throat irritation. Fortunately, these effects abate in a few days. Nicotine nasal spray should be avoided by patients with sinus problems, allergies, or asthma.

Bupropion SR

Bupropion SR [Zyban, Buproban], an atypical antidepressant, was the first non-nicotine drug approved as an aid to smoking cessation. The drug is structurally similar to amphetamine and, like amphetamine, causes CNS stimulation and suppresses ap-

petite. In people trying to quit cigarettes, bupropion reduces the urge to smoke and reduces some symptoms of nicotine withdrawal (eg, irritability, anxiety). The drug is effective in the presence and absence of depression. Although the mechanism of action is uncertain, benefits may derive from blocking uptake of norepinephrine and dopamine. For use in depression, bupropion is sold under the trade name Wellbutrin.

Like the NRT products, bupropion SR doubles the cessation success rate. In one trial, patients were given bupropion SR (100, 150, or 300 mg/day) or placebo. At 7 weeks, abstinence rates were 19% with placebo, and 29%, 39%, and 44% with increasing dosages of bupropion SR. At 12 weeks, abstinence rates were lower: 12% with placebo and 20%, 23%, and 23% with increasing dosages of bupropion SR. Combining a nicotine patch with bupropion SR is somewhat more effective than either treatment alone.

Adverse effects are generally mild. The most common are dry mouth and insomnia. High doses (above 450 mg/day) are associated with a 0.4% risk of seizures. However, at the doses employed for smoking cessation (300 mg/day), seizures have not been reported. Nonetheless, bupropion SR should be avoided in patients with seizure risk factors, such as head trauma, history of seizures, anorexia nervosa, cocaine use, and alcohol withdrawal. Because it suppresses appetite, bupropion SR can cause weight loss. However, since weight gain is common among ex-smokers, appetite reduction may be an added benefit, not a drawback. Bupropion SR should not be combined with a monoamine oxidase inhibitor. Nor should it be given to patients taking Wellbutrin, which is just another name for bupropion itself. Benefits and risks during pregnancy are discussed in Box 39-1.

The usual regimen is 150 mg in the morning for 3 days, followed by 150 mg twice a day for 7 to 12 weeks. To minimize interference with sleep, the second dose should be taken as early in the day as possible—but at least 8 hours after the morning dose. Because onset of effects is delayed, dosing should begin 1 to 2 weeks before attempting to give up cigarettes.

The basic pharmacology of bupropion is discussed in Chapter 32.

Varenicline

Varenicline [Chantix, Champix \clubsuit], a partial agonist at nicotinic receptors, is our most effective aid to smoking cessation. In clinical trials, more patients achieved abstinence with varenicline than with bupropion SR or the nicotine patch. Estimated abstinence rates after 6 months were 33.2% with varenicline, 24.2% with bupropion SR, and 23.4% with a nicotine patch. The most common side effect is nausea. The most troubling side effects are psychologic changes. Unlike bupropion SR and NRT, varenicline does *not* reduce weight gain that occurs with smoking cessation.

Mechanism of Action. Varenicline acts as a *partial agonist* at a subset of nicotinic receptors—known as $\alpha_4\beta_2$ nicotinic receptors—whose activation promotes release of dopamine, the compound that mediates the pleasurable effects of nicotine. Compared with nicotine, varenicline binds $\alpha_4\beta_2$ receptors with greater affinity. Hence, when varenicline is present, access of nicotine to these receptors is blocked. Because varenicline is a partial agonist, receptor binding results in mild activation, which promotes some dopamine release, and thereby helps reduce both nicotine craving and the intensity of withdrawal symptoms. At the same time, the presence of varenicline prevents intense recep-

tor activation by nicotine itself, and thereby blocks the reward that nicotine can provide.

Pharmacokinetics. Varenicline is readily absorbed from the GI tract, both in the presence and absence of food. Plasma levels peak about 4 hours after dosing. Binding to plasma proteins is low (20%). Metabolism is minimal, and hence most of each dose (92%) is excreted unchanged in the urine. The plasma half-life is 17 to 24 hours. Moderate to severe renal impairment delays excretion and increases varenicline blood levels.

Adverse Effects. In clinical trials, dose-dependent *nausea* was the most common adverse effect, occurring in 30% to 40% of users. Nausea is mild to moderate initially, and becomes less severe over time. Other common reactions include sleep disturbances (18%), headaches (15%), abnormal dreams (13%), constipation (8%), dry mouth (6%), flatulence (6%), vomiting (5%), and altered sense of taste (5% to 8%). Mild physical dependence develops, but there have been no reports of abuse or addictive behavior. Rarely, varenicline has been associated with seizures, diabetes, dizziness, disturbed vision, and moderate and severe skin reactions, although a causal relationship has not been established.

Postmarketing reports indicate that varenicline can cause serious *neuropsychiatric effects*, including mood changes, erratic behavior, and suicidality. As of February 2008, there were 491 reports of suicidal thoughts and 39 successful suicides—out of more than 5 million people using the drug. At this time, we don't know if varenicline was the cause of suicidality, or if these patients had an underlying psychiatric illness. All patients should be advised to contact their prescriber if they experience a significant change in behavior or mental status. Varenicline should be used with caution in patients with a history of psychiatric disease.

In 2011, the FDA warned that varenicline can increase the risk of cardiovascular events (eg, angina pectoris, peripheral edema, hypertension, nonfatal myocardial infarction) in patients with stable cardiovascular disease. After that, a Canadian study revealed a similar risk in patients *without* cardiovascular disease. Fortunately, cardiovascular risk appears to be small—much smaller than the risk posed by smoking. Nonetheless, patients should be warned about cardiovascular risk and instructed to notify the prescriber if they experience new or worsening cardiovascular symptoms, and should seek immediate medical attention if symptoms of myocardial infarction appear.

Owing to concerns about unpredictable physical and psychiatric adverse effects, United States authorities have banned use of varenicline by truck drivers, bus drivers, airplane pilots, and air traffic controllers.

Drug Interactions. Varenicline does not affect the major components of the cytochrome P450 system. Studies with bupropion, transdermal nicotine, digoxin, warfarin, cimetidine, and metformin have shown no significant interactions. To date, no clinically significant interactions with other drugs have been reported.

Preparations, Dosage, and Administration. Varenicline is formulated in 0.5- and 1-mg tablets. To reduce nausea, each dose should be taken after eating and with a full glass of water. Dosing should begin 8 to 35 days before smoking is stopped. Titrate dosage as follows: on days 1 through 3, take 0.5 mg once daily; on days 4 through 7, take 0.5 mg twice daily; then take 1 mg twice daily for 12 weeks. If abstinence

has been achieved, an additional 12 weeks of treatment is recommended. Patients who fail to stop smoking after the initial 12 weeks, or who relapse after a full course of treatment, should be encouraged to try again when conditions are deemed favorable. Patients with severe renal impairment should begin therapy at 0.5 mg once daily and increase to 0.5 mg twice daily, if tolerated. Patients with end-stage renal disease undergoing dialysis should take a maximum of 0.5 mg once daily. Dosage adjustment is unnecessary in patients with mild to moderate renal impairment.

Nortriptyline and Clonidine

Nortriptyline [Aventyl, Pamelor] and clonidine [Catapres] are second-line drugs for helping people quit smoking. Neither product is FDA approved for this use. Nortriptyline is a tricyclic antidepressant (see Chapter 32). Clonidine is a centrally acting α_2 agonist used primarily for hypertension (see Chapter 19). Both drugs cause dry mouth, sedation, and dizziness—but the intensity is greater with clonidine. For nortriptyline, dosing is initiated at 25 mg/day starting 10 to 28 days before the quitting date, and then gradually increased to 75 to 100 mg/day. For clonidine, the dosage is 0.1 to 0.3 mg twice a day.

Nicotine Conjugate Vaccine

A nicotine conjugate vaccine [NicVAX] is in clinical trials. The vaccine helps smokers quit by stimulating production of antibodies that bind with nicotine in blood, thereby preventing nicotine from binding with its receptors in the

brain and periphery. In clinical trials, vaccinees were unable to experience pleasure from nicotine, indicating the vaccine had blocked passage of nicotine across the blood-brain barrier. In addition, compared with placebo recipients, more vaccinees were able to stop smoking, and more were able to abstain a long time. Since antibody production should persist, vaccination may be especially good for preventing relapse. To date, NicVAX has not been directly compared with other pharmacologic aids to smoking cessation.

Products That Are Not Recommended

According to *Treating Tobacco Use and Dependence: 2008 Update*, there is insufficient proof to recommend the following drugs as aids to smoking cessation: naltrexone, silver acetate, beta blockers, benzodiazepines, and antidepressants other than bupropion SR and nortriptyline, including the selective serotonin reuptake inhibitors.

Although not mentioned in the 2008 Update, *electronic cigarettes*, or *e-cigarettes*, should be avoided. E-cigarettes are battery-powered, cigarette-shaped devices that release a puff of vaporized nicotine, sometimes together with flavoring and other chemicals. According to analyses conducted by the FDA, the amount of nicotine per puff can vary widely, and the vapor may contain trace amounts of diethylene glycol and/or other contaminants. E-cigarettes are promoted on the internet as aids to quit smoking, but are not FDA-approved for this use (or any other use, for that matter). At this writing, the FDA is attempting to regulate e-cigarettes as drug-delivery devices (which seems reasonable), but is meeting resistance from the courts. The bottom line? Since the dose of nicotine with e-cigarettes is unpredictable, and since data on safety and efficacy are lacking, the use of e-cigarettes should be discouraged—especially since products of known safety and efficacy are available.

KEY POINTS

- Cigarette smoking kills about 443,000 American adults each year, making smoking the largest preventable cause of premature death.
- The principal cause of death among smokers is lung cancer, followed closely by heart disease.
- Nicotine in cigarette smoke is absorbed from the lungs, whereas nicotine in cigar smoke and smokeless tobacco is absorbed from the mouth.
- By activating nicotinic receptors in sympathetic ganglia and the adrenal medulla, nicotine causes vasoconstriction, increases heart rate, and increases force of ventricular contraction, thereby elevating blood pressure and increasing cardiac work. These effects underlie cardiovascular deaths.
- Through actions in the CNS, nicotine increases alertness, facilitates memory, improves cognitive function, reduces aggression, and suppresses appetite. In addition, by promoting release of dopamine, nicotine activates the same pleasure circuit involved in addiction to cocaine, amphetamines, and opioids.
- Although tolerance develops to some effects of nicotine, very little tolerance develops to cardiovascular effects: Veteran smokers continue to experience an increase in blood pressure and cardiac work whenever they light up.
- Nicotine causes physical dependence. Withdrawal is characterized by craving, nervousness, restlessness, irritability, impatience, increased hostility, insomnia, impaired concentration, increased appetite, and weight gain.
- Nicotine for replacement therapy is available in five FDA-approved delivery systems: chewing gum, lozenges, transdermal patches, nasal spray, and an inhaler.
- Although nicotine is harmful during pregnancy, NRT is probably safer than smoking, and hence use of NRT during pregnancy is worth consideration.
- Bupropion SR [Zyban, Buproban], which blocks reuptake of norepinephrine and dopamine, helps smokers quit by reducing nicotine craving and withdrawal symptoms.
- Varenicline [Chantix, Champix] acts as a partial agonist at a specific subset of nicotinic receptors, and thereby reduces nicotine craving and withdrawal symptoms. In addition, the drug blocks access of nicotine itself to those receptors, and thereby prevents nicotine from producing pleasurable effects.
- The most effective drug/therapies for smoking cessation are varenicline alone and the nicotine patch combined with PRN nicotine nasal spray or nicotine gum.
- With the aid of counseling and pharmacotherapy, about 30% of smokers who attempt to quit can expect to achieve long-term abstinence.

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Drug Abuse IV: Major Drugs of Abuse Other Than Alcohol and Nicotine

Heroin, Oxycodone, and Other Opioids
 General CNS Depressants
 Barbiturates
 Benzodiazepines
 Psychostimulants
 Cocaine
 Methamphetamine
 Marijuana and Related Preparations
 Psychedelics
 d-Lysergic Acid Diethylamide (LSD)
 Salvia
 Mescaline, Psilocin, Psilocybin,
 and Dimethyltryptamine
 Dissociative Drugs
 Phencyclidine
 Ketamine
 Dextromethorphan
 3,4-Methylenedioxymethamphetamine
 (MDMA, Ecstasy)
 Inhalants
 Anabolic Steroids

Box 40-1. Date-Rape Drugs: Rohypnol and GHB

In this chapter, we discuss all of the major drugs of abuse except alcohol (Chapter 38) and nicotine and tobacco (Chapter 39). As indicated in Table 40-1, abused drugs fall into seven major categories: (1) opioids, (2) psychostimulants, (3) depressants, (4) psychedelics, (5) dissociative drugs, (6) anabolic steroids, and (7) miscellaneous drugs of abuse. The basic pharmacology of many of these drugs is presented in previous chapters, and hence their discussion here is brief. Agents that have not been addressed previously (eg, marijuana, *d*-lysergic acid diethylamide [LSD]) are discussed in depth. Structural formulas of representative controlled substances are shown in Figure 40-1. Street names for abused drugs are given in Table 40-2.

HEROIN, OXYCODONE, AND OTHER OPIOIDS

The opioids (eg, heroin, oxycodone, meperidine) are major drugs of abuse. As a result, most opioids are classified as Schedule II substances. The basic pharmacology of the opioids is discussed in Chapter 28.

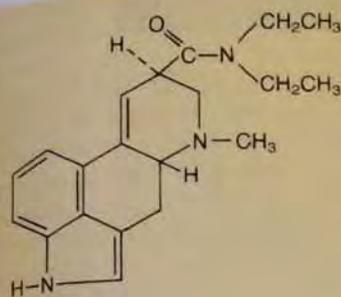
TABLE 40-1 ■ Pharmacologic Categorization of Abused Drugs

Category	Examples
Opioids	Heroin Morphine Meperidine Oxycodone Hydromorphone
Psychostimulants	Cocaine Dextroamphetamine Methamphetamine Methylphenidate
Depressants	
Barbiturates	Amobarbital Secobarbital Pentobarbital Phenobarbital
Benzodiazepines	Diazepam Flunitrazepam Lorazepam
Miscellaneous	Alcohol Methaqualone Gamma-hydroxybutyrate Meprobamate
Psychedelics	LSD Mescaline Psilocybin Dimethyltryptamine
Dissociative Drugs	Phencyclidine Ketamine
Anabolic Steroids	Nandrolone Oxandrolone Testosterone
Miscellaneous	Dextromethorphan Marijuana Nicotine Nitrous oxide Amyl nitrite

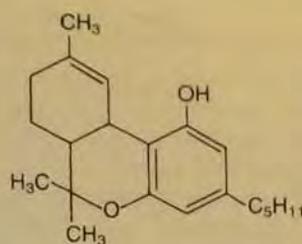
Patterns of Use

Opioid abuse is encountered in all segments of society. Formerly, opioid abuse was limited almost exclusively to lower socioeconomic groups residing in cities. Today, however, opioid abuse is more widespread, occurring in small towns as well as big cities, and among the rich and middle class as well as the poor.

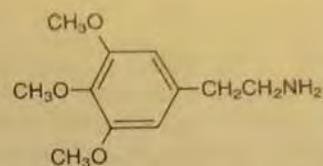
For most abusers, initial exposure to opioids occurs either socially (ie, illicitly) or in the context of pain management in



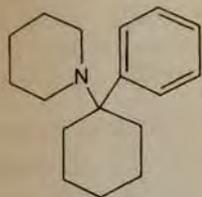
LSD



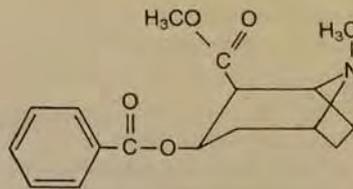
THC



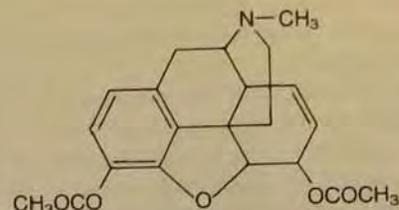
MESCALINE



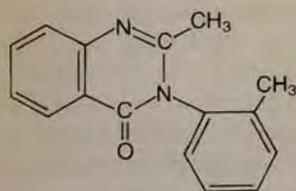
PHENCYCLIDINE



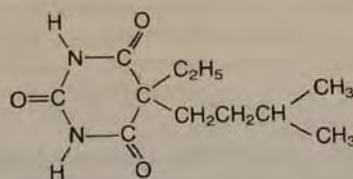
COCAINE



HEROIN



METHAQUALONE



AMOBARBITAL

Figure 40-1 • Structural formulas of representative drugs of abuse.
(LSD = *d*-lysergic acid diethylamide; THC = tetrahydrocannabinol.)

a medical setting. The overwhelming majority of individuals who go on to abuse opioids begin their drug use illicitly. Only an exceedingly small percentage of those exposed to opioids therapeutically develop a pattern of compulsive drug use.

Opioid abuse by healthcare providers deserves special consideration. It is well established that physicians, nurses, and pharmacists, as a group, abuse opioids to a greater extent than all other groups with similar educational backgrounds. The vulnerability of healthcare professionals to opioid abuse is due primarily to drug access.

Subjective and Behavioral Effects

Moments after IV injection, heroin produces a sensation in the lower abdomen similar to sexual orgasm. This initial reaction, known as a "rush" or "kick," persists for about 45 seconds. After this, the user experiences a prolonged sense of euphoria (well-being); there is a feeling that "all is well with the world." These extended effects, rather than the initial rush, are the primary reason for opioid abuse.

Interestingly, when individuals first use opioids, nausea and vomiting are prominent, and an overall sense of *dyspho-*

ria may be felt. In many cases, were it not for peer pressure, individuals would not continue opioid use long enough to allow these unpleasant reactions to be replaced by a more agreeable experience.

Preferred Drugs and Routes of Administration

Which opioids do people abuse? Practically all of them. In the past, heroin was the most commonly abused opioid drug. But no longer. Prescription opioid analgesics are now abused much more commonly than heroin: In 2009, more than 5.3 million Americans reported past-month abuse of these drugs.

Heroin. Among street users, heroin is the traditional opioid of choice. Why? Because of its high lipid solubility, heroin crosses the blood-brain barrier with ease, causing effects that are both immediate and intense. This combination of speed and intensity sets heroin apart from other opioids. According to the 2008 National Survey on Drug Use and Health, 213,000 Americans age 12 and older reported past-month abuse of heroin.

Heroin can be administered in several ways. The order of preference is IV injection, smoking, and nasal inhalation (known

TABLE 40-2 ■ Some Street Names for Abused Drugs

Drug	Street Names
Opioids	
Heroin	H, Harry, horse, junk, smack, skag
Hydrocodone	Hydro, vikes, vico
Hydromorphone	Juice
Methadone	Dolly
Oxycodone	Hillbilly heroin, OC, oxy, oxycottons
Psychedelics	
<i>d</i> -Lysergic acid diethylamide	LSD, LSD-25, acid, blotter, microdot
Dimethyltryptamine	DMT, businessman's trip
Mescaline	Peyote, cactus buttons
2,5-Dimethoxy-4-methylamphetamine	DOM, STP
Psilocybin	Magic mushrooms
Psilocin	Magic mushrooms
Salvia	Magic mint, sage of seers, Sally D
Psychostimulants	
Amphetamine	Bennies, hearts, whites, cartwheels
Dextroamphetamine	Dexies, oranges, footballs
Methamphetamine	Speed, bombita, crank, crystal meth, ice, glass
Methylphenidate	Kiddie dope, R-ball, vitamin R
Biphetamine	Black beauties
Cocaine	Coke, crack, snow, blow, flake, nose candy, toot
General CNS Depressants	
Amobarbital	Blue devils
Flunitrazepam [Rohypnol]*	Forget-me pill, Roche, R2, roofies, rope, rophies
Gamma-hydroxybutyrate (GHB)*	Grievous bodily harm, Georgia homeboy, liquid ecstasy
Pentobarbital	Yellow jackets
Secobarbital	Red devils
Methaqualone	Ludes, spoors
Dissociative Drugs	
Phencyclidine	PCP, angel dust, dummy dust, hog, ozone, peace pill, rocket fuel, sheets, wack
Ketamine	Special K, vitamin K, cat Valium
Miscellaneous Agents	
3,4-Methylenedioxymethamphetamine	MDMA, ecstasy, hug, XTC, the love drug
Marijuana	Pot, grass, reefer, weed, Panama red, Acapulco gold, Mary Jane, many others
Combinations	
Heroin + cocaine	Speedball
Heroin + crack cocaine	Moon rock
Heroin + marijuana	Atom bomb
Marijuana + phencyclidine	Killer joints, crystal supergrass

*Associated with sexual assault.

as sniffing or snorting). Intravenous injection produces effects with the greatest intensity and fastest onset (7 to 8 seconds). When heroin is smoked or snorted, effects develop more slowly, peaking in 10 to 15 minutes. Among users who seek addiction treatment, injection is the predominant method of administration. However, because sniffing and smoking are safer and easier than injection, these routes have become increasingly popular.

It should be noted that, when heroin is administered orally or subcutaneously, as opposed to intravenously, its effects cannot be distinguished from those of morphine and other opioids. This observation is not surprising given that, once in the brain, heroin is rapidly converted into morphine, its active form.

Oxycodone. In some parts of the United States, people are abusing the *controlled-release* formulation of oxycodone [Oxy-

Contin], an opioid similar to morphine. The controlled-release tablets were designed to provide steady levels of oxycodone over an extended time, and are safe and effective when swallowed intact. However, abusers do not ingest the tablets whole. Rather, they crush the tablets, and then either snort the powder, or dissolve it in water and then inject it IV. As a result, the entire dose is absorbed *immediately*, producing blood levels that are dangerously high. Hundreds of deaths have been reported. The risk of respiratory depression and death is greatest in people who have not developed tolerance to opioids.

In an effort to reduce OxyContin abuse, the controlled-release tablets were reformulated in 2010. The new formulation bears the imprint OP, rather than OC, which appeared on the old formulation. Compared with the old tablets, OxyCon-

tin OP tablets are much harder to crush into a powder. And if exposed to water or alcohol, the tablets just form a gummy blob, rather than a solution that can be drawn into a syringe and injected. However, there is no evidence that OxyContin OP tablets are less subject to abuse, diversion, overdose, or addiction than the old tablets. As noted in Chapter 28, oxycodone is also available in a tamper resistant *immediate-release* formulation, sold as Oxecta.

Meperidine. Nurses and physicians who abuse opioids often select meperidine [Demerol], a drug with distinct advantages for these users. First, unlike heroin, meperidine is highly effective when administered orally, and hence abuse need not be associated with telltale signs of repeated injections. Second, meperidine produces less pupillary constriction than other opioids, thereby minimizing awkward questions about miosis. Lastly, meperidine has minimal effects on smooth muscle function, making constipation and urinary retention less problematic than with other opioids.

Tolerance and Physical Dependence

Tolerance. With prolonged opioid use, tolerance develops to some pharmacologic effects, but not others. Effects to which tolerance does develop include euphoria, respiratory depression, and nausea. In contrast, little or no tolerance develops to constipation and miosis. Because tolerance to respiratory depression develops in parallel with tolerance to euphoria, respiratory depression does not increase as higher doses are taken to produce desired subjective effects. Persons tolerant to one opioid are cross-tolerant to other opioids. However, there is no cross-tolerance between opioids and general central nervous system (CNS) depressants (eg, barbiturates, benzodiazepines, alcohol).

Physical Dependence. Long-term use produces substantial physical dependence. The abstinence syndrome resulting from opioid withdrawal is described in Chapter 28. It is important to note that, although the opioid withdrawal syndrome can be extremely unpleasant, it is rarely dangerous.

Following the acute abstinence syndrome, which fades in 10 days, opioid addicts may experience a milder but protracted phase of withdrawal. This second phase, which may persist for months, is characterized by insomnia, irritability, and fatigue. Gastrointestinal hyperactivity and premature ejaculation may also occur.

Treatment of Acute Toxicity

Treatment of acute opioid toxicity is discussed at length in Chapter 28 and summarized here. Overdose produces a classic triad of symptoms: *respiratory depression, coma, and pinpoint pupils*. *Naloxone* [Narcan], an opioid antagonist, is the treatment of choice. This agent rapidly reverses all signs of opioid poisoning. However, dosage must be titrated carefully. Why? Because if too much is given, the addict will swing from a state of intoxication to one of withdrawal. Owing to its short half-life, naloxone must be re-administered every few hours until opioid concentrations have dropped to nontoxic levels, which may take days. Failure to repeat naloxone dosing may result in the death of patients who had earlier been rendered symptom free.

Nalmefene [Revex], a long-acting opioid antagonist, is an alternative to naloxone. Because of its long half-life, nalmefene does not require repeated dosing—an obvious advantage. However, if the dose is excessive, nalmefene will put

opioid-dependent patients into prolonged withdrawal—an obvious disadvantage.

Detoxification

Persons who are physically dependent on opioids experience unpleasant symptoms if drug use is abruptly discontinued. Techniques for minimizing discomfort are presented below.

Methadone Substitution. Methadone, a long-acting oral opioid, is the agent most commonly employed for easing withdrawal. The first step in methadone-aided withdrawal is to substitute methadone for the opioid upon which the addict is dependent. Because opioids display cross-dependence with one another, methadone will prevent an abstinence syndrome. Once the subject has been stabilized on methadone, withdrawal is accomplished by administering methadone in gradually smaller doses. The resultant abstinence syndrome is mild, with symptoms resembling those of moderate influenza. The entire process of methadone substitution and withdrawal takes about 10 days.

When substituting methadone for another opioid, suppression of the abstinence syndrome requires that methadone dosage be closely matched to the existing degree of physical dependence. Hence, to ensure that methadone dosing is adequate, the extent of physical dependence must be assessed. This can be accomplished by taking a history on the extent of drug use and by observing the patient for symptoms of withdrawal. Of the two approaches, observation is the more reliable. Estimates of drug use based on patient histories may be unreliable because (1) street users don't know the purity of the drugs they have taken, (2) claims of drug use may be inflated in hopes of receiving larger doses of methadone, and (3) addicts from the ranks of the healthcare professions may report minimal consumption to downplay the extent of abuse. Because information from addicts is not likely to permit accurate assessment of dependence, it is essential to observe the patient to make certain methadone dosage is sufficient to suppress withdrawal.

Use of methadone for *maintenance therapy* and *suppressive therapy* is discussed separately below.

Buprenorphine. As discussed in Chapter 28, buprenorphine is an agonist-antagonist opioid. Like methadone, buprenorphine can be substituted for the opioid upon which an addict is physically dependent, and can thereby prevent symptoms of withdrawal. After the addict is stabilized on buprenorphine, the dosage is gradually reduced, thereby keeping symptoms of withdrawal to a minimum. Use of buprenorphine for *maintenance therapy* is discussed below.

Clonidine-Assisted Withdrawal. Clonidine is a centrally acting α_2 -adrenergic agonist. When administered to an individual physically dependent on opioids, clonidine can suppress some symptoms of abstinence. Clonidine is most effective against symptoms related to autonomic hyperactivity (nausea, vomiting, diarrhea). Modest relief is provided from muscle aches, restlessness, anxiety, and insomnia. Opioid craving is not diminished. The basic pharmacology of clonidine is discussed in Chapter 19.

Rapid and Ultrarapid Withdrawal. In both procedures, the addict is given an opioid antagonist (naloxone or naltrexone) to precipitate immediate withdrawal, and thereby accelerate the withdrawal process. The ultrarapid procedure is carried out under general anesthesia or heavy sedation with IV midazolam [Versed]. In both procedures, clonidine may be added to ease symptoms. These procedures permit a rapid switch to maintenance therapy with an opioid antagonist. However, they are no more effective than standard withdrawal techniques, and they are considerably more expensive.

Drugs for Long-Term Management of Opioid Addiction

Three kinds of drugs are employed for long-term management: *opioid agonists*, *opioid agonist-antagonists*, and *opioid antagonists*. Opioid agonists (methadone) and agonist-antagonists

TABLE 40-3 • Drugs for Long-Term Management of Opioid Addiction

Drug	Trade Name	Formulation	Dosing Schedule	CSA Schedule	Comments
Opioid Agonist					
Methadone	Methadose, Diskets	Dispersible tablets used to make an oral suspension	Once a day	II	Methadone maintenance may be provided only by Opioid Treatment Programs certified by the federal Substance Abuse and Mental Health Services Administration and approved by the designated state authority.
	Methadose	Concentrated oral liquid	Once a day		
Opioid Agonist-Antagonist					
Buprenorphine	Subutex	Sublingual tablet	Once a day	III	Subutex and Suboxone may be prescribed in a primary care setting by any physician or nurse practitioner who has received authorized training and has registered with the Substance Abuse and Mental Health Services Administration.
	Suboxone*	Sublingual tablet	Once a day		
	Suboxone*	Sublingual film	Once a day		
	Probuphine†	Sustained-release subdermal implant	Lasts at least 6 months		
Opioid Antagonist					
Naltrexone	ReVia	Oral tablet	Once a day	NR	Naltrexone is not a controlled substance and hence prescribers do not require special training or certification. IM naltrexone [Vivitrol] is the only drug approved for opioid addictions that is given monthly, rather than daily. Before receiving naltrexone, patients must undergo opioid detoxification.
	Vivitrol	Extended-release suspension for IM injection	Once a month		

CSA = Controlled Substances Act, NR = not regulated under the CSA.

*In addition to buprenorphine, Suboxone contains naloxone, an opioid antagonist, to discourage IV dosing.

†Probuphine is not approved in the United States or Canada.

(buprenorphine) substitute for the abused opioid and are given to patients who are not yet ready for detoxification. In contrast, opioid antagonists (naltrexone) are used to discourage renewed opioid use after detoxification has been accomplished. Drugs used for long-term management of opioid addiction are summarized in Table 40-3.

Methadone. In addition to its role in facilitating opioid withdrawal, methadone [Methadose, Diskets] can be used for *maintenance therapy* and *suppressive therapy*. These strategies are employed to modify drug-using behavior in addicts who are not ready to try withdrawal.

Methadone maintenance consists of transferring the addict from the abused opioid to oral methadone. By taking methadone, the addict avoids both withdrawal and the need to procure illegal drugs. Maintenance dosing is done once a day. Maintenance is most effective when done in conjunction with nondrug measures directed at altering patterns of drug use.

Suppressive therapy is done to prevent the reinforcing effects of opioid-induced euphoria. Suppression is achieved by giving the addict progressively larger doses of methadone until a very high dose (120 mg/day) is reached. Building up to this dose creates a high degree of tolerance, and hence no subjective effects are experienced from the methadone itself. Because cross-tolerance exists among opioids, once the patient is tolerant to methadone, taking street drugs, even in

high doses, cannot produce significant desirable effects. As a result, individuals made tolerant with methadone will be less likely to seek out illicit opioids.

Use of methadone to treat opioid addicts is restricted to Opioid Treatment Programs approved by the designated state authority and certified by the federal Substance Abuse and Mental Health Services Administration. These restrictions on the nonanalgesic use of methadone are needed to control abuse of methadone, a Schedule II drug with the same abuse liability as morphine and other strong opioids. Because the number of certified clinics is limited, gaining access to one is hard in many parts of the country.

The basic pharmacology of methadone is presented in Chapter 28.

Buprenorphine. Buprenorphine [Subutex, Suboxone], an agonist-antagonist opioid, was approved for treating addiction in 2002. As discussed in Chapter 28, the drug is a partial agonist at mu receptors and a full antagonist at kappa receptors. Buprenorphine can be used for maintenance therapy and to facilitate detoxification (see above). When used for maintenance, buprenorphine alleviates craving, reduces use of illicit opioids, and increases retention in therapeutic programs.

Unlike methadone, which is available only through certified Opioid Treatment Programs, buprenorphine can be prescribed and dispensed in general medical settings, such as

primary care offices. Prescribers must receive at least 8 hours of authorized training, and must register with the Substance Abuse and Mental Health Services Administration.

Buprenorphine has several properties that make it attractive for treating addiction. Because it is a partial agonist at mu receptors, it has a low potential for abuse—but can still suppress craving for opioids. If the dosage is sufficiently high, buprenorphine can completely block access of strong opioids to mu receptors, and can thereby prevent opioid-induced euphoria. With buprenorphine, there is a ceiling to respiratory depression, which makes it safer than methadone. Development of physical dependence is low, and hence withdrawal is relatively mild.

Buprenorphine is currently available in three formulations that are dosed once a day. One formulation—sublingual tablets marketed as *Subutex*—contains buprenorphine alone. The other two formulations—sublingual tablets and sublingual films, both marketed as *Suboxone*—contain buprenorphine combined with naloxone. *Subutex* is used for the first few days of treatment, and then *Suboxone* is used for long-term maintenance. What's the purpose of the naloxone in *Suboxone*? It's there to discourage IV abuse. If taken IV, the naloxone in *Suboxone* will precipitate withdrawal. However, with sublingual administration, very little naloxone is absorbed, and hence, when the drug is administered as intended, the risk of withdrawal is low. Nonetheless, because there is a small risk with sublingual *Suboxone*, treatment is initiated with *Subutex*, thereby allowing substitution of buprenorphine for the abused opioid. Thereafter, *Suboxone* is taken for maintenance.

An investigational buprenorphine formulation—sustained-release subdermal implants [*Probuphine*]—has effects that persist for at least 6 months, an obvious advantage over the once-daily formulations when adherence is hard to achieve.

The basic pharmacology of buprenorphine is presented in Chapter 28.

Naltrexone. After a patient has undergone opioid detoxification, naltrexone [*ReVia*, *Vivitrol*], a pure opioid antagonist, can be used to discourage renewed opioid abuse. Benefits derive from blocking euphoria and all other opioid-induced effects. By preventing pleasurable effects, naltrexone eliminates the reinforcing properties of opioid use. When the former addict learns that taking an opioid cannot produce the desired response, drug-using behavior will cease. Naltrexone is not a controlled substance, and hence prescribers require no special training or certification.

Naltrexone is available in oral and IM formulations. The oral formulation, sold as *ReVia*, is dosed once a day. The IM formulation, sold as *Vivitrol*, is dosed once a month. At this time, *Vivitrol* is the only long-acting drug for managing opioid addiction. All other drugs must be taken every day.

The basic pharmacology of naltrexone is presented in Chapter 28.

Sequelae of Compulsive Opioid Use

Surprisingly, chronic opioid use has very few *direct* detrimental effects. Addicts in treatment programs have been maintained on high doses of methadone for a decade with no significant impairment of health. Furthermore, individuals on methadone maintenance can be successful socially and at work. It appears, then, that opioid use is not necessarily as-

sociated with poor health, lack of productivity, or inadequate social interaction.

Although opioids have few direct ill effects, there are many *indirect* hazards. These risks stem largely from the lifestyle of the opioid user and from impurities common to street drugs. Infections secondary to sharing nonsterile needles occur frequently. The infections that opioid abusers acquire include septicemia, subcutaneous ulcers, tuberculosis, hepatitis C, and HIV. Foreign-body emboli have resulted from impurities in opioid preparations. Opioid users suffer an unusually high death rate. Some deaths reflect the violent nature of the subculture in which opioid use often takes place. Many others result from accidental overdose.

GENERAL CNS DEPRESSANTS

The family of CNS depressants consists of barbiturates, benzodiazepines, alcohol, and other agents. With the exception of the benzodiazepines, all of these drugs are more alike than different. The benzodiazepines have properties that set them apart. The basic pharmacology of the benzodiazepines, barbiturates, and most other CNS depressants is presented in Chapter 34; the pharmacology of alcohol is presented in Chapter 38. Discussion here is limited to abuse of these drugs. Two CNS depressants notorious for their roles in date rape are discussed in Box 40-1.

Barbiturates

The barbiturates embody all of the properties that typify general CNS depressants, and hence can be considered prototypes of the group. Depressant effects are dose dependent and range from mild sedation to sleep to coma to death. With prolonged use, barbiturates produce tolerance and physical dependence.

The abuse liability of the barbiturates stems from their ability to produce subjective effects similar to those of alcohol. The barbiturates with the highest potential for abuse have a short to intermediate duration of action. These agents—amobarbital, pentobarbital, and secobarbital—are classified under Schedule II of the Controlled Substances Act. Other barbiturates appear under Schedules III and IV (see Table 37-3). Despite legal restrictions, barbiturates are available cheaply and in abundance.

Tolerance. Regular use of barbiturates produces tolerance to some effects, but not to others. Tolerance to subjective effects is significant. As a result, progressively larger doses are needed to produce desired psychologic responses. Unfortunately, very little tolerance develops to respiratory depression. Consequently, as barbiturate use continues, the dose needed to produce subjective effects moves closer and closer to the dose that can cause respiratory arrest. (Note that this differs from the pattern seen with opioids, in which tolerance to subjective effects and to respiratory depression develop in parallel.) Individuals tolerant to barbiturates show cross-tolerance with other CNS depressants (eg, alcohol, benzodiazepines, general anesthetics). However, little or no cross-tolerance develops to opioids.

Physical Dependence and Withdrawal Techniques. Chronic barbiturate use can produce substantial physical de-

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DATE-RAPE DRUGS: ROHYPNOL AND GHB

Two powerful sedative-hypnotics—Rohypnol and gamma-hydroxybutyrate (GHB)—are notorious for facilitating rape. Use of either drug to commit sexual assault is a federal crime, punishable under the *Drug-Induced Rape Prevention and Punishment Act*. Street names for Rohypnol include roofies, Roche, rope, rophies, R2, forget-me pill, and Mexican Valium. Street names for GHB include Georgia homeboy, grievous bodily harm, and liquid ecstasy.

Rohypnol

Rohypnol is the trade name for flunitrazepam, a potent benzodiazepine. Like diazepam [Valium] and other benzodiazepines, Rohypnol causes sedation, psychomotor slowing, muscle relaxation, and retrograde amnesia. When used to facilitate sexual assault, the drug is slipped into the victim's drink. The combination of alcohol and flunitrazepam produces a vulnerable state characterized by suggestibility, impaired judgment, loss of inhibition, extreme sleepiness, weakness, and inability to remember what happened after the drugs took effect; most victims eventually lose consciousness. Because an intoxicated person is considered legally incapable of consent, performing sex with such a person is considered an aggressive criminal act, and can be prosecuted as felony sexual assault. Unfortunately, owing to Rohypnol-induced amnesia, the victim is often unsure that rape actually took place, and certainly can't attest to details. As a result, prosecution is difficult. Two precautions can reduce the risk of being secretly drugged: In public settings (parties, nightclubs, etc.), never leave a drink unattended, and never accept a drink from a person you don't know and trust.

Facilitation of rape is neither the only nor the principal reason for Rohypnol abuse. Most people take it just to get high. As a rule, the drug is combined with another abused substance, typically alcohol or heroin. Because Rohypnol is relatively cheap (about \$5 a dose), the drug is especially popular among high school and college students. In the United States, abuse of Rohypnol is most common in the East and Southwest.

Rohypnol, manufactured by Hoffmann LaRoche, is available for medical use in several countries, but not the United States or Canada. In Europe, Rohypnol is widely prescribed for relieving insomnia. Effects begin within 30 minutes, peak in 2 hours, and persist for 8 hours. The principal difference between Rohypnol and other benzodiazepines is that Rohypnol is very potent—about 10 times more potent than diazepam. Hence, a small dose has a big effect. One source claims that taking 2 mg of Rohypnol is like drinking an entire six-pack of beer.

To make secretive use of Rohypnol more difficult, Hoffmann LaRoche reformulated the pill. The new formulation dissolves more slowly than the old one and contains a dye that turns pale drinks bright blue and makes dark drinks murky. In addition, the pill contains insoluble particles that float on top of all drinks. However, since flunitrazepam is also made in clandestine laboratories, not all formulations produce these conspicuous effects.

Because of its abuse potential, the legal status of flunitrazepam has changed. Initially, this drug, like all other benzodiaz-

epines, was classified under Schedule IV. In 1995, the World Health Organization reclassified it under Schedule III. In the United States, importation of flunitrazepam has been banned, and the Drug Enforcement Agency is considering placing it in Schedule I.

In 1996, Congress passed the *Drug-Induced Rape Prevention and Punishment Act*. The law imposes a maximum prison term of 20 years for importing and distributing 1 gm or more of flunitrazepam. The act also stiffens the penalty for administering a controlled substance without consent and with the intent of committing rape or any other violent crime.

GHB

Gamma-hydroxybutyrate, or GHB, has two notable actions: It depresses CNS function and, by causing release of growth hormone, it promotes muscle growth. During the 1990s, GHB gained popularity as a drug of abuse, primarily among adolescents and young adults. The drug is taken in social settings (parties, raves, clubs, etc.) to produce relaxation, euphoria, and disinhibition. Athletes take it to increase strength. And predators give it clandestinely to facilitate sexual assault. When used for assault, GHB is much like Rohypnol. The perpetrator simply slips a few drops of the colorless, odorless, tasteless liquid into the intended victim's drink and then, within 20 minutes, the GHB produces incoordination, confusion, and deep sedation, along with amnesia about what has taken place.

The pharmacology of GHB is similar to that of other CNS depressants. This is no surprise given that GHB is a metabolite of gamma-aminobutyric acid, the major inhibitory transmitter in the brain. When taken in moderate doses, GHB produces sedation, relaxation, and mild euphoria. Overdose produces significant respiratory depression, which is made worse by concurrent use of alcohol. Seizures may occur, especially with combined use of methamphetamine. Overdose can also cause nausea, vomiting, bradycardia, hypothermia, agitation, delirium, unconsciousness, and coma. GHB has been linked to more than 200 deaths and thousands of emergency department admissions.

Repeated use of GHB appears to cause tolerance and physical dependence. Tolerance is indicated by the need for bigger and bigger doses to produce relaxation and euphoria. Physical dependence is indicated by signs of withdrawal—agitation, delirium, tachycardia, insomnia, anxiety, tremors, sweating—when regular use stops.

GHB has only one approved use: reduction of cataplexy in patients with narcolepsy (see Chapter 107). The drug is regulated as a Schedule III substance.

A precursor of GHB, known as *1,4-butanediol*, undergoes conversion to GHB in the body, and hence has effects identical to those of GHB itself. Butanediol is used as an industrial solvent, and is also available as a "dietary supplement." The supplements are claimed to enhance muscle growth, fight aging, increase sexual desire, promote relaxation, and elevate mood. Trade names for the supplements include Thunder Nectar, Inner G, and Zen.

pendence. Cross-dependence exists between barbiturates and other CNS depressants, but not with opioids. When physical dependence is great, the associated abstinence syndrome can be severe—sometimes fatal (see Chapter 34). In contrast, the opioid abstinence syndrome, although unpleasant, is rarely life threatening.

One technique for easing barbiturate withdrawal employs phenobarbital, a barbiturate with a long half-life. Because of cross-dependence, substitution of phenobarbital for the abused barbiturate suppresses symptoms of abstinence. Once the patient has been stabilized, the dosage of phenobarbital is gradually tapered off, thereby minimizing symptoms of abstinence.

Acute Toxicity. Overdose with barbiturates produces a triad of symptoms: *respiratory depression, coma, and pinpoint pupils*—the same symptoms that accompany opioid poisoning. Treatment is directed at maintaining respiration and removing the drug; endotracheal intubation and ventilatory assistance may be required. Details of management are presented in Chapter 34. Barbiturate overdose has no specific antidote. Naloxone, which reverses poisoning by opioids, is not effective against poisoning by barbiturates.

Benzodiazepines

Benzodiazepines differ significantly from barbiturates. Benzodiazepines are much safer than the barbiturates, and overdose with *oral benzodiazepines alone* is rarely lethal. However, the risk of death is greatly increased when oral benzodiazepines are combined with other CNS depressants (eg, alcohol, barbiturates) or when benzodiazepines are administered IV. If severe overdose occurs, signs and symptoms can be reversed with *flumazenil* [Romazicon, Anexate[®]], a benzodiazepine antagonist. As a rule, tolerance and physical dependence are only moderate when benzodiazepines are taken for legitimate indications, but can be substantial when these drugs are abused. In patients who develop physical dependence, the abstinence syndrome can be minimized by withdrawing benzodiazepines very slowly—over a period of months. The abuse liability of the benzodiazepines is much lower than that of the barbiturates. As a result, all benzodiazepines are classified under Drug Enforcement Agency (DEA) Schedule IV. Benzodiazepines are discussed at length in Chapter 34.

PSYCHOSTIMULANTS

Discussion here focuses on two CNS stimulants that have a high potential for abuse: cocaine and methamphetamine. Because of their considerable abuse liability, these drugs are classified as Schedule II agents. (If they lacked approved medical uses, they would be classified in Schedule I.) In addition to stimulating the CNS, methamphetamine and cocaine can stimulate the heart, blood vessels, and other structures under sympathetic control. Because of these peripheral actions, these stimulants are also referred to as *sympathomimetics*.

Stimulants with little or no abuse potential are not addressed in this chapter. Included in this group are Schedule III stimulants (eg, benzphetamine), Schedule IV stimulants (eg, diethylpropion), and stimulants that are not regulated at all (eg, caffeine, ephedrine).

Cocaine

Cocaine is a stimulant extracted from the leaves of the coca plant. The drug has CNS effects similar to those of the amphetamines. In addition, cocaine can produce local anesthesia (see Chapter 26) as well as vasoconstriction and cardiac stimulation. Among abusers, a form of cocaine known as “crack” is used widely. Crack is extremely addictive, and the risk of lethal overdose is high.

According to the National Survey on Drug Use and Health (NSDUH), cocaine use has declined somewhat. In 2008, 5.1 million Americans age 12 and older reported using cocaine in any form, compared with 5.5 million in 2005. Use of crack cocaine has also declined, from 1.4 million in 2005 to 1.1 million in 2008.

Forms. Cocaine is available in two forms: *cocaine hydrochloride* and *cocaine base* (alkaloidal cocaine, freebase cocaine, “crack”). Cocaine base is heat stable, whereas cocaine hydrochloride is not. Cocaine hydrochloride is available as a white powder that is frequently diluted (“cut”) before sale. Cocaine base is sold in the form of crystals (“rocks”) that consist of nearly pure cocaine. Cocaine base is widely known by the street name “crack,” a term inspired by the sound the crystals make when heated.

Routes of Administration. Cocaine *hydrochloride* is usually administered *intranasally*. The drug is “snorted” and absorbed across the nasal mucosa into the bloodstream. A few users (about 5%) administer cocaine hydrochloride IV. Cocaine hydrochloride cannot be smoked because it is unstable at high temperature.

Cocaine *base* is administered by *smoking*, a process referred to as “freebasing.” Smoking delivers large amounts of cocaine to the lungs, where absorption is very rapid. Subjective and physiologic effects are equivalent to those elicited by IV injection.

Subjective Effects and Addiction. At usual doses, cocaine produces euphoria similar to that produced by amphetamines. In a laboratory setting, individuals familiar with the effects of cocaine are unable to distinguish between cocaine and amphetamine. How does cocaine cause euphoria? The drug inhibits neuronal reuptake of dopamine, and thereby increases activation of dopamine receptors in the brain’s reward circuit.

As with many other psychoactive drugs, the intensity of subjective responses depends on the rate at which plasma drug levels rise. Since cocaine levels rise relatively slowly with intranasal administration, and almost instantaneously with IV injection or smoking, responses produced by intranasal cocaine are much less intense than those produced by the other two routes.

When crack cocaine is smoked, desirable subjective effects begin to fade within minutes and are often replaced by dysphoria. In an attempt to avoid dysphoria and regain euphoria, the user may administer repeated doses at short intervals. This usage pattern—termed *binging*—can rapidly lead to addiction.

Acute Toxicity: Symptoms and Treatment. Overdose is frequent, and deaths have occurred. Mild overdose produces agitation, dizziness, tremor, and blurred vision. Severe overdose can produce hyperpyrexia, convulsions, ventricular dysrhythmias, and hemorrhagic stroke. Angina pectoris and myocardial infarction may develop secondary to coronary artery spasm. Psychologic manifestations of overdose include

severe anxiety, paranoid ideation, and hallucinations (visual, auditory, and/or tactile). Because cocaine has a short half-life, symptoms subside in 1 to 2 hours.

Although there is no specific antidote to cocaine toxicity, most symptoms can be controlled with drugs. Intravenous *diazepam* or *lorazepam* can reduce anxiety and suppress seizures. *Diazepam* may also alleviate hypertension and dysrhythmias, since these result from increased central sympathetic activity. If hypertension is severe, it can be corrected with intravenous *nitroprusside* or *phentolamine*. Dysrhythmias associated with prolonging the QT interval may respond to *hypertonic sodium bicarbonate*. Although beta blockers can suppress dysrhythmias, they might further compromise coronary perfusion (by preventing beta₂-mediated coronary vasodilation). Reduction of thrombus formation with aspirin can lower the risk of myocardial ischemia. Hyperthermia should be reduced with external cooling.

Chronic Toxicity. When administered intranasally on a long-term basis, cocaine can cause atrophy of the nasal mucosa and loss of sense of smell. In extreme cases, necrosis and perforation of the nasal septum occur. Nasal pathology results from local ischemia secondary to chronic vasoconstriction. Injury to the lungs can occur from smoking cocaine base.

Use During Pregnancy. Cocaine is highly lipid soluble and readily crosses the placenta, allowing it to accumulate in the fetal circulation. However, according to a report in *JAMA* (March 28, 2001, pages 1613–1625), fetal injury from cocaine is minimal—and, in all likelihood, considerably less than injury caused by tobacco or alcohol. Specifically, the *JAMA* report noted that there is no solid proof that *in utero* exposure to cocaine diminishes growth, affects developmental scores during the first 6 years, produces any lasting effect on motor development, or causes significant alterations in responses to behavioral stimuli. In short, available data fail to show that prenatal cocaine exposure has major adverse developmental effects.

Tolerance, Dependence, and Withdrawal. In animal models, regular administration of cocaine results in increased sensitivity to the drug, not tolerance. Whether this holds true for humans is not clear.

The degree of physical dependence produced by cocaine is in dispute. Some observers report little or no evidence of withdrawal following cocaine discontinuation. In contrast, others report symptoms similar to those associated with amphetamine withdrawal: dysphoria, craving, fatigue, depression, and prolonged sleep.

Treatment of Cocaine Addiction. Although achieving complete abstinence from cocaine is extremely difficult, treatment can greatly reduce cocaine use. For the cocaine addict, psychosocial therapy is the cornerstone of treatment. This therapy is directed at motivating users to commit to a drug-free life, and then helping them work toward that goal. A combination of individual therapy and group drug counseling is most effective, producing a 70% reduction in cocaine use at 12-month follow-up.

Can medication help with cocaine addiction? To date, no drug has been proved broadly effective in treating cocaine abuse. However, ongoing work with three agents is encouraging:

- **Anticocaine vaccine**—Subjects receiving the vaccine develop antibodies that bind with cocaine, and thereby render the cocaine inactive. The higher the antibody titer, the greater the reduction in cocaine use.

- **Disulfiram [Antabuse]**—Subjects receiving a combination of disulfiram plus cognitive behavioral therapy reduced their cocaine use from 2 or 3 times daily to 0.5 times daily. Disulfiram is the same drug we discussed in Chapter 38 for treating alcohol abuse.
- **Vigabatrin [Sabril]**—Compared with addicts taking placebo, those taking vigabatrin had a fourfold greater reduction in cocaine use: By the end of a 9-week trial, 28% of addicts taking vigabatrin achieved total abstinence, compared with 7.5% of addicts taking placebo. Unfortunately, vigabatrin can cause severe visual field defects, raising the question of whether its risks in this situation might outweigh its benefits. The basic pharmacology of vigabatrin is presented in Chapter 24 (Drugs for Epilepsy).

Methamphetamine

The basic pharmacology of the amphetamine family is discussed in Chapter 36. Discussion here is limited to abuse of methamphetamine.

Description and Routes. Methamphetamine is white, crystalline powder that readily dissolves in water or alcohol. The drug may be swallowed, “snorted,” smoked, or injected IV. Owing to its potential for abuse, methamphetamine is classified as a Schedule II drug.

Patterns of Use. Methamphetamine use is declining. According to the 2008 National Survey on Drug Use and Health, use of methamphetamine by Americans age 12 and older declined by more than 50% between 2006 and 2008. Among high school seniors interviewed in 2009, only 1.2% reported past-year use of the drug, compared with 4.7% interviewed in 1999.

Subjective and Behavioral Effects. As discussed in Chapter 36, amphetamines act primarily by increasing the release of norepinephrine (NE) and dopamine (DA), and partly by reducing the reuptake of both transmitters. By doing so, methamphetamine produces arousal and elevation of mood. Euphoria is likely and talkativeness is prominent. A sense of increased physical strength and mental capacity occurs. Self-confidence rises. Users feel little or no need for food and sleep. Orgasm is delayed, intensified, and more pleasurable.

Adverse Psychologic Effects. All amphetamines can produce a psychotic state characterized by delusions, paranoia, and auditory and visual hallucinations, making patients look like they have schizophrenia. Although psychosis can be triggered by a single dose, it occurs more commonly with long-term abuse. Methamphetamine-induced psychosis usually resolves spontaneously following drug withdrawal. If needed, an antipsychotic agent (eg, haloperidol) can be given to suppress symptoms.

Adverse Cardiovascular Effects. Because of its sympathomimetic actions, methamphetamine can cause vasoconstriction and excessive stimulation of the heart, leading to hypertension, angina pectoris, and dysrhythmias. Overdose may also cause cerebral and systemic vasculitis and renal failure. Changes in cerebral blood vessels can lead to stroke. Vasoconstriction can be relieved with an alpha-adrenergic blocker (eg, phentolamine). Cardiac stimulation can be reduced with a beta blocker (eg, labetalol).

Other Adverse Effects. By suppressing appetite, methamphetamine can cause significant weight loss. Use during pregnancy increases the risk of preterm birth, hypertension,

placental abruption, intrauterine growth restriction, and neonatal death. Heavy use can promote severe tooth decay, known informally as “meth mouth.” Causes include reduced salivation, grinding and clenching of the teeth, increased consumption of sugary drinks, and neglect of oral hygiene. Lastly, methamphetamine can cause direct injury to dopaminergic nerve terminals in the brain, leading to prolonged deficits in cognition and memory.

Tolerance, Dependence, and Withdrawal. Long-term use results in tolerance to mood elevation, appetite suppression, and cardiovascular effects. Although physical dependence is only moderate, psychologic dependence can be intense. Methamphetamine withdrawal can produce dysphoria and a strong sense of craving. Other symptoms include fatigue, prolonged sleep, excessive eating, and depression. Depression can persist for months and is a common reason for resuming drug use.

Treatment. Methamphetamine addiction responds well to cognitive behavioral therapy. One such approach, known as the Matrix Model, combines group therapy, individual therapy, family education, drug testing, and encouragement to participate in non-drug-related activities. At this time, no medications are approved for treatment. However, encouraging results have been achieved with two drugs: *bupropion* [Wellbutrin, Zyban], currently approved for major depression and smoking cessation, and *modafinil* [Provigil, Alertec \clubsuit], a nonamphetamine stimulant currently approved for narcolepsy, shift-work sleep disorder, and obstructive sleep apnea/hypopnea syndrome.

MARIJUANA AND RELATED PREPARATIONS

Marijuana is the most commonly used illicit drug in the United States. Over 95 million Americans have tried it at least once. In 2009, more than 28 million Americans age 12 and older used marijuana at least once within the past year. Among youth, rates of daily marijuana use are the highest since the 1970s. Results of the 2009 Monitoring the Future survey show that 11.8% of 8th-graders, 26.7% of 10th-graders, and 32.8% of 12th-graders reported using marijuana in the past year.

Cannabis sativa, the Source of Marijuana

Marijuana is prepared from *Cannabis sativa*, the Indian hemp plant—an unusual plant in that it has separate male and female forms. Psychoactive compounds are present in all parts of the male and female plants. However, the greatest concentration of psychoactive substances is found in the flowering tops of the females.

The two most common *Cannabis* derivatives are *marijuana* and *hashish*. Marijuana is a preparation consisting of leaves and flowers of male and female plants. Alternative names for marijuana include *grass*, *weed*, *pot*, and *dope*. The terms *joint* and *reefer* refer to marijuana cigarettes. Hashish is a dried preparation of the resinous exudate from female flowers. Hashish is considerably more potent than marijuana.

Psychoactive Component

The major psychoactive substance in *Cannabis sativa* is *delta-9-tetrahydrocannabinol* (THC), an oily chemical with high lipid solubility. The structure of THC appears in Figure 40-1.

The THC content of *Cannabis* preparations is variable. The highest concentrations are found in the flowers of the female plant. The lowest concentrations are in the seeds. Depending on growing conditions and the strain of the plant, THC in marijuana preparations may range from 1% to 11%.

Mechanism of Action

Psychologic effects of THC result from activating specific cannabinoid receptors in the brain. The endogenous ligand for these receptors appears to be *anandamide*, a derivative of arachidonic acid unique to the brain. The concentration of cannabinoid receptors is highest in brain regions associated with pleasure, memory, thinking, concentration, appetite, sensory perception, time perception, and coordination of movement.

There is evidence that marijuana may act in part through the same reward system as do opioids and cocaine. Both heroin and cocaine produce pleasurable sensations by promoting release of dopamine in the brain's reward circuit. In rats, intravenous THC also causes dopamine release. Interestingly, release of dopamine by THC is blocked by naloxone, a drug that blocks the effects of opioids. This suggests that THC causes release of dopamine by first causing release of endogenous opioids.

Pharmacokinetics

Administration by Smoking. When marijuana or hashish is smoked, about 60% of the THC content is absorbed. Absorption from the lungs is rapid. Subjective effects begin in minutes and peak 10 to 20 minutes later. Effects from a single marijuana cigarette may persist for 2 to 3 hours. Termination results from metabolism of THC to inactive products.

Oral Administration. When marijuana or hashish is ingested, practically all of the THC undergoes absorption. However, the majority is inactivated on its first pass through the liver. Hence only 6% to 20% of absorbed drug actually reaches the systemic circulation. Because of this extensive first-pass metabolism, oral doses must be 3 to 10 times greater than smoked doses to produce equivalent effects. With oral dosing, effects are delayed and prolonged: Responses begin in 30 to 50 minutes and persist up to 12 hours.

Behavioral and Subjective Effects

Marijuana produces three principal subjective effects: *euphoria*, *sedation*, and *hallucinations*. This set of responses is unique to marijuana; no other psychoactive drug causes all three. Because of this singular pattern of effects, marijuana is in a class by itself.

Effects of Low to Moderate Doses. Responses to low doses of THC are variable and depend on several factors, including dosage size and route, setting of drug use, and expectations and previous experience of the user. The following effects are common: euphoria and relaxation; gaiety and a heightened sense of the humorous; increased sensitivity to visual and auditory stimuli; enhanced sense of touch, taste, and smell; increased appetite and ability to appreciate the flavor of food; and distortion of time perception such that short spans seem much longer than they really are. In addition to these effects, which might be considered pleasurable (or at least innocuous), moderate doses can produce undesirable responses. Among these are impairment of short-term memory; decreased capacity to perform multistep tasks; slowed reaction time and impairment of motor coordination (which

can make driving dangerous); altered judgment and decision making (which can lead to high-risk sexual behavior); temporal disintegration (inability to distinguish between past, present, and future); depersonalization (a sense of strangeness about the self); decreased ability to perceive the emotions of others; and reduced interpersonal interaction.

High-Dose Effects. In high doses, marijuana can have serious adverse psychologic effects. The user may experience hallucinations, delusions, and paranoia. Euphoria may be displaced by intense anxiety, and a dissociative state may occur in which the user feels "outside of himself or herself." In extremely high doses, marijuana can produce a state resembling toxic psychosis, which may persist for weeks. Because of the widespread use of marijuana, psychiatric emergencies caused by the drug are relatively common.

Not all users are equally vulnerable to the adverse psychologic effects of marijuana. Some individuals experience ill effects only at extremely high doses. In contrast, others routinely experience adverse effects at moderate doses.

Effects of Chronic Use. Chronic, excessive use of marijuana is associated with a behavioral phenomenon known as an *amotivational syndrome*, characterized by apathy, dullness, poor grooming, reduced interest in achievement, and disinterest in the pursuit of conventional goals. The precise relationship between marijuana and development of the syndrome is not known, nor is it certain what other factors may contribute. Available data do not suggest that the amotivational syndrome is due to organic brain damage.

Role in Schizophrenia. Marijuana use is associated with an increased risk of schizophrenia. In young people with no history of psychotic symptoms, marijuana increases the risk of symptom occurrence. In people who already have symptoms, marijuana may prolong symptom persistence. In the stabilized schizophrenic, marijuana may precipitate an acute psychotic episode.

Physiologic Effects

Cardiovascular Effects. Marijuana produces a dose-related increase in heart rate. Increases of 20 to 50 beats/min are typical. However, rates up to 140 beats/min are not uncommon. Pretreatment with propranolol prevents marijuana-induced tachycardia but does not block the drug's subjective effects. Marijuana causes orthostatic hypotension and pronounced reddening of the conjunctivae. These responses apparently result from vasodilation.

Respiratory Effects. When used *acutely*, marijuana produces *bronchodilation*. However, when smoked chronically, the drug causes airway constriction. In addition, chronic use is closely associated with development of bronchitis, sinusitis, and asthma. Lung cancer is another possible outcome. Animal studies have shown that tar from marijuana smoke is a more potent carcinogen than tar from cigarettes.

Effects on Reproduction. Research in animals has shown multiple effects on reproduction. In males, marijuana decreases spermatogenesis and testosterone levels. In females, the drug reduces levels of follicle-stimulating hormone, luteinizing hormone, and prolactin.

Multiple effects may be seen in babies and children who were exposed to marijuana *in utero*. Some babies present with trembling, altered responses to visual stimuli, and a high-pitched cry. Preschoolers may have a decreased ability to perform tasks that involve memory and sustained attention.

Schoolchildren may exhibit deficits in memory, attentiveness, and problem solving.

Altered Brain Structure. Long-term marijuana use is associated with structural changes in the brain. Specifically, the volume of the hippocampus and amygdala is reduced, by an average of 12% and 7.1%, respectively. We don't know if volume reduction is due to reduced cell size, reduced synaptic density, or loss of glial cells and/or neurons. Interestingly, hippocampal volume loss occurs primarily in the left hemisphere.

Tolerance and Dependence

When taken in extremely high doses, marijuana can produce tolerance and physical dependence. Neither effect, however, is remarkable. Some tolerance develops to the cardiovascular, perceptual, and motor effects of marijuana. Little or no tolerance develops to subjective effects.

To demonstrate physical dependence on marijuana, the drug must be given in very high doses—and even then the degree of dependence is only moderate. Symptoms brought on by abrupt discontinuation of high-dose marijuana include irritability, restlessness, nervousness, insomnia, reduced appetite, and weight loss. Tremor, hyperthermia, and chills may occur too. Symptoms subside in 3 to 5 days. With moderate marijuana use, no withdrawal symptoms occur.

Therapeutic Use

In the United States, there are no approved medical uses for marijuana itself. However, there *are* FDA-approved uses for two *purified* cannabinoids: THC and dronabinol, an analog of THC. A third cannabinoid preparation—nabiximols—is approved in Canada.

Approved Uses for Cannabinoids. Suppression of Emesis. Intense nausea and vomiting are common side effects of cancer chemotherapy. In certain patients, these responses can be suppressed more effectively with cannabinoids than with traditional antiemetics (eg, prochlorperazine, metoclopramide). At this time, two cannabinoids—*dronabinol* [Marinol] and *nabilone* [Cesamet]—are available for antiemetic use. Dronabinol, a synthetic form of THC, is a Schedule III drug. Nabilone, a THC derivative, is a schedule II drug. Dosage forms and dosages are presented in Chapter 80.

Appetite Stimulation. Dronabinol is FDA approved for stimulating appetite in patients with AIDS. By relieving anorexia, treatment may prevent or reverse loss of weight.

Relief of Neuropathic Pain. In 2005, Canadian regulators approved *nabiximols* [Sativex ♦], administered by oral spray, for treating neuropathic pain caused by multiple sclerosis (MS). Nabiximols is a mixture of two cannabinoids: THC and cannabidiol. Because the cannabinoids in Sativex are absorbed through the oral mucosa, the product has a rapid onset (like smoked marijuana), while being devoid of the dangerous tars in marijuana smoke. In the United States, nabiximols is under study for treating intractable cancer pain. However, the drug is not yet approved in the United States, and cannot be legally imported, owing to its current classification as a Schedule I substance.

Unapproved Uses for Cannabinoids. Glaucoma. In patients with glaucoma, smoking marijuana may reduce intraocular pressure. Unfortunately, marijuana may also reduce blood flow to the optic nerve. We don't know if the drug improves vision.

Multiple Sclerosis. Whether smoked or ingested, marijuana appears to reduce spasticity and tremor of MS. Oral cannabinoids may also reduce urge incontinence. As discussed above, cannabinoids can reduce neuropathic pain of MS.

Medical Research on Marijuana. Proponents of making marijuana available by prescription argue that smoked marijuana can reduce chronic pain, suppress nausea caused by chemotherapy, improve appetite in patients with AIDS, lower intraocular pressure in patients with glaucoma, and suppress spasticity associated with MS and spinal cord injury. However, the evidence supporting most of these claims is weak—largely because federal regulations had effectively barred marijuana research.

In 1999, two developments opened the doors to marijuana research. First, an expert panel, convened by the National Academy of Sciences' Institute of Medicine, recommended that clinical trials on marijuana proceed. Because smoking marijuana poses a risk of lung cancer and other respiratory disorders, the panel also recommended development of a rapid-onset nonsmoked delivery system. In response to this report and to pressure from scientists and voters, the government created new guidelines that loosened restraints on marijuana research. Under the guidelines, researchers will be allowed to purchase marijuana directly from the federal government. (On behalf of the government, the University of Mississippi maintains a plot of marijuana on 1.8 closely guarded acres.) The only catch is that all proposed research must be approved by the FDA, the National Institute on Drug Abuse, and the DEA. Despite these formidable obstacles, at least one institute—the Center for Medicinal Cannabis Research (CMCR) at the University of California—has begun coordinating and supporting research on medical marijuana. Trials will focus on HIV-related cachexia, neuropathic pain, nausea and vomiting associated with cancer chemotherapy, and muscle spasticity associated with MS and other diseases.

Legal Status of Medical Marijuana. United States. Fourteen states* and the District of Columbia have enacted laws that eliminate criminal penalties for medical use of marijuana, and at least 12 more states are considering doing the same. Because of the new state laws, patients can now possess and use small amounts of marijuana for medical purposes. In most of these states, qualified patients must have a debilitating medical condition plus documentation from their physician that medical use of marijuana "may be of benefit."

What about federal marijuana regulations? Because marijuana is classified by the DEA as a Schedule I substance, physicians still cannot *prescribe* the drug—all they can do is *suggest* it may be of benefit. Furthermore, in 2005, the U.S. Supreme Court ruled that DEA legislation trumps the new state laws, and hence people who use or provide medical marijuana can still be prosecuted under federal law, even in states where medical marijuana has been legalized. In a (delayed) response to this ruling, the Department of Justice, in 2009, instructed U.S. Attorneys not to use federal resources to prosecute people whose actions comply with state laws that allow medical marijuana use. Hence, although patients may be breaking federal law, the Department of Justice will not prosecute them.

*Alaska, California, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Jersey, New Mexico, Oregon, Rhode Island, Vermont, and Washington.

Canada. Medical use of marijuana has been legal in Canada since 2001, when the Marijuana Medical Access Regulations took effect. Patients with documentation from a physician can get their marijuana through Health Canada, or they can get a license to grow their own. Marijuana supplies for Health Canada are grown and distributed by Prairie Plant Systems.

Comparison of Marijuana with Alcohol

In several important ways, responses to marijuana and alcohol are quite different. Whereas increased hostility and aggression are common sequelae of alcohol consumption, aggressive behavior is rare among marijuana users. Although loss of judgment and control can occur with either drug, these losses are greater with alcohol. For the marijuana user, increased appetite and food intake are typical. In contrast, heavy drinkers often suffer nutritional deficiencies. Lastly, whereas marijuana can cause toxic psychosis, dissociative phenomena, and paranoia, these severe acute psychologic reactions rarely occur with alcohol.

PSYCHEDELICS

The psychedelics are a fascinating drug family for which LSD can be considered the prototype. Other family members include mescaline, dimethyltryptamine (DMT), psilocin, and salvia. The psychedelics are so named because of their ability to produce what has been termed a *psychedelic state*. Individuals in this state show an increased awareness of sensory stimuli and are likely to perceive the world around them as beautiful and harmonious; the normally insignificant may assume exceptional meaning, the "self" may seem split into an "observer" and a "doer," and boundaries between "self" and "nonself" may fade, producing a sense of unity with the cosmos.

Psychedelic drugs are often referred to as *hallucinogens* or *psychotomimetics*. These names reflect their ability to produce hallucinations as well as mental states that resemble psychoses.

Although psychedelics can cause hallucinations and psychotic-like states, these are not their most characteristic effects. The characteristic that truly distinguishes the psychedelics from other agents is their *ability to bring on the same types of alterations in thought, perception, and feeling that otherwise occur only in dreams*. In essence, the psychedelics seem able to activate mechanisms for dreaming without causing unconsciousness.

d-Lysergic Acid Diethylamide (LSD)

History. The first person to experience LSD was a Swiss chemist named Albert Hofmann. In 1943, 5 years after LSD was first synthesized, Hofmann accidentally ingested a minute amount of the drug. The result was a dream-like state accompanied by perceptual distortions and vivid hallucinations. The high potency and unusual actions of LSD led to speculation that it might provide a model for studying psychosis. Unfortunately, that speculation did not prove correct: Extensive research has shown that the effects of LSD cannot be equated with idiopathic psychosis. With the realization that LSD did not produce a "model psychosis," medical interest in the drug

declined. Not everyone, however, lost interest; during the 1960s, nonmedical experimentation flourished. This widespread use caused substantial societal concern, and, by 1970, LSD had been classified as a Schedule I substance. Nonetheless, street use of LSD continues.

Mechanism of Action. LSD acts at multiple sites in the brain and spinal cord. However, effects are most prominent in the cerebral cortex and the locus ceruleus. Effects are thought to result from activation of serotonin₂ receptors. This concept has been reinforced by the observation that *ritanserin*, a selective blocker of serotonin₂ receptors, can prevent the effects of LSD in animals.

Time Course. LSD is usually administered orally but can also be injected or smoked. With oral dosing, initial effects can be felt in minutes. Over the next few hours, responses become progressively more intense, and then subside 8 to 12 hours later.

Subjective and Behavioral Effects. Responses to LSD can be diverse, complex, and changeable. The drug can alter thinking, feeling, perception, sense of self, and sense of relationship with the environment and other people. LSD-induced experiences may be sublime or terrifying. Just what will be experienced during any particular "trip" cannot be predicted.

Perceptual alterations can be dramatic. Colors may appear iridescent or glowing; kaleidoscopic images may appear; and vivid hallucinations may occur. Sensory experiences may merge so that colors seem to be heard and sounds seem to be visible. Afterimages may occur, causing current perceptions to overlap with preceding perceptions. The LSD user may feel a sense of wonderment and awe at the beauty of commonplace things.

LSD can have a profound impact on affect. Emotions may range from elation, good humor, and euphoria to sadness, dysphoria, and fear. The intensity of emotion may be overwhelming.

Thoughts may turn inward. Attitudes may be re-evaluated, and old values assigned new priorities. A sense of new and important insight may be felt. However, despite the intensity of these experiences, enduring changes in beliefs, behavior, and personality are rare.

Physiologic Effects. LSD has few physiologic effects. Activation of the sympathetic nervous system can produce tachycardia, elevation of blood pressure, mydriasis, piloerection, and hyperthermia. Neuromuscular effects (tremor, incoordination, hyperreflexia, and muscular weakness) may also occur.

Tolerance and Dependence. Tolerance to LSD develops rapidly. Substantial tolerance can be seen after just three or four daily doses. Tolerance to subjective and behavioral effects develops to a greater extent than to cardiovascular effects. Cross-tolerance exists with LSD, mescaline, and psilocybin, but not with DMT. Since DMT is similar to LSD, the absence of cross-tolerance is surprising. There is no cross-tolerance with amphetamines or THC. Upon cessation of LSD use, tolerance rapidly fades. Abrupt withdrawal of LSD is not associated with an abstinence syndrome. Hence there is no evidence for physical dependence.

Toxicity. Toxic reactions are primarily psychologic. LSD has never been a direct cause of death, although fatalities have occurred from accidents and suicides.

Acute panic reactions are relatively common and may be associated with a fear of disintegration of the self. Such "bad

trips" can usually be managed by a process of "talking down" (providing emotional support and reassurance in a nonthreatening environment). Panic episodes can also be managed with an antianxiety agent, such as diazepam. Neuroleptics (eg, haloperidol, chlorpromazine) may actually intensify the experience, and hence their use is questionable.

A small percentage of former LSD users experience episodic visual disturbances, referred to as *flashbacks* by users and *hallucinogen persisting perception disorder* (HPPD) by clinicians. These disturbances may manifest as geometric pseudohallucinations, flashes of color, or positive afterimages. Visual disturbances may be precipitated by several factors, including marijuana use, fatigue, stress, and anxiety. Phenothiazines exacerbate these experiences rather than provide relief. HPPD appears to be caused by permanent changes in the visual system.

In addition to panic reactions and visual disturbances, LSD can cause other adverse psychologic effects. Depressive episodes, dissociative reactions, and distortions of body image may occur. When an LSD experience has been intensely terrifying, the user may be left with persistent residual fear. The drug may also cause prolonged psychotic reactions. In contrast to acute effects, which differ substantially from symptoms of schizophrenia, prolonged psychotic reactions mimic schizophrenia faithfully.

Potential Therapeutic Uses. LSD has no recognized therapeutic applications. The drug has been evaluated in subjects with alcoholism, opioid addiction, and psychiatric disorders, including depression, anxiety, and obsessive-compulsive disorder. In addition, LSD has been studied as a possible means of promoting psychologic well-being in patients with terminal cancer. With the possible exception of some psychiatric disorders (eg, depression, anxiety), LSD has proved either ineffective or impractical.

Salvia

Salvia divinorum is a hallucinogenic herb native to southern Mexico and to Central and South America. Its primary psychoactive component is *salvinorin A*, a potent activator of kappa opioid receptors. *S. divinorum* belongs to the genus *Salvia*, part of the mint family, commonly known as sage—hence its colorful street names: Magic Mint, Diviner's Sage, and Sage of the Seers. *Salvia* is legal in some states, illegal in others, and not yet regulated under the Controlled Substances Act.

Salvia is used extensively in the United States, primarily by teens and young adults. In 2009, 5.7% of high school seniors reported using the drug in the past year. About 1.8 million Americans over the age of 12 report having used *salvia* at least once in their lives.

How is *salvia* administered? Among Mexican Indians, the traditional method is to chew the leaves or drink a liquid extract. In contrast, recreational users usually smoke the dried leaves, either in a pipe or rolled in a joint. When the smoke is inhaled, *salvinorin A* undergoes rapid absorption from the lungs. As a result, psychologic effects begin quickly (in less than 1 minute) and then quickly fade (typically in 5 to 10 minutes).

Like other psychedelic drugs, *salvia* induces a dream-like state of unreality. Users may lose awareness of their own bodies and of the room they are in. They may feel they are floating, traveling through time and space, or merging with or

transforming into objects. Some feel they are being twisted or pulled. There may be a sense of overlapping realities and of being in several places at once. Speech may become slurred, and sentences may lack fluent structure. Uncontrollable laughter may break out. Possible physical effects include chills, dizziness, nausea, incoordination, and bradycardia. Whether saliva poses long-term health risks has not been studied. However, we do know that Mexican Indians have used the drug for generations, with no apparent ill effects.

Mescaline, Psilocin, Psilocybin, and Dimethyltryptamine

In addition to LSD and salvia, the family of psychedelic drugs includes mescaline, psilocin, psilocybin, dimethyltryptamine (DMT), and several related compounds. Some psychedelics are synthetic and some occur naturally. DMT and LSD represent the synthetic compounds. Mescaline, a constituent of the peyote cactus, and psilocin and psilocybin, constituents of "magic mushrooms," represent compounds found in nature.

The subjective and behavioral effects of the miscellaneous psychedelic drugs are similar to those of LSD. Like LSD, these drugs can elicit modes of thought, perception, and feeling that are normally restricted to dreams. In addition, they can cause hallucinations and induce mental states that resemble psychosis.

The miscellaneous psychedelics differ from LSD with respect to potency and time course. LSD is the most potent of the psychedelics, producing its full spectrum of effects at doses as low as 0.5 mcg/kg. Psilocin and psilocybin are 100 times less potent than LSD, and mescaline is 4000 times less potent than LSD. Whereas the effects of LSD are prolonged (responses may last 12 or more hours), the effects of mescaline and DMT are shorter: Responses to mescaline usually fade within 8 to 12 hours, and responses to DMT fade within 1 to 2 hours.

None of these psychedelics is approved for medical use. The use of psilocybin in patients with terminal cancer and obsessive-compulsive disorder is under investigation.

DISSOCIATIVE DRUGS

The dissociative drugs—phencyclidine and ketamine—were originally developed as surgical anesthetics. When taken recreationally, these drugs distort perception of sight and sound, and produce feelings of dissociation (detachment) from the environment. High doses can produce sedation, immobility, analgesia, and amnesia.

Phencyclidine

Phencyclidine ("PCP," "angel dust," "peace pill") was originally developed as an anesthetic for animals. The drug was tried briefly as a general anesthetic for humans, but was withdrawn owing to severe emergence delirium. Although rejected for therapeutic use, phencyclidine has become widely used as a drug of abuse, largely because it can be synthesized easily by amateur chemists, making it cheap and abundant. The popularity of phencyclidine is disturbing in that a high incidence of adverse effects make phencyclidine one of the most dangerous drugs of abuse.

Chemistry and Pharmacokinetics

Chemistry. Phencyclidine is a weak organic base with high lipid solubility. The drug is chemically related to ketamine, an unusual general anesthetic (see Chapter 27 and below). The structural formula of phencyclidine appears in Figure 40-1.

Pharmacokinetics. Phencyclidine can be administered orally, intranasally, intravenously, and by smoking. For administration by smoking, the drug is usually sprinkled on plant matter (eg, oregano, parsley, tobacco, marijuana). Because of its high lipid solubility, phencyclidine is readily absorbed from all sites.

Once absorbed, phencyclidine undergoes substantial gastrointestinal recirculation. Because it is a base, phencyclidine in the blood can be drawn into the acidic environment of the stomach (by the pH partitioning effect); from the stomach, the drug re-enters the intestine, from which it is reabsorbed into the blood. This cycling from blood to GI tract and back prolongs the drug's sojourn in the body. Elimination occurs eventually through a combination of hepatic metabolism and renal excretion.

Mechanism of Action

Phencyclidine acts in the cerebral cortex and limbic system, where it blocks a subset of receptors for glutamate, known as *N*-methyl-D-aspartate (NMDA) receptor complexes. These glutamate receptors are involved in multiple processes, including learning, memory, emotionality, and perception of pain.

Subjective and Behavioral Effects

Phencyclidine produces a unique set of effects. Hallucinations are prominent. In addition, the drug can produce CNS depression, CNS excitation, and analgesia.

Effects of Low to Moderate Doses. At low doses, phencyclidine produces effects like those of alcohol. Low-dose intoxication is characterized by euphoria, release of inhibitions, and emotional lability. Nystagmus, slurred speech, and motor incoordination may occur too.

As dosage increases, the clinical picture becomes more variable and complex. Symptoms include excitation, disorientation, anxiety, disorganized thoughts, altered body image, and reduced perception of tactile and painful stimuli. Mood may be volatile and hostile. Bizarre behavior may develop. Heart rate and blood pressure are elevated.

High-Dose (Toxic) Effects. High doses can cause severe adverse physiologic and psychologic effects. Death may result from several causes.

Psychologic effects include hallucinations, confusional states, combativeness, and psychosis. The psychosis closely resembles schizophrenia and may persist for weeks. Individuals with pre-existing psychoses are especially vulnerable to psychotogenic effects. Suicide has been attempted.

Physiologic effects of high-dose phencyclidine are varied. Extreme overdose can produce hypertension, coma, seizures, and muscular rigidity associated with severe hyperthermia and rhabdomyolysis.

Managing Toxicity. Treatment is primarily supportive. Psychotic reactions are best managed by isolation from external stimuli. "Talking down" is not effective, and the benefits of antipsychotic drugs, such as haloperidol, are limited. Physical restraint may be needed to prevent self-inflicted

harm and to protect others from assault. If respiration is depressed, mechanical support of ventilation may be needed. Severe hypertension can be managed with diazoxide, a vasodilator. Seizures can be controlled with IV diazepam. If fever is high, external cooling can lower temperature. By promoting muscle relaxation, dantrolene can reduce heat generation and rhabdomyolysis.

Elimination of phencyclidine can be accelerated by continuous gastric lavage and by acidification of the urine with ammonium chloride. Continuous lavage is effective because gastroenteric recirculation keeps delivering drug to the stomach. Acidification of urine may promote phencyclidine excretion by reducing tubular reabsorption of this weak base.

Ketamine

Ketamine is a dissociative anesthetic used in animals and humans (see Chapter 27, General Anesthetics). As discussed in Chapter 32, the drug can also produce rapid relief of depression. Medicinal ketamine is formulated as an injectable liquid. For recreational use, the liquid is evaporated off, leaving a powder that can be snorted or ingested. Doses typically range from 50 to 200 mg. Much of the ketamine sold on the street was diverted from veterinary offices. Ketamine is regulated as a Schedule III substance.

Ketamine is similar to phencyclidine in structure, mechanism, and effects, although its duration of action is shorter. When the drug is snorted, effects begin in 5 to 15 minutes and persist about an hour. Moderate doses produce effects ranging from a dream-like state to a pleasant sensation of floating to a sense of being separated from one's body. Some users experience a state known as the *K-hole*, likened to a near-death experience in which there is a sense of rising above one's body. For some, the *K-hole* experience is accompanied by a sense of inner peace and radiant light. For others, the *K-hole* experience is characterized by a terrifying sense of nearly complete sensory detachment. At high doses, ketamine can cause hallucinations, delirium, amnesia, elevation of blood pressure, and potentially fatal disruption of respiration. Even higher doses can produce unconsciousness and fatal cardiovascular collapse.

Because of its depressant and amnesic effects, ketamine has been used to facilitate sexual assault. The drug is colorless, tasteless, and odorless, and hence can be added to a beverage without detection. The use of two other drugs—gamma-hydroxybutyrate (GHB) and Rohypnol—to facilitate sexual assault is discussed in Box 40-1.

DEXTROMETHORPHAN

Dextromethorphan (DXM) is a cough suppressant widely available in over-the-counter cough and cold remedies (see Chapter 77). At the low doses needed for cough suppression, DXM is devoid of psychologic effects. However, at doses 5 to 10 times higher, DXM can cause euphoria, disorientation, paranoia, and altered sense of time, as well as visual, auditory, and tactile hallucinations. These effects are produced by dextromethorphan, a metabolite of DXM that blocks receptors for NMDA. Note that this is the same mechanism used by phencyclidine and ketamine. Many of the products that contain DXM also contain other drugs, including acetaminophen,

antihistamines, phenylephrine, and pseudoephedrine. Therefore, when excessive doses are taken, users are subject to toxicity from these compounds as well as from DXM itself. The principal users of DXM are adolescents and teenagers. Between 1999 and 2004, reports of DXM abuse in these groups rose 10-fold. Many products contain DXM, including Coricidin HBP Cough & Cold, Robitussin, Vicks NyQuil Cough Syrup, and Theraflu Thin Strips.

3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, ECSTASY)

MDMA, also known as "ecstasy," is a complex drug with stimulant and psychedelic properties. The drug is structurally related to methamphetamine (a stimulant) and mescaline (a hallucinogen). Low doses produce mild LSD-like psychedelic effects; higher doses produce amphetamine-like stimulant effects. These effects result from (1) blocking reuptake of serotonin, and (2) promoting the release of serotonin, dopamine, and norepinephrine. Although MDMA can produce effects that are clearly pleasurable, it can also be dangerous; the biggest concerns are neurotoxicity, seizures, excessive cardiovascular stimulation, and hyperthermia and its sequelae. MDMA is classified as a Schedule I drug.

Time Course and Dosage. MDMA is usually dosed orally, but may also be snorted, injected, or inserted as a rectal suppository. With oral administration, effects begin in 20 minutes, peak in 2 to 3 hours, and persist 4 to 5 hours. The usual dose is 100 mg or less.

Who Uses MDMA and Why? MDMA is used primarily by adolescents and young adults, who often take it at nightclubs and all-night dance parties, known as "raves." The drug is used by young people in cities, in the suburbs, and in the country. According to a survey conducted in 2009, 1.3% of 8th-graders, 3.7% of 10th-graders, and 4.3% of 12th-graders had used MDMA in the past year.

Why do people take MDMA? Because it makes them feel really good. The drug can elevate mood, increase sensory awareness, and heighten sensitivity to music. It can also facilitate interpersonal relationships: Users report a sense of closeness with others, lowering of defenses, reduced anxiety, enhanced communication, and increased sociability.

Adverse Effects. Unfortunately, MDMA is not free of risks. The drug can injure serotonergic neurons, stimulate the heart, and raise body temperature to a dangerous level. In addition, it can cause neurologic effects (eg, seizures, spasmodic jerking, jaw clenching, teeth grinding) and a host of adverse psychologic effects (eg, confusion, anxiety, paranoia, panic attacks, visual hallucinations, and suicidal thoughts and behavior). Every year, MDMA is associated with several thousand admissions to emergency departments, mainly because of seizures.

MDMA can damage serotonergic neurons, perhaps irreversibly. When administered to rats and primates in doses only 2 to 4 times greater than those that produce hallucinations in humans, MDMA causes *irreversible destruction of serotonergic neurons*, resulting in passivity and insomnia. At least three lines of evidence suggest that MDMA is also neurotoxic in humans: (1) MDMA causes dose-related impairment of memory, a brain function mediated in part by sero-

tonin. Memory impairment persists long after MDMA was last taken. (2) The cerebrospinal fluid of long-term MDMA users contains abnormally low concentrations of serotonin metabolites, suggesting a loss of serotonergic neurons. (3) Using positron emission tomography to study former MDMA users, researchers demonstrated decreased binding of a ligand selective for the serotonin transporter, indicating damage to serotonergic neurons. In this study, reductions in ligand binding correlated with the extent of MDMA use, and not with the duration of abstinence.

MDMA can cause hyperthermia in association with dehydration, hyponatremia, and rhabdomyolysis (disintegration of muscle tissue). Treatment consists of rapid cooling, rehydration, and administering dantrolene [Dantrium], a drug that relaxes skeletal muscle, thereby reducing heat generation and the risk of rhabdomyolysis. The risk of hyperthermia and dehydration could be greatly reduced by providing ample fluids at raves and other events where MDMA is likely to be used.

Because of its amphetamine-like actions, MDMA can increase heart rate, blood pressure, and myocardial oxygen consumption. Remarkably, the increases in heart rate and blood pressure equal those produced by maximal doses of dobutamine, a powerful adrenergic agonist (see Chapter 17). Cardiovascular stimulation poses a special risk to users with heart disease.

Potential Medical Use. Despite its potential for adverse effects, MDMA also has the potential for therapeutic good, owing largely to its ability to decrease feelings of fear and defensiveness and promote feelings of love, trust, and compassion. In 2004, the FDA approved two small clinical trials of MDMA, one in patients with post-traumatic stress disorder, and the other in patients with severe anxiety related to terminal cancer.

INHALANTS

The inhalants are a diverse group of drugs that have one characteristic in common: administration by inhalation. These drugs can be divided into three classes: anesthetics, volatile nitrites, and organic solvents.

Anesthetics

Provided that dosage is modest, anesthetics produce subjective effects similar to those of alcohol (euphoria, exhilaration, loss of inhibitions). The anesthetics that have been abused most are *nitrous oxide* ("laughing gas") and *ether*. One reason for the popularity of these drugs is ease of administration: Both agents can be used without exotic equipment. For nitrous oxide, ready availability also promotes use: Small cylinders of the drug, marketed for aerating whipping cream, can be purchased without restriction.

Volatile Nitrites

Four volatile nitrites—*amyl nitrite*, *butyl nitrite*, *isobutyl nitrite*, and *cyclohexyl nitrite*—are subject to abuse. These drugs are abused by homosexual males because of an ability to relax the anal sphincter, and by males in general because of a reputed ability to prolong and intensify sexual orgasm.

The most pronounced pharmacologic effect of volatile nitrites is *venodilation*, which causes pooling of blood in veins,

which in turn causes a profound drop in systolic blood pressure. The result is dizziness, lightheadedness, palpitations, and possibly pulsatile headache. Effects begin seconds after inhalation and fade rapidly. The primary toxicity is methemoglobinemia, which can be treated with methylene blue and supplemental oxygen.

Nitrites are available from medical and nonmedical sources. Amyl nitrite is used for angina pectoris. Cyclohexyl nitrite is present in room odorizers. Butyl nitrite and isobutyl nitrite are present in products made solely for recreational use. Trade names for butyl nitrite and isobutyl nitrite include Climax, Rush, and Locker Room. On the street, preparations of amyl nitrite are known as "poppers" or "snappers." These terms reflect the popping sound made by amyl nitrite ampules when snapped open to allow inhalation.

Organic Solvents

A wide assortment of solvents have been inhaled to induce intoxication. These compounds include *toluene*, *gasoline*, *lighter fluid*, *paint thinner*, *nail-polish remover*, *benzene*, *acetone*, *chloroform*, and *model-airplane glue*. These agents are used primarily by children and the very poor—people who, because of age or insufficient funds, lack access to more conventional drugs of abuse. In recent years, use of inhalants by young children and teens has been rising.

Administration. Solvents are administered by three processes, referred to as "bagging," "huffing," and "sniffing." Bagging is performed by pouring solvent in a bag and inhaling the vapor. Huffing is performed by pouring the solvent on a rag and inhaling the vapor. Sniffing is performed by inhaling the solvent directly from its container.

Acute Pharmacologic Effects. The acute effects of organic solvents are somewhat like those of alcohol (euphoria, impaired judgment, slurred speech, flushing, CNS depression). In addition, these compounds can cause visual hallucinations and disorientation with respect to time and place. High doses can cause sudden death. Possible causes include anoxia, respiratory depression, vagal stimulation (which slows heart rate), and dysrhythmias.

Chronic Toxicity. Prolonged use is associated with multiple toxicities. For example, chloroform is toxic to the heart, liver, and kidneys; and toluene can cause severe brain damage and bone marrow depression. Many solvents can damage the heart; fatal dysrhythmias have occurred secondary to drug-induced heart block.

Management. Management of acute toxicity is strictly supportive. The objective is to stabilize vital signs. We have no antidotes for volatile solvents.

ANABOLIC STEROIDS

Many athletes take anabolic steroids (androgens) to enhance athletic performance. The principal benefit is increased muscle mass and strength. Because of the massive doses that are employed, the risk of adverse effects is substantial. With long-term steroid use, an addiction syndrome develops. Because of their abuse potential, most androgens are now classified as Schedule III drugs (see Table 37-3). The basic pharmacology of androgens and their abuse by athletes are discussed in Chapter 65.

KEY POINTS

- Abuse of OxyContin and other opioid analgesics is now much more common than abuse of heroin.
- Because heroin is very lipid soluble, initial effects are more intense and occur faster than with other opioids.
- Among healthcare providers who abuse opioids, meperidine [Demerol] is a drug of choice. Why? Because meperidine is orally active, causes minimal pupillary constriction, and causes less constipation and urinary retention than other opioids.
- With opioids, tolerance to respiratory depression develops in parallel with tolerance to euphoria. As a result, respiratory depression does not increase as higher doses are taken to produce desired subjective effects.
- Persons tolerant to one opioid are cross-tolerant to all other opioids.
- Although the opioid withdrawal syndrome can be extremely unpleasant, it is rarely dangerous.
- Opioid overdose produces a classic triad of symptoms: respiratory depression, coma, and pinpoint pupils. Death can result.
- Naloxone, an opioid antagonist, is the treatment of choice for opioid overdose.
- Naloxone dosage must be titrated carefully, because too much naloxone will transport the patient from a state of intoxication to one of withdrawal. Also, since the half-life of naloxone is shorter than the half-lives of the opioids, naloxone must be administered repeatedly until the crisis is over.
- Because of cross-dependence, methadone can ease withdrawal symptoms in opioid-dependent individuals. To ease withdrawal, methadone is substituted for the abused opioid and then gradually tapered.
- In opioid abusers who are not ready for withdrawal, methadone can be used for maintenance therapy or for suppressive therapy. In maintenance therapy, the methadone dosage is equivalent to the dosage of the abused opioid, thereby preventing withdrawal. In suppressive therapy, the abuser is rendered opioid tolerant with very high doses of methadone; as a result, use of street opioids can no longer produce subjective effects.
- Buprenorphine is an alternative to methadone for detoxification and maintenance of opioid addicts.
- In contrast to methadone, which is available only through approved Opioid Treatment Programs, buprenorphine can be prescribed in a primary care setting by any physician or nurse practitioner who has (1) received at least 8 hours of approved training and (2) registered with the Substance Abuse and Mental Health Services Administration.
- After an opioid addict has undergone detoxification, naltrexone, an opioid antagonist, can be used to discourage renewed opioid abuse.
- A sustained-release IM formulation of naltrexone can be dosed just once a month, unlike all other drugs for managing opioid addiction, which must be dosed once a day.
- With barbiturates, tolerance develops to subjective effects but not to respiratory depression. As a result, as increasingly large doses are taken to produce subjective effects, the risk of serious respiratory depression increases. (Note that this differs from the situation with opioids.)
- Individuals who are tolerant to barbiturates show cross-tolerance with other CNS depressants (eg, alcohol, benzodiazepines, general anesthetics) but not with opioids.
- Individuals who are physically dependent on barbiturates show cross-dependence with other CNS depressants, but not with opioids.
- When physical dependence on barbiturates (and other CNS depressants) is great, the associated abstinence syndrome can be severe—sometimes fatal. (Note that this differs from the situation with opioids.)
- Overdose with barbiturates produces the same triad of symptoms seen with opioids: respiratory depression, coma, and pinpoint pupils. Death can result.
- In contrast to opioid overdose, barbiturate overdose has no antidote, and hence treatment is only supportive.
- In contrast to overdose with opioids or barbiturates, overdose with benzodiazepines alone is rarely fatal.
- If necessary, benzodiazepine overdose can be treated with flumazenil, a benzodiazepine antagonist.
- The psychologic effects of cocaine result from activation of dopamine receptors secondary to cocaine-induced blockade of dopamine reuptake.
- Severe overdose with cocaine can produce hyperpyrexia, convulsions, ventricular dysrhythmias, and hemorrhagic stroke; death has occurred. Psychologic effects of overdose include severe anxiety, paranoid ideation, and hallucinations.
- There is no specific antidote to cocaine overdose. Intravenous diazepam can suppress anxiety, seizures, hypertension, and dysrhythmias. Intravenous nitroprusside or phentolamine can treat severe hypertension.
- In animals, regular use of cocaine produces sensitization—not tolerance. Whether this is true for humans is unclear.
- Whether cocaine causes significant physical dependence is in dispute.
- Psychosocial therapy is considered the cornerstone of cocaine addiction treatment. Adding disulfiram may also help.
- In addition to CNS stimulation, methamphetamine causes vasoconstriction and stimulates the heart. Cardiovascular stimulation may result in hypertension, angina, dysrhythmias, and stroke.
- Regular use of methamphetamine can produce a state that closely resembles paranoid schizophrenia.
- Although physical dependence on methamphetamine is only moderate, psychologic dependence can be intense. Withdrawal can produce dysphoria and a strong sense of craving.
- The major psychoactive substance in marijuana is delta-9-tetrahydrocannabinol (THC).
- THC produces its psychologic effects by activating cannabinoid receptors in the brain.
- Marijuana has three principal subjective effects: euphoria, sedation, and hallucinations.

- Physiologic effects of marijuana, as well as tolerance and physical dependence, are minimal.
- Marijuana has no approved medical uses, although THC and other purified cannabinoids do.
- Psychedelic drugs produce alterations in thought, perception, and feeling that otherwise occur only in dreams.
- Psychedelic drugs are also known as hallucinogens or psychotomimetics—names that reflect their ability to produce hallucinations and mental states that resemble psychosis.
- Lysergic acid diethylamide (LSD) can be considered the prototype of the psychedelic drugs.
- LSD produces its effects by activating serotonin₂ receptors in the brain.
- Although tolerance develops to LSD, physiologic effects and physical dependence are minimal.
- Acute panic reactions to LSD can be managed by “talking down” and by treatment with benzodiazepines. Neuroleptic drugs (eg, haloperidol) may intensify the reaction.
- LSD users may experience episodic visual disturbances after discontinuing the drug. In many cases, the underlying cause is a permanent change in the visual system.
- Some LSD users experience prolonged psychotic reactions that closely resemble schizophrenia.
- Phencyclidine (PCP) is a dissociative anesthetic that produces alcohol-like effects at low doses and hallucinations and psychotic reactions at high doses.
- Extreme overdose with phencyclidine can produce hypertension, coma, and seizures, as well as muscular rigidity associated with severe hyperthermia and rhabdomyolysis.
- There is no specific antidote to phencyclidine overdose. “Talking down” is not effective, and antipsychotic drugs are of limited help.
- Ecstasy (MDMA) produces psychedelic effects at low doses and amphetamine-like stimulation at higher doses.
- Ecstasy can cause irreversible destruction of serotonergic neurons.

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Review of Renal Anatomy and Physiology

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Physiology

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Adverse Impact on Extracellular Fluid

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Other High-Ceiling Diuretics

Thiazides and Related Diuretics

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Other Thiazide-Type Diuretics

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Triamterene

Amiloride

Mannitol, an Osmotic Diuretic

Diuretics are drugs that increase the output of urine. These agents have two major applications: (1) treatment of hypertension and (2) mobilization of edematous fluid associated with heart failure, cirrhosis, or kidney disease. In addition, because of their ability to maintain urine flow, diuretics are used to prevent renal failure.

REVIEW OF RENAL ANATOMY AND PHYSIOLOGY

Understanding the diuretic drugs requires a basic knowledge of the anatomy and physiology of the kidney. Therefore, let's review these topics before discussing the diuretics themselves.

Anatomy

The basic functional unit of the kidney is the *nephron*. As indicated in Figure 41-1, the nephron has four functionally distinct regions: (1) the *glomerulus*, (2) the *proximal convoluted tubule*, (3) the *loop of Henle*, and (4a, 4b) the *distal convoluted tubule*. All nephrons are oriented within the kidney such that the upper portion of Henle's loop is located in the renal cortex and the lower end of the loop descends toward the renal *medulla*. Without this orientation, the kidney could not produce concentrated urine.

In addition to the nephrons, the *collecting ducts* (the tubules into which the nephrons pour their contents) play a critical role in kidney function. As suggested by Figure 41-1,

the final segment of the distal convoluted tubule (4b) plus the collecting duct into which it empties (5) can be considered a single functional unit: the *distal nephron*.

Physiology

Overview of Kidney Functions

The kidney serves three basic functions: (1) cleansing of extracellular fluid (ECF) and maintenance of ECF volume and composition; (2) maintenance of acid-base balance; and (3) excretion of metabolic wastes and foreign substances (eg, drugs, toxins). Of the three, maintenance of ECF volume and composition is the one that diuretics affect most.

The Three Basic Renal Processes

Effects of the kidney on ECF are the net result of three basic processes: (1) *filtration*, (2) *reabsorption*, and (3) *active secretion*. In order to cleanse the entire ECF, a huge volume of plasma must be filtered. Furthermore, in order to maintain homeostasis, practically everything that has been filtered must be reabsorbed—leaving behind only a small volume of urine for excretion.

Filtration. Filtration occurs at the *glomerulus* and is the first step in urine formation. Virtually all small molecules (electrolytes, amino acids, glucose, drugs, metabolic wastes) that are present in plasma undergo filtration. In contrast, cells and large molecules (lipids, proteins) remain behind in the blood. The most prevalent constituents of the filtrate are sodium ions and chloride ions. Bicarbonate ions and potassium ions are also present, but in smaller amounts.

The filtration capacity of the kidney is very large. Each minute the kidney produces 125 mL of filtrate, which adds up to 180 L/day. Since the total volume of ECF is only 12.5 L, the kidneys can process the equivalent of all the ECF in the body every 100 minutes. Hence, the ECF undergoes complete cleansing about 14 times each day.

Be aware that filtration is a *nonselective process*, and therefore cannot regulate the composition of urine. Reabsorption and secretion—processes that display a significant degree of selectivity—are the primary determinants of what the urine ultimately contains. Of the two, reabsorption is by far the more important.

Reabsorption. Greater than 99% of the water, electrolytes, and nutrients that are filtered at the glomerulus undergo reabsorption. This conserves valuable constituents of the filtrate while allowing wastes to undergo excretion. Reabsorption of solutes (eg, electrolytes, amino acids, glucose) takes place by way of *active transport*. Water then follows passively along the osmotic gradient created by solute reuptake. Specific sites along the nephron at which reabsorption takes place are discussed below. Diuretics work primarily by interfering with reabsorption.

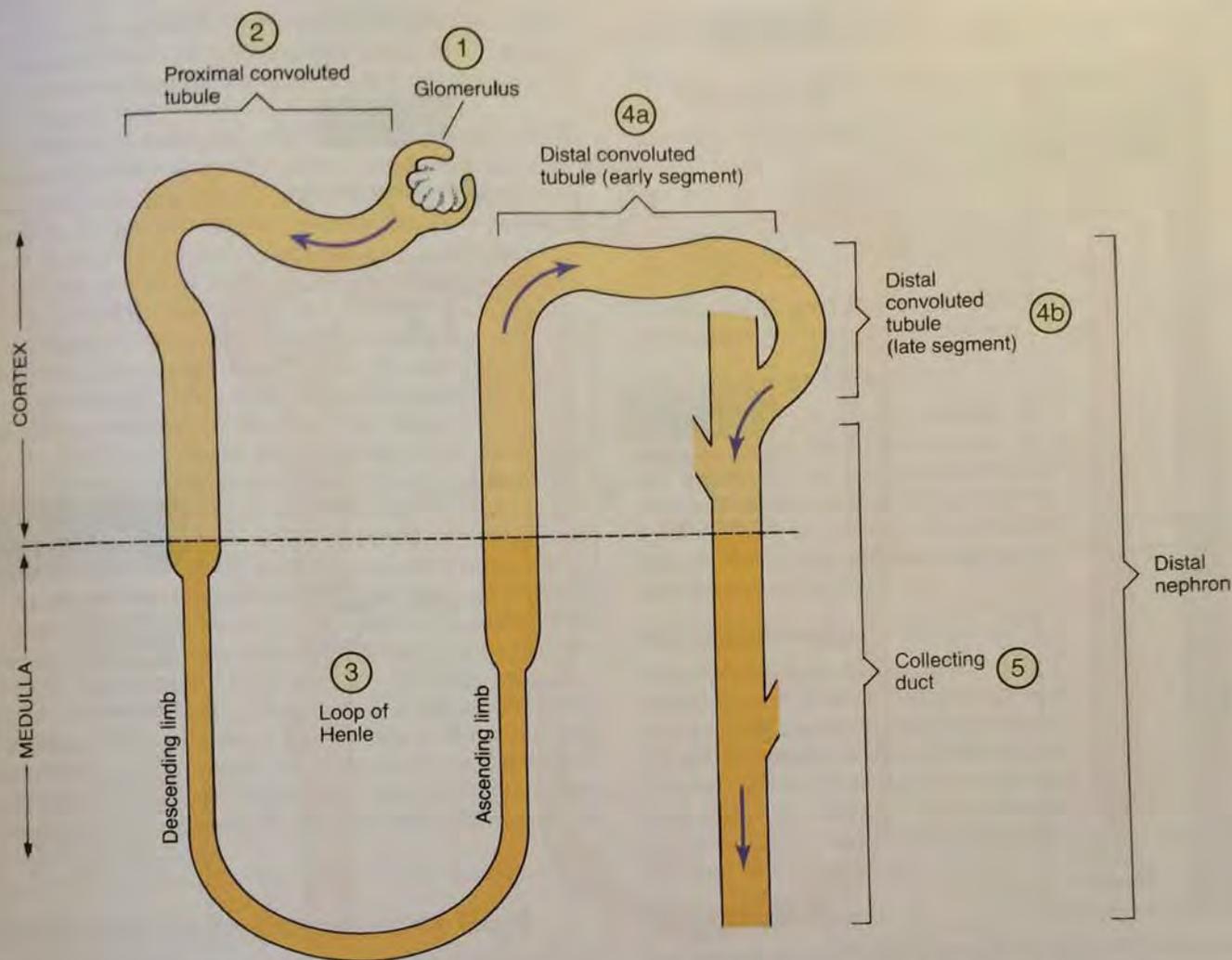


Figure 41-1 ■ Schematic representation of a nephron and collecting duct.

Active Tubular Secretion. The kidney has two major kinds of “pumps” for active secretion. These pumps transport compounds from the plasma into the lumen of the nephron. One pump transports *organic acids* and the other transports *organic bases*. Together, these pumps can promote the excretion of a wide assortment of molecules, including metabolic wastes, drugs, and toxins. The pumps for active secretion are located in the *proximal convoluted tubule*.

Processes of Reabsorption That Occur at Specific Sites Along the Nephron

Because most diuretics act by disrupting solute reabsorption, to understand the diuretics, we must first understand the major processes by which nephrons reabsorb filtered solutes. Because sodium and chloride ions are the predominant solutes in the filtrate, reabsorption of these ions is of greatest interest. As we discuss reabsorption, numeric values are given for the percentage of solute reabsorbed at specific sites along the nephron. Bear in mind that these values are only approximate. Figure 41-2 depicts the sites of sodium and chloride reabsorption, indicating the amount of reabsorption that occurs at each site.

Proximal Convoluted Tubule. The proximal convoluted tubule (PCT) has a high reabsorptive capacity. As indicated in Figure 41-2, a large fraction (about 65%) of filtered sodium and

chloride is reabsorbed at the PCT. In addition, essentially all of the bicarbonate and potassium in the filtrate is reabsorbed here. As sodium, chloride, and other solutes are actively reabsorbed, water follows passively. Since solutes and water are reabsorbed to an equal extent, the tubular urine remains isotonic (300 mOsm/L). By the time the filtrate leaves the PCT, sodium and chloride are the only solutes that remain in significant amounts.

Loop of Henle. The *descending limb* of the loop of Henle is freely permeable to water. Hence, as tubular urine moves down the loop and passes through the hypertonic environment of the renal medulla, water is drawn from the loop into the interstitial space. This process decreases the volume of the tubular urine and causes the urine to become concentrated (tonicity increases to about 1200 mOsm/L).

Within the thick segment of the *ascending limb* of the loop of Henle, about 20% of filtered sodium and chloride is reabsorbed (see Fig. 41-2). Since, unlike the descending limb, the ascending limb is not permeable to water, water must remain in the loop as reabsorption of sodium and chloride takes place. This process causes the tonicity of the tubular urine to return to that of the original filtrate (300 mOsm/L).

Distal Convoluted Tubule (Early Segment). About 10% of filtered sodium and chloride is reabsorbed in the early segment of the distal convoluted tubule. Water follows passively.

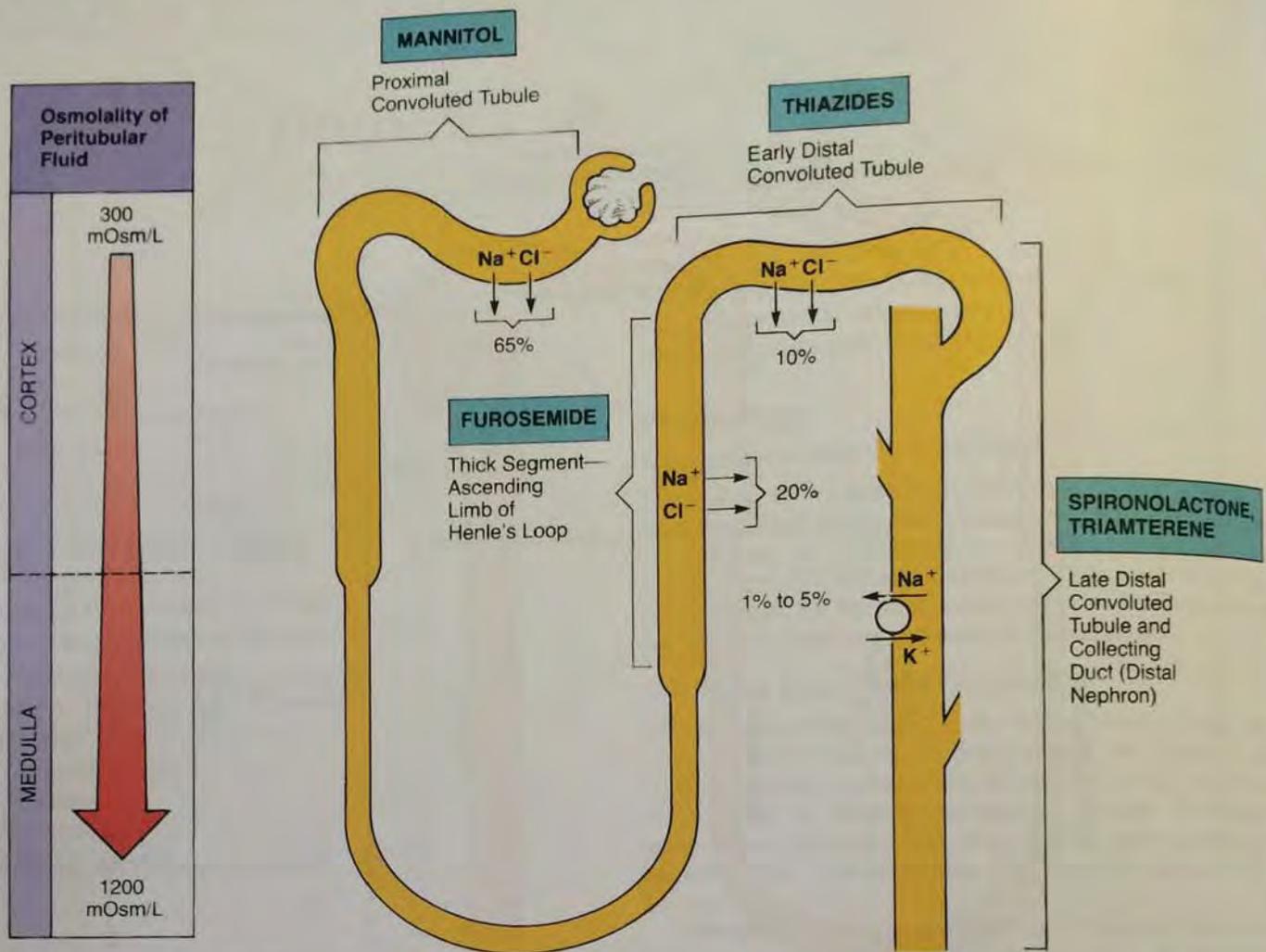


Figure 41-2 ■ Schematic diagram of a nephron showing sites of sodium absorption and diuretic action.

The percentages indicate how much of the filtered sodium and chloride is reabsorbed at each site.

Distal Nephron: Late Distal Convoluted Tubule and Collecting Duct. The distal nephron is the site of two important processes. The first involves exchange of sodium for potassium and is under the influence of aldosterone. The second determines the final concentration of the urine and is regulated by antidiuretic hormone (ADH).

Sodium-Potassium Exchange. Aldosterone, the principal mineralocorticoid of the adrenal cortex, stimulates reabsorption of sodium from the distal nephron. At the same time, aldosterone causes potassium to be secreted. Although not directly coupled, these two processes—sodium retention and potassium excretion—can be viewed as an exchange mechanism. This exchange is shown schematically in Figure 41-2. Aldosterone promotes sodium-potassium exchange by stimulating cells of the distal nephron to synthesize more of the pumps responsible for sodium and potassium transport.

Regulation of Urine Concentration by ADH. Although of great physiologic significance, ADH has little to do with the actions of diuretics. Hence, discussion of this physiologically important topic is presented in small type

ADH acts on the collecting duct to regulate conservation of water. To understand the effects of ADH, we need to know four facts:

- In the absence of ADH, the collecting duct is impermeable to water.
- The collecting duct is oriented such that it begins in the cortex of the kidney and then passes down through the hypertonic renal medulla (see Fig. 41-2).
- Tubular urine entering the collecting duct is isotonic (300 mOsm/L).
- ADH acts on the collecting duct to increase its permeability to water.

By rendering the collecting duct permeable to water, ADH allows water to be drawn from the duct as it passes through the hypertonic renal medulla. Because of this water reabsorption, urine that entered the duct in a relatively dilute state becomes concentrated and reduced in volume.

In the absence of ADH, water cannot be reabsorbed in the collecting duct. As a result, large volumes of dilute urine are produced. The clinical syndrome resulting from ADH deficiency is known as *diabetes insipidus*.

INTRODUCTION TO DIURETICS

How Diuretics Work

Most diuretics share the same basic mechanism of action: blockade of sodium and chloride reabsorption. By blocking the reabsorption of these prominent solutes, diuretics create

osmotic pressure within the nephron that prevents the passive reabsorption of water. Hence, diuretics cause water and solutes to be retained within the nephron, and thereby promote the excretion of both.

The increase in urine flow that a diuretic produces is directly related to the amount of sodium and chloride reabsorption that it blocks. Accordingly, drugs that block solute reabsorption to the greatest degree produce the most profound diuresis. Since the amount of solute in the nephron becomes progressively smaller as filtrate flows from the proximal tubule to the collecting duct, drugs that act early in the nephron have the opportunity to block the greatest amount of solute reabsorption. As a result, these agents produce the greatest diuresis. Conversely, since most of the filtered solute has already been reabsorbed by the time the filtrate reaches the distal parts of the nephron, diuretics that act at distal sites have very little reabsorption available to block. Consequently, such agents produce relatively scant diuresis.

It is instructive to look at the quantitative relationship between blockade of solute reabsorption and production of diuresis. Recall that the kidneys produce 180 L of filtrate a day, practically all of which is normally reabsorbed. With filtrate production at this volume, a diuretic will increase daily urine output by 1.8 L for each 1% of solute reabsorption that is blocked. A 3% blockade of solute reabsorption will produce 5.4 L of urine a day—a rate of fluid loss that would reduce body weight by 12 pounds in 24 hours. Clearly, with only a small blockade of reabsorption, diuretics can produce a profound effect on the fluid and electrolyte composition of the body.

Adverse Impact on Extracellular Fluid

In order to promote excretion of water, diuretics must interfere with the normal operation of the kidney. By doing so, diuretics can cause *hypovolemia* (from excessive fluid loss), *acid-base imbalance*, and *altered electrolyte levels*. These adverse effects can be minimized by using short-acting diuretics and by timing drug administration such that the kidney is allowed to operate in a drug-free manner between periods of diuresis. Both measures will give the kidney periodic opportunities to readjust the ECF so as to compensate for any undesired alterations produced under the influence of diuretics.

Classification of Diuretics

There are four major categories of diuretic drugs: (1) *high-ceiling (loop) diuretics* (eg, furosemide); (2) *thiazide diuretics* (eg, hydrochlorothiazide); (3) *osmotic diuretics* (eg, mannitol); and (4) *potassium-sparing diuretics*. The last group, the potassium-sparing agents, can be subdivided into *aldosterone antagonists* (eg, spironolactone) and *nonaldosterone antagonists* (eg, triamterene).

In addition to the four major categories of diuretics, there is a fifth group: the *carbonic anhydrase inhibitors*. Although the carbonic anhydrase inhibitors are classified as diuretics, these drugs are employed primarily to lower intraocular pressure (IOP) and not to increase urine production. Consequently, the carbonic anhydrase inhibitors are discussed in Chapter 104 (Drugs for the Eye) rather than here.

HIGH-CEILING (LOOP) DIURETICS

The high-ceiling agents are the most effective diuretics available. These drugs produce more loss of fluid and electrolytes than any other diuretics. Because their site of action is in the loop of Henle, the high-ceiling agents are also known as *loop diuretics*.

Furosemide

Furosemide [Lasix] is the most frequently prescribed loop diuretic and will serve as our prototype for the group.

Mechanism of Action

Furosemide acts in the thick segment of the ascending limb of Henle's loop to block reabsorption of sodium and chloride (see Fig. 41-2). By blocking solute reabsorption, furosemide prevents passive reabsorption of water. Since a substantial amount (20%) of filtered NaCl is normally reabsorbed in the loop of Henle, interference with reabsorption here can produce profound diuresis.

Pharmacokinetics

Furosemide can be administered orally, IV, and IM. With oral administration, diuresis begins in 60 minutes and persists for 8 hours. Oral therapy is used when rapid onset is not required. Effects of intravenous furosemide begin within 5 minutes and last for 2 hours. Intravenous therapy is used in critical situations (eg, pulmonary edema) that demand immediate mobilization of fluid. Furosemide undergoes hepatic metabolism followed by renal excretion.

Therapeutic Uses

Furosemide is a powerful drug that is generally reserved for situations that require rapid or massive mobilization of fluid. This drug should be avoided when less efficacious diuretics (thiazides) will suffice. Conditions that justify use of furosemide include (1) pulmonary edema associated with congestive heart failure (CHF); (2) edema of hepatic, cardiac, or renal origin that has been unresponsive to less efficacious diuretics; and (3) hypertension that cannot be controlled with other diuretics. Furosemide is especially useful in patients with severe renal impairment, since, unlike the thiazides (see below), the drug can promote diuresis even when renal blood flow and glomerular filtration rate (GFR) are low. If treatment with furosemide alone is insufficient, a thiazide diuretic may be added to the regimen. There is no benefit to combining furosemide with another high-ceiling agent.

Adverse Effects

Hyponatremia, Hypochloremia, and Dehydration.

Furosemide can produce excessive loss of sodium, chloride, and water. Severe dehydration can result. Signs of evolving dehydration include dry mouth, unusual thirst, and oliguria (scanty urine output). Impending dehydration can also be anticipated from excessive loss of weight. If dehydration occurs, furosemide should be withheld.

Dehydration can promote thrombosis and embolism. Symptoms include headache and pain in the chest, calves, or pelvis. The prescriber should be notified if these develop.

The risk of dehydration and its sequelae can be minimized by initiating therapy with low doses, adjusting the dosage carefully, monitoring weight loss every day, and administering furosemide on an intermittent schedule.

Hypotension. Furosemide can cause a substantial drop in blood pressure. At least two mechanisms are involved: (1) loss of volume and (2) relaxation of venous smooth muscle, which reduces venous return to the heart. Signs of hypotension include dizziness, lightheadedness, and fainting. If blood pressure falls precipitously, furosemide should be discontinued. Because of the risk of hypotension, blood pressure should be monitored routinely.

Outpatients should be taught to monitor their blood pressure and instructed to notify the prescriber if it drops substantially. Also, patients should be informed about symptoms of postural hypotension (dizziness, lightheadedness) and advised to sit or lie down if these occur. Patients should be taught that postural hypotension can be minimized by rising slowly.

Hypokalemia. Potassium is lost through increased secretion in the distal nephron. If serum potassium falls below 3.5 mEq/L, fatal dysrhythmias may result. As discussed below under *Drug Interactions*, loss of potassium is of special concern for patients taking digoxin, a drug for heart failure. Hypokalemia can be minimized by consuming potassium-rich foods (eg, dried fruits, nuts, spinach, citrus fruits, potatoes, bananas), taking potassium supplements, or using a potassium-sparing diuretic.

Ototoxicity. Rarely, loop diuretics cause hearing impairment. With furosemide, deafness is transient. With ethacrynic acid (another loop diuretic), irreversible hearing loss may occur. The ability to impair hearing is unique to the high-ceiling agents. Diuretics in other classes are not ototoxic. Because of the risk of hearing loss, caution is needed when high-ceiling diuretics are used in combination with other ototoxic drugs (eg, aminoglycoside antibiotics).

Hyperglycemia. Elevation of plasma glucose is a potential, albeit uncommon, complication of furosemide therapy. Hyperglycemia appears to result from inhibition of insulin release. Increased glycogenolysis and decreased glycogen synthesis may also contribute. When furosemide is taken by a diabetic patient, he or she should be especially diligent about monitoring blood glucose content.

Hyperuricemia. Elevation of plasma uric acid is a frequent side effect of treatment. For most patients, furosemide-induced hyperuricemia is asymptomatic. However, for patients predisposed to gout, elevation of uric acid may precipitate a gouty attack. Patients should be informed about symptoms of gout (tenderness or swelling in joints) and instructed to notify the prescriber if these develop.

Use in Pregnancy. When administered to pregnant laboratory animals, high-ceiling diuretics have caused maternal death, abortion, fetal resorption, and other adverse effects. There are no definitive studies on loop diuretics during human pregnancy. However, given the toxicity displayed in animals, prudence dictates that pregnant women use these drugs only if absolutely required.

Impact on Lipids, Calcium, and Magnesium. Furosemide reduces high-density lipoprotein (HDL) cholesterol and raises low-density lipoprotein (LDL) cholesterol and triglycerides. Although these undesirable effects by themselves can increase the risk of coronary heart disease, they are more than balanced by the beneficial effects of the diuretic therapy on the heart. That is, despite adverse effects on lipids, high-ceiling diuretics reduce the risk of coronary mortality by 25%.

Furosemide increases urinary excretion of magnesium, posing a risk of magnesium deficiency. Symptoms include muscle weakness, tremor, twitching, and dysrhythmias.

Furosemide increases urinary excretion of calcium. This action has been exploited to treat hypercalcemia.

Drug Interactions

Digoxin. Digoxin is used for heart failure (see Chapter 48) and cardiac dysrhythmias (see Chapter 49). In the presence of low potassium, the risk of serious digoxin-induced toxicity (ventricular dysrhythmias) is greatly increased. Since high-ceiling diuretics promote potassium loss, use of these drugs in combination with digoxin can increase the dysrhythmia risk. This interaction is unfortunate in that most patients who take digoxin for heart failure must also take a diuretic as well. To reduce the risk of toxicity, potassium levels should be monitored routinely, and, when indicated, potassium supplements or a potassium-sparing diuretic should be given.

Ototoxic Drugs. The risk of furosemide-induced hearing loss is increased by concurrent use of other ototoxic drugs—especially aminoglycoside antibiotics (eg, gentamicin). Accordingly, combined use of these drugs should be avoided.

Potassium-Sparing Diuretics. The potassium-sparing diuretics (eg, spironolactone, triamterene) can help counterbalance the potassium-wasting effects of furosemide, thereby reducing the risk of hypokalemia.

Lithium. Lithium is used to treat bipolar disorder (see Chapter 33). In patients with low sodium, excretion of lithium is reduced. Hence, by lowering sodium levels, furosemide can cause lithium to accumulate to toxic levels. Accordingly, lithium levels should be monitored, and, if they climb too high, lithium dosage should be reduced.

Antihypertensive Agents. The hypotensive effects of furosemide add with those of other hypotensive drugs. To avoid excessive reduction of blood pressure, patients may need to reduce or eliminate use of other hypotensive medications.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs). Aspirin and other NSAIDs can attenuate the diuretic effects of furosemide. The mechanism appears to be inhibition of prostaglandin synthesis in the kidney. (Part of the diuretic effect of furosemide results from increasing renal blood flow, which is thought to occur through a prostaglandin-mediated process. By inhibiting prostaglandin synthesis, NSAIDs prevent the increase in renal blood flow, and thereby partially blunt diuretic effects.)

Preparations, Dosage, and Administration

Oral. Furosemide [Lasix] is available in tablets (20, 40, and 80 mg) and in solution (8 and 10 mg/mL) for oral use. The initial dosage for adults is 20 to 80 mg/day as a single dose. The maximum daily dosage is 600 mg. Twice-daily dosing (8:00 AM and 2:00 PM) is common. Dosing late in the day produces nocturia and should be avoided.

Parenteral. Furosemide is available in solution (10 mg/mL) for IV and IM administration. The usual dosage for adults is 20 to 40 mg, repeated in 1 or 2 hours if needed. Intravenous administration should be done slowly (over 1 to 2 minutes). For high-dose therapy, furosemide can be administered by continuous infusion at a rate of 4 mg/min or slower.

Other High-Ceiling Diuretics

In addition to furosemide, three other high-ceiling agents are available: *ethacrynic acid* [Edecrin], *torsemide* [Demadex], and *bumetanide* [Bumex]. All three are much like furosemide. They all promote diuresis by inhibiting sodium and chloride reabsorption in the thick ascending limb of the loop of Henle. All are approved for edema caused by heart failure, chronic renal disease, and cirrhosis, but only torsemide, like furosemide, is also approved for hypertension. All can cause ototoxicity, hypovolemia, hypotension, hypokalemia, hyperuricemia, hyperglycemia, and disruption of lipid metabolism, specifically, reduction of HDL cholesterol and elevation of LDL cholesterol and triglycerides. Lastly, they all share the same drug interactions: Their effects can be blunted by NSAIDs, they can intensify ototoxicity caused by aminoglycosides, they can increase cardiotoxicity caused by digoxin, and they can cause lithium to accumulate to toxic levels. Routes, dosages, and time courses are summarized in Table 41-1.

TABLE 41-1 ■ High-Ceiling (Loop) Diuretics: Routes, Time Course, and Dosage

Drug	Route	Time Course		Dosage (mg)	Doses/Day
		Onset (min)	Duration (hr)		
Furosemide [Lasix]	Oral	Within 60	6-8	20-80	1-2
	IV or IM	Within 5	2	20-40	
Ethacrynic acid [Edecrin]	Oral	Within 30	6-8	50-100	1-2
	IV	Within 5	2	50	1-2
Bumetanide [Burinex [®] , generic only in United States]	Oral	30-60	4-6	0.5-2	1
	IV	Within a few	0.5-1	0.5-1	1-3
Torsemide [Demadex]	Oral	Within 60	6-8	5-20	1
	IV	Within 10	6-8	5-20	1

THIAZIDES AND RELATED DIURETICS

The thiazide diuretics (also known as benzothiadiazides) have effects similar to those of the loop diuretics. Like the loop diuretics, thiazides increase renal excretion of sodium, chloride, potassium, and water. In addition, thiazides elevate plasma levels of uric acid and glucose. The principal difference between the thiazides and high-ceiling agents is that the maximum diuresis produced by the thiazides is considerably lower than the maximum diuresis produced by the high-ceiling agents. In addition, whereas loop diuretics can be effective even when urine flow is scant, thiazides cannot.

Hydrochlorothiazide

Hydrochlorothiazide [HydroDIURIL, others] is the most widely used thiazide diuretic and will serve as our prototype for the group. Because of its use in hypertension, a very common disorder, hydrochlorothiazide is one of our most widely used drugs.

Mechanism of Action

Hydrochlorothiazide promotes urine production by blocking the reabsorption of sodium and chloride in the *early segment of the distal convoluted tubule* (see Fig. 41-2). Retention of sodium and chloride in the nephron causes water to be retained as well, thereby producing an increased flow of urine. Since only 10% of filtered sodium and chloride is normally reabsorbed at the site where thiazides act, the maximum urine flow these drugs can produce is lower than with the high-ceiling drugs.

The ability of thiazides to promote diuresis is dependent on adequate kidney function. These drugs are ineffective when GFR is low (less than 15 to 20 mL/min). Hence, in contrast to the high-ceiling agents, thiazides cannot be used to promote fluid loss in patients with severe renal impairment.

Pharmacokinetics

Diuresis begins about 2 hours after oral administration. Effects peak within 4 to 6 hours, and may persist up to 12 hours. Most of the drug is excreted unchanged in the urine.

Therapeutic Uses

Essential Hypertension. The primary indication for hydrochlorothiazide is hypertension, a condition for which thia-

zides are often drugs of first choice. For many hypertensive patients, blood pressure can be controlled with a thiazide alone, although many other patients require multiple-drug therapy. The role of thiazides in hypertension is discussed in Chapter 47.

Edema. Thiazides are preferred drugs for mobilizing edema associated with mild to moderate heart failure. They are also given to mobilize edema associated with hepatic or renal disease.

Diabetes Insipidus. Diabetes insipidus is a rare condition characterized by excessive production of urine. In patients with this disorder, thiazides reduce urine production by 30% to 50%. The mechanism of this paradoxical effect is unclear.

Protection Against Postmenopausal Osteoporosis. Thiazides promote tubular reabsorption of calcium, and may thereby decrease the risk of osteoporosis in postmenopausal women. Here's how. Prior to menopause, estrogen from the ovaries acts on renal tubules to promote calcium reabsorption. When menopause occurs, estrogen levels drop, allowing renal excretion of calcium to increase. The resultant decrease in circulating calcium promotes mobilization of calcium from bone, and thereby increases the risk of osteoporosis. Since thiazides promote renal calcium retention, they may counteract the calcium loss associated with menopause, and may thereby help preserve bone integrity.

Adverse Effects

The adverse effects of thiazide diuretics are similar to those of the high-ceiling agents. In fact, with the exception that thiazides are not ototoxic, the adverse effects of the thiazides and loop diuretics are nearly identical.

Hyponatremia, Hypochloremia, and Dehydration. Loss of sodium, chloride, and water can lead to hyponatremia, hypochloremia, and dehydration. However, since the diuresis produced by thiazides is moderate, these drugs have a smaller impact on sodium, chloride, and water than do the loop diuretics. To evaluate fluid and electrolyte status, electrolyte levels should be determined periodically, and the patient should be weighed on a regular basis.

Hypokalemia. Like the high-ceiling diuretics, the thiazides can cause hypokalemia from excessive potassium excretion. As noted, potassium loss is of particular concern for patients taking digoxin. Potassium levels should be measured periodically, and, if serum potassium falls below 3.5 mEq/L, treatment with potassium supplements or a potassium-sparing diuretic should be instituted. Hypokalemia can be minimized by eating potassium-rich foods.

Use in Pregnancy and Lactation. The thiazides have direct and indirect effects on the developing fetus. By reducing

TABLE 41-2 • Thiazides and Related Diuretics: Dosages and Time Course of Effects

Generic Name	Trade Name	Time Course		Optimal Oral Adult Dosage (mg/day)
		Onset (hr)	Duration (hr)	
Thiazides				
Chlorothiazide	Diuril	1–2	6–12	500–1000
Hydrochlorothiazide	HydroDIURIL, Hydro-Par, Ezide, Microzide	2	6–12	12.5–25
Methyclothiazide	Enduron	2	24	2.5–5
Related Drugs				
Chlorthalidone	Thalitone	2	24–72	50–100
Indapamide	Lozide ⁺ , generic only in the United States	1–2	Up to 36	2.5–5
Metolazone	Zaroxolyn	1	12–24	2.5–20

maternal blood volume, thiazides can decrease placental perfusion, and may thereby compromise fetal nutrition and growth. Furthermore, thiazides can cross the placental barrier to produce fetal harm directly. Potential effects include electrolyte imbalance, hypoglycemia, jaundice, and hemolytic anemia. Because of the potential for fetal harm, *thiazides should not be used routinely during pregnancy*. Edema of pregnancy is not an indication for diuretic therapy, except when severe. In contrast, edema from pathologic causes (eg, heart failure, cirrhosis) does constitute a legitimate indication for thiazide use.

Thiazides enter breast milk and can be hazardous to the nursing infant. Women taking thiazides should be cautioned against breast-feeding.

Hyperglycemia. Like the loop diuretics, the thiazides can elevate plasma levels of glucose. Significant hyperglycemia develops only in diabetic patients, who should be especially diligent about monitoring blood glucose. To maintain normal glucose levels, the diabetic patient may require larger doses of insulin or an oral hypoglycemic drug.

Hyperuricemia. The thiazides, like the loop diuretics, can cause retention of uric acid, thereby elevating plasma uric acid. Although hyperuricemia is usually asymptomatic, it may precipitate gouty arthritis in patients with a history of the disorder. Plasma levels of uric acid should be measured periodically.

Impact on Lipids and Magnesium. Thiazides can increase levels of LDL cholesterol, total cholesterol, and triglycerides. Thiazides increase excretion of magnesium, sometimes causing magnesium deficiency. Symptoms include muscle weakness, tremor, twitching, and dysrhythmias.

Drug Interactions

The important drug interactions of the thiazides are nearly identical to those of the loop diuretics. By promoting potassium loss, thiazides can increase the risk of toxicity from *digoxin*. By lowering blood pressure, thiazides can augment the effects of other *antihypertensive drugs*. By promoting sodium loss, thiazides can reduce renal excretion of *lithium*, thereby causing the drug to accumulate, possibly to toxic levels. *NSAIDs* may blunt the diuretic effects of thiazides. By counterbalancing the potassium-wasting effects of the thiazides, the *potassium-sparing diuretics* can help prevent excessive potassium loss. In contrast to the loop diuretics, the thiazides can be combined with *ototoxic agents* without an increased risk of hearing loss.

Preparations, Dosage, and Administration

Hydrochlorothiazide [HydroDIURIL, others] is supplied in capsules (12.5 mg) and tablets (12.5, 25, 50, and 100 mg). Like most other thiazides, hydrochlorothiazide is administered only by mouth. The usual adult dosage is 25 to

50 mg once or twice daily. To minimize nocturia, the drug should not be administered late in the day. To minimize electrolyte imbalance, the drug should be administered on an intermittent basis (eg, every other day). In addition to being marketed alone, hydrochlorothiazide is available in fixed-dose combinations with potassium-sparing diuretics and a long list of other drugs: beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, reserpine, hydralazine, clonidine, methyldopa, and prazosin (see Table 47-6).

Other Thiazide-Type Diuretics

In addition to hydrochlorothiazide, five other thiazides (and related drugs) are approved for use in the United States (Table 41-2). All have pharmacologic properties similar to those of hydrochlorothiazide. With the exception of chlorothiazide, these drugs are administered only by mouth. Chlorothiazide can be administered IV as well as PO. Although the thiazides differ from one another in milligram potency (see Table 41-2), at therapeutically equivalent doses, all elicit the same degree of diuresis. Although most have the same onset time (1 to 2 hours), these drugs differ significantly with respect to duration of action. As with hydrochlorothiazide, disturbance of electrolyte balance can be minimized through alternate-day dosing. Nocturia can be minimized by avoiding dosing in the late afternoon. Table 41-2 lists three drugs—chlorthalidone, indapamide, and metolazone—that are not true thiazides. However, these agents are very similar to thiazides both in structure and function, and hence are included in the group.

POTASSIUM-SPARING DIURETICS

The potassium-sparing diuretics can elicit two potentially useful responses. First, they produce a modest increase in urine production. Second, they produce a substantial *decrease in potassium excretion*. Because their diuretic effects are limited, the potassium-sparing drugs are rarely employed alone to promote diuresis. However, because of their marked ability to decrease potassium excretion, these drugs are often used to counteract potassium loss caused by thiazide and loop diuretics.

There are two subcategories of potassium-sparing diuretics: *aldosterone antagonists* and *nonaldosterone antagonists*. In the United States, only one aldosterone antagonist—spironolactone—is used for diuresis.* Two nonaldosterone antagonists—triamterene and amiloride—are currently employed.

*Another aldosterone antagonist—*eplerenone* [Inspra]—is available, but the drug is not considered a diuretic. The basic pharmacology of eplerenone and its main use, heart failure, are discussed in Chapters 44 and 48, respectively.

TABLE 41-3 ■ Potassium-Sparing Diuretics: Names, Dosages, and Time Course of Effects

Generic Name	Trade Name	Time Course		Usual Adult Dosage (mg/day)
		Onset (hr)	Duration (hr)	
Spirolactone	Aldactone	24-48	48-72	25-200
Triamterene	Dyrenium	2-4	12-16	200-300
Amiloride	Midamor	2	24	5-20

Spirolactone

Mechanism of Action

Spirolactone [Aldactone] blocks the actions of aldosterone in the distal nephron. Since aldosterone acts to promote sodium uptake in exchange for potassium secretion (see Fig. 41-2), inhibition of aldosterone has the opposite effect: *retention of potassium and increased excretion of sodium*. The diuresis caused by spiro lactone is scanty because most of the filtered sodium load has already been reabsorbed by the time the filtrate reaches the distal nephron. (Recall that the degree of diuresis a drug produces is directly proportional to the amount of sodium reuptake that it blocks.)

As indicated in Table 41-3, the effects of spiro lactone are delayed, taking up to 48 hours to develop. Why the delay? Recall that aldosterone acts by stimulating cells of the distal nephron to synthesize the proteins required for sodium and potassium transport. By preventing aldosterone's action, spiro lactone blocks the synthesis of *new* proteins, but does not stop existing transport proteins from doing their job. Hence, effects are not visible until the existing proteins complete their normal life cycle—a process that takes 1 or 2 days.

Therapeutic Uses

Hypertension and Edema. Spirolactone is used primarily for hypertension and edema. Although it can be employed alone, the drug is used most commonly in combination with a thiazide or loop diuretic. The purpose of spiro lactone in these combinations is to counteract the potassium-wasting effects of the more powerful diuretics. Spirolactone also makes a small contribution to diuresis.

Heart Failure. In patients with severe heart failure, spiro lactone reduces mortality and hospital admissions. Benefits derive from protective effects of aldosterone blockade in the heart and blood vessels (see Chapter 48).

Other Uses. In addition to the applications discussed above, spiro lactone can be used for primary hyperaldosteronism (Chapter 60), premenstrual syndrome (Chapter 61), polycystic ovary syndrome (Chapter 63), and acne in young women (Chapter 105).

Adverse Effects

Hyperkalemia. The potassium-sparing effects of spiro lactone can result in hyperkalemia, a condition that can produce fatal dysrhythmias. Although hyperkalemia is most likely when spiro lactone is used alone, it can also develop when spiro lactone is used in conjunction with potassium-wasting agents (thiazides and high-ceiling diuretics). If serum potassium rises above 5 mEq/L, or if signs of hyperkalemia develop (eg, abnormal heart rhythm), spiro lactone should be discontinued and potassium intake restricted. Injection of

insulin can help lower potassium levels by promoting potassium uptake into cells.

Endocrine Effects. Spirolactone is a steroid derivative with a structure similar to that of steroid hormones (eg, progesterone, estradiol, testosterone). As a result, spiro lactone can cause a variety of endocrine effects, including *gynecomastia, menstrual irregularities, impotence, hirsutism, and deepening of the voice*.

Benign and Malignant Tumors. When given long term to rats in doses 25 to 250 times those used in humans, spiro lactone has caused benign adenomas of the thyroid and testes, malignant mammary tumors, and proliferative changes in the liver. The risk of tumors in humans from use of normal doses is unknown.

Drug Interactions

Thiazide and Loop Diuretics. Spirolactone is frequently combined with thiazide and loop diuretics. The goal is to counteract the potassium-wasting effects of the more powerful diuretic.

Agents That Raise Potassium Levels. Because of the risk of hyperkalemia, *spiro lactone must never be combined with potassium supplements, salt substitutes (which contain potassium chloride), or another potassium-sparing diuretic*. In addition, three groups of drugs—*angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and direct renin inhibitors*—can elevate potassium levels (by suppressing aldosterone secretion), and hence should be combined with spiro lactone only when clearly necessary.

Preparations, Dosage, and Administration

Spirolactone [Aldactone] is dispensed in tablets (25, 50, and 100 mg) for oral dosing. The usual adult dosage is 25 to 100 mg/day. Spirolactone is also marketed in a fixed-dose combination with hydrochlorothiazide under the trade name *Aldactazide*.

Triamterene

Mechanism of Action

Like spiro lactone, triamterene [Dyrenium] disrupts sodium-potassium exchange in the distal nephron. However, in contrast to spiro lactone, which reduces ion transport *indirectly* through blockade of aldosterone, triamterene is a *direct inhibitor of the exchange mechanism itself*. The net effect of inhibition is a decrease in sodium reabsorption and a reduction in potassium secretion. Hence, sodium excretion is increased, while potassium is conserved. Because it inhibits ion transport directly, triamterene acts much more quickly than spiro lactone. As indicated in Table 41-3, initial responses develop in hours, compared with days for spiro lactone. As with spiro lactone, diuresis with triamterene is scant.

Therapeutic Uses

Triamterene can be used alone or in combination with other diuretics to treat *hypertension* and *edema*. When used alone, triamterene produces mild diuresis. When combined with other diuretics (eg, furosemide, hydrochlorothiazide), triamterene augments diuresis and helps counteract the potassium-wasting effects of the more powerful diuretic. It is the latter effect for which triamterene is principally employed.

Adverse Effects

Hyperkalemia. Excessive potassium accumulation is the most significant adverse effect. Hyperkalemia is most likely when triamterene is used alone, but can also occur when the drug is combined with thiazides or high-ceiling agents. Triamterene should never be used in conjunction with another potassium-sparing diuretic or with potassium supplements or salt substitutes. In addition, caution is needed if the drug is combined with an ACE inhibitor, angiotensin receptor blocker, or direct renin inhibitor.

Other Adverse Effects. Relatively common side effects include *nausea*, *vomiting*, *leg cramps*, and *dizziness*. Blood dyscrasias occur rarely.

Preparations, Dosage, and Administration

Triamterene [Dyrenium] is available in 50- and 100-mg capsules for oral use. The usual initial dosage is 100 mg twice a day. The maximum dosage is 300 mg/day. Triamterene is also marketed in fixed-dose combinations with hydrochlorothiazide under the trade names Dyazide and Maxzide.

Amiloride

Pharmacologic Properties. Amiloride [Midamor] has actions similar to those of triamterene. Both drugs inhibit potassium loss by direct blockade of sodium-potassium exchange in the distal nephron. Also, both drugs produce only modest diuresis. Although it can be employed alone as a diuretic, amiloride is used primarily to counteract potassium loss caused by more powerful diuretics (thiazides, high-ceiling agents). The major adverse effect is hyperkalemia. Accordingly, concurrent use of other potassium-sparing diuretics or potassium supplements must be avoided. Caution is needed if the drug is combined with an ACE inhibitor, angiotensin receptor blocker, or direct renin inhibitor.

Preparations, Dosage, and Administration. Amiloride [Midamor] is supplied in 5-mg tablets for oral use. Dosing is begun at 5 mg/day and may be increased to a maximum of 20 mg/day. Amiloride is available in a fixed-dose combination with hydrochlorothiazide under the trade name Moduretic.

MANNITOL, AN OSMOTIC DIURETIC

Osmotic diuretics differ from other diuretics with regard to mechanism and uses. At this time, mannitol is the only osmotic diuretic available in the United States. Three related drugs—urea, glycerin, and isosorbide—have been withdrawn.

Mechanism of Diuretic Action

Mannitol [Osmitol] is a simple six-carbon sugar that embodies the four properties of an ideal osmotic diuretic. Specifically, the drug

- Is freely filtered at the glomerulus.
- Undergoes minimal tubular reabsorption.
- Undergoes minimal metabolism.
- Is pharmacologically inert (ie, it has no direct effects on the biochemistry or physiology of cells).

Following IV administration, mannitol is filtered by the glomerulus. However, unlike other solutes, the drug undergoes minimal reabsorption. As a

result, most of the filtered drug remains in the nephron, creating an osmotic force that inhibits passive reabsorption of water. Hence, urine flow increases. The degree of diuresis produced is directly related to the concentration of mannitol in the filtrate: The more mannitol present, the greater the diuresis. Mannitol has no significant effect on the excretion of potassium and other electrolytes.

Pharmacokinetics

Mannitol does not diffuse across the GI epithelium and cannot be transported by the uptake systems that absorb dietary sugars. Accordingly, in order to reach the circulation, the drug must be given parenterally. Following IV injection, mannitol distributes freely to extracellular water. Diuresis begins in 30 to 60 minutes and persists 6 to 8 hours. Most of the drug is excreted intact in the urine.

Therapeutic Uses

Prophylaxis of Renal Failure. Under certain conditions (eg, dehydration, severe hypotension, hypovolemic shock), blood flow to the kidney is decreased, causing a great reduction in filtrate volume. When the volume of filtrate is this low, transport mechanisms of the nephron are able to reabsorb virtually all of the sodium and chloride present, causing complete reabsorption of water as well. As a result, urine production ceases, and kidney failure ensues. The risk of renal failure can be reduced with mannitol. Here's how. Because filtered mannitol is not reabsorbed—even when filtrate volume is small—filtered mannitol will remain in the nephron, drawing water with it. Hence, mannitol can preserve urine flow and may thereby prevent renal failure. Thiazides and loop diuretics are not as effective for this application because, under conditions of low filtrate production, there is such an excess of reabsorptive capacity (relative to the amount of filtrate) that these drugs are unable to produce sufficient blockade of reabsorption to promote diuresis.

Reduction of Intracranial Pressure. Intracranial pressure (ICP) that has been elevated by cerebral edema can be reduced with mannitol. The drug lowers ICP because its presence in the blood vessels of the brain creates an osmotic force that draws edematous fluid from the brain into the blood. There is no risk of increasing cerebral edema because mannitol cannot exit the capillary beds of the brain.

Reduction of Intraocular Pressure. Mannitol and other osmotic agents can lower IOP. How? By rendering the plasma hyperosmotic with respect to intraocular fluids, mannitol creates an osmotic force that draws ocular fluid into the blood. Use of mannitol to lower IOP is reserved for patients who have not responded to more conventional treatment.

Adverse Effects

Edema. Mannitol can leave the vascular system at all capillary beds except those of the brain. When the drug exits capillaries, it draws water along, causing edema. Mannitol must be used with extreme caution in patients with heart disease, since it may precipitate CHF and pulmonary edema. If signs of pulmonary congestion or CHF develop, use of the drug must cease immediately. Mannitol must also be discontinued if patients with heart failure or pulmonary edema develop renal failure. Why? Because the resultant accumulation of mannitol would increase the risk of cardiac or pulmonary injury.

Other Adverse Effects. Common responses include headache, nausea, and vomiting. Fluid and electrolyte imbalance may also occur.

Preparations, Dosage, and Administration

Mannitol [Osmitol] is administered by IV infusion. Solutions for IV use range in concentration from 5% to 25%. Dosing is complex and varies with the objective of therapy (prevention of renal failure, lowering of ICP, lowering of IOP). The usual adult dosage for preventing renal failure is 50 to 100 gm over 24 hours. The infusion rate should be set to elicit a urine flow of at least 30 to 50 mL/hr. It should be noted that mannitol may crystallize out of solution if exposed to low temperature. Accordingly, preparations should be observed for crystals prior to use. Preparations that contain crystals should be warmed (to redissolve the mannitol) and then cooled to body temperature for administration. A filter needle is employed to withdraw mannitol from the vial, and an in-line filter is used to prevent crystals from entering the circulation. If urine flow declines to a very low rate or ceases entirely, the infusion should be stopped.

KEY POINTS

- More than 99% of the water, electrolytes, and nutrients that are filtered at the glomerulus undergo reabsorption.
- Most diuretics block active reabsorption of sodium and chloride, and thereby prevent passive reabsorption of water.
- The amount of diuresis produced is directly related to the amount of sodium and chloride reabsorption blocked.
- Drugs that act early in the nephron are in a position to block the greatest amount of solute reabsorption, and hence produce the greatest diuresis.
- High-ceiling diuretics (loop diuretics) block sodium and chloride reabsorption in the loop of Henle.
- High-ceiling diuretics produce the greatest diuresis.
- In contrast to thiazide diuretics, high-ceiling diuretics are effective even when the glomerular filtration rate is low.
- High-ceiling diuretics can cause dehydration through excessive fluid loss.
- High-ceiling diuretics can cause hypotension by decreasing blood volume and relaxing venous smooth muscle.
- High-ceiling diuretics can cause hearing loss, which, fortunately, is usually reversible.
- Hypokalemia caused by high-ceiling diuretics is a special problem for patients taking digoxin.
- Thiazide diuretics block sodium and water reabsorption in the early distal convoluted tubule.
- Thiazide diuretics produce less diuresis than high-ceiling diuretics.
- Thiazide diuretics are ineffective when glomerular filtration rate is low.
- Like the high-ceiling diuretics, thiazide diuretics can cause dehydration and hypokalemia. However, thiazides do not cause hearing loss.
- Thiazide-induced hypokalemia is a special problem for patients taking digoxin.
- Potassium-sparing diuretics act by directly or indirectly blocking sodium-potassium “exchange” in the distal convoluted tubule.
- Potassium-sparing diuretics cause only modest diuresis.
- Potassium-sparing diuretics are used primarily to counteract potassium loss in patients taking high-ceiling diuretics or thiazides.
- The principal adverse effect of potassium-sparing diuretics is hyperkalemia.
- Because of the risk of hyperkalemia, potassium-sparing diuretics should not be combined with one another or with potassium supplements, and they should be used cautiously in patients taking ACE inhibitors, angiotensin receptor blockers, or direct renin inhibitors.
- High-ceiling diuretics and thiazides are used to treat hypertension and edema associated with heart failure, cirrhosis, and kidney disease.

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Summary of Major Nursing Implications*

HIGH-CEILING (LOOP) DIURETICS

Bumetanide
Ethacrynic acid
Furosemide
Torsemide

Preadministration Assessment

Therapeutic Goal

High-ceiling diuretics are indicated for patients with (1) pulmonary edema associated with congestive heart failure; (2) edema of hepatic, cardiac, or renal origin that has been unresponsive to less effective diuretics; (3) hypertension that cannot be controlled with thiazide and potassium-sparing diuretics; and (4) all patients who need diuretic therapy but have low renal blood flow

Baseline Data

For all patients, obtain baseline values for weight, blood pressure (sitting and supine), pulse, respiration, and electrolytes (sodium, potassium, chloride). For patients with edema, record sites and extent of edema. For patients with ascites, measure abdominal girth. For acutely ill patients (eg, severe CHF), assess lung sounds.

Identifying High-Risk Patients

Use with *caution* in patients with cardiovascular disease, renal impairment, diabetes mellitus, or a history of gout, and in patients who are pregnant or taking digoxin, lithium, ototoxic drugs, NSAIDs, or antihypertensive drugs.

Implementation: Administration

Routes

Furosemide and Bumetanide. Oral, IV, IM.

Ethacrynic Acid and Torsemide. Oral, IV.

Administration

Oral. Dosing may be done once daily, twice daily, or on alternate days. **Instruct patients who are using once-a-day or alternate-day dosing to take their medication in the morning. Instruct patients using twice-a-day dosing to take their medication at 8:00 AM and 2:00 PM (to minimize nocturia).**

Advise patients to administer furosemide with food if GI upset occurs.

Parenteral. Administer IV injections slowly (over 1 to 2 minutes). For high-dose therapy, administer by continuous infusion. Discard discolored solutions.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Promoting Adherence

Increased frequency of urination is inconvenient and can discourage adherence. **To promote adherence, inform patients that treatment will increase urine volume and frequency of voiding, and that these effects will subside 6 to 8 hours after dosing. Inform patients that nighttime diuresis can be minimized by avoiding dosing late in the day.**

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor blood pressure and pulse rate, weigh the patient daily, and evaluate for decreased edema.

Monitor intake and output. Notify the prescriber if oliguria (urine output less than 25 mL/hr) or anuria (no urine output) develops.

Instruct outpatients to weigh themselves daily (using the same scale), preferably in the morning before eating. Also, instruct them to maintain a weight record, and to report excessive weight gain or weight loss.

In acute conditions requiring rapid diuresis and careful monitoring, a Foley catheter may be used. The catheter should be emptied prior to drug injection, and output should be monitored hourly and recorded.

Minimizing Adverse Effects

Hyponatremia, Hypochloremia, and Dehydration.

Loss of sodium, chloride, and water can cause hyponatremia, hypochloremia, and severe dehydration. Signs of dehydration include dry mouth, unusual thirst, and oliguria. Withhold the drug if these appear.

Dehydration can promote thromboembolism. Monitor the patient for symptoms (headache; pain in the chest, calves, or pelvis), and notify the prescriber if these develop.

The risk of dehydration and its sequelae can be minimized by (1) initiating therapy with low doses, (2) adjusting the dosage carefully, (3) monitoring weight loss daily, and (4) using an intermittent dosing schedule.

Hypotension. Monitor blood pressure. If it falls precipitously, withhold medication and notify the prescriber.

Teach patients to monitor their blood pressure and instruct them to notify the prescriber if it drops substantially.

Inform patients about signs of postural hypotension (dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that postural hypotension can be minimized by rising slowly, and by dangling legs off the bed before standing.

Hypokalemia. If serum potassium falls below 3.5 mEq/L, fatal dysrhythmias may result. Hypokalemia can be minimized by consuming potassium-rich foods (eg, nuts, dried fruits, spinach, citrus fruits, potatoes, bananas), taking potassium supplements, or using a potassium-sparing diuretic. **Teach patients the signs and symptoms of hypokalemia (eg, irregular heartbeat, muscle weakness, cramping, flaccid paralysis, leg discomfort, extreme thirst, confusion), and stress the importance of showing up for regular blood tests.**

Ototoxicity. Inform patients about possible hearing loss and instruct them to notify the prescriber if a hearing deficit develops. Exercise caution when high-ceiling diuretics are used concurrently with other ototoxic drugs, especially aminoglycosides.

Hyperglycemia. High-ceiling diuretics may elevate blood glucose levels in diabetic patients. **Advise these patients to be especially diligent about monitoring blood glucose.**

Hyperuricemia. High-ceiling diuretics frequently cause asymptomatic hyperuricemia, although gout-prone patients may experience a gouty attack. **Inform patients about signs of gout (tenderness or swelling in joints), and instruct them to notify the prescriber if these occur.**

Minimizing Adverse Interactions

Digoxin. By lowering potassium levels, high-ceiling diuretics increase the risk of fatal dysrhythmias from digoxin. Serum potassium levels must be monitored and maintained above 3.5 mEq/L.

Lithium. High-ceiling diuretics can suppress lithium excretion, thereby causing the drug to accumulate, possibly to toxic levels. Plasma lithium should be monitored routinely. If drug levels become elevated, lithium dosage should be reduced.

Ototoxic Drugs. The risk of hearing loss from high-ceiling diuretics is increased in the presence of other ototoxic drugs, especially aminoglycosides. Exercise caution when such combinations are employed.

THIAZIDES AND RELATED DIURETICS

Chlorothiazide
Chlorthalidone
Hydrochlorothiazide
Indapamide
Methyclothiazide
Metolazone

Thiazide diuretics have actions much like those of the high-ceiling diuretics. Hence, nursing implications for the thiazides are nearly identical to those of the high-ceiling agents.

Preadministration Assessment

Therapeutic Goal

Thiazide diuretics are indicated for hypertension and edema.

Baseline Data

For all patients, obtain baseline values for weight, blood pressure (sitting and supine), pulse, respiration, and electrolytes (sodium, chloride, potassium). For patients with edema, record sites and extent of edema.

Identifying High-Risk Patients

Use with *caution* in patients with cardiovascular disease, renal impairment, diabetes mellitus, or a history of gout and in patients taking digoxin, lithium, or antihypertensive drugs. *Generally avoid* in women who are pregnant or breast-feeding.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Implementation: Administration

Routes

Oral. All thiazide-type diuretics.
Intravenous. Chlorothiazide.

Administration

Dosing may be done once daily, twice daily, or on alternate days. **When once-a-day dosing is employed, instruct patients to take their medicine early in the day to minimize nocturia. When twice-a-day dosing is employed, instruct patients to take their medicine at 8:00 AM and 2:00 PM.**

Advise patients to administer thiazides with or after meals if GI upset occurs.

Promoting Adherence

See nursing implications for *High-Ceiling (Loop) Diuretics*.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See nursing implications for *High-Ceiling (Loop) Diuretics*.

Minimizing Adverse Effects

Like the high-ceiling diuretics, thiazides can cause *hyponatremia, hypochloremia, dehydration, hypokalemia, hypotension, hyperglycemia, and hyperuricemia*. For implications regarding these effects, see nursing implications for *High-Ceiling (Loop) Diuretics*.

Thiazides can cause fetal harm and can enter breast milk. Avoid these drugs during pregnancy unless absolutely required. **Caution women not to breast-feed.**

Minimizing Adverse Interactions

Like high-ceiling diuretics, thiazides can interact adversely with *digoxin* and *lithium*. For implications regarding these interactions, see nursing implications for *High-Ceiling (Loop) Diuretics*.

POTASSIUM-SPARING DIURETICS

Amiloride
Spironolactone
Triamterene

Preadministration Assessment

Therapeutic Goal

Potassium-sparing diuretics are given primarily to counterbalance the potassium-losing effects of thiazide diuretics and high-ceiling diuretics.

Baseline Data

Obtain baseline values for serum potassium, along with baseline values for weight, blood pressure (sitting and supine), pulse, respiration, sodium, and chloride. For patients with edema, record sites and extent of edema.

Identifying High-Risk Patients

Potassium-sparing diuretics are *contraindicated* for patients with hyperkalemia and for patients taking potassium supplements or another potassium-sparing diuretic. Use with *caution* in patients taking ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors.

Implementation: Administration

Route

Oral.

Administration

Advise patients to take these drugs with or after meals if GI upset occurs.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor serum potassium levels on a regular basis. The objective is to maintain serum potassium levels between 3.5 and 5 mEq/L.

Minimizing Adverse Effects

Hyperkalemia. Hyperkalemia is the principal adverse effect. **Instruct patients to restrict intake of potassium-rich foods (eg, nuts, dried fruits, spinach, citrus fruits, potatoes, bananas).** If serum potassium levels rise above 5 mEq/L, or if signs of hyperkalemia develop (eg, abnormal cardiac rhythm), withhold medication and notify the prescriber. Insulin can be given to (temporarily) drive potassium levels down.

Endocrine Effects. *Spironolactone* may cause *menstrual irregularities* and *impotence*. **Inform patients about these effects, and instruct them to notify the prescriber if they occur.**

Minimizing Adverse Interactions

Drugs That Raise Potassium Levels. Owing to a risk of hyperkalemia, don't combine a potassium-sparing diuretic with potassium supplements, salt substitutes, or with another potassium-sparing diuretic. Generally avoid combined use with ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors.

*Patient education information is highlighted as **blue text**.

Agents Affecting the Volume and Ion Content of Body Fluids

Disorders of Fluid Volume and Osmolality

Volume Contraction

Volume Expansion

Acid-Base Disturbances

Respiratory Alkalosis

Respiratory Acidosis

Metabolic Alkalosis

Metabolic Acidosis

Potassium Imbalances

Regulation of Potassium Levels

Hypokalemia

Hyperkalemia

Magnesium Imbalances

Hypomagnesemia

Hypermagnesemia

The drugs discussed in this chapter are used to correct disturbances in the volume and ionic composition of body fluids. Three groups of agents are considered: (1) drugs used to correct disorders of fluid volume and osmolality, (2) drugs used to correct disturbances of hydrogen ion concentration (acid-base status), and (3) drugs used to correct electrolyte imbalances.

DISORDERS OF FLUID VOLUME AND OSMOLALITY

Good health requires that both the volume and osmolality of extracellular and intracellular fluids remain within a normal range. If a substantial alteration in either the volume or osmolality of these fluids develops, significant harm can result.

Maintenance of fluid volume and osmolality is primarily the job of the kidneys, and, even under adverse conditions, renal mechanisms usually succeed in keeping the volume and composition of body fluids within acceptable limits. However, circumstances can arise in which the regulatory capacity of the kidneys is exceeded. When this occurs, disruption of fluid volume, osmolality, or both can result.

Abnormal states of hydration can be divided into two major categories: volume contraction and volume expansion. *Volume contraction* is defined as a decrease in total body water; conversely, *volume expansion* is defined as an increase in total body water. States of volume contraction

and volume expansion have three subclassifications based on alterations in extracellular osmolality. For volume contraction, the subcategories are *isotonic contraction*, *hypertonic contraction*, and *hypotonic contraction*. Volume expansion may also be subclassified as *isotonic*, *hypertonic*, or *hypotonic*. Descriptions and causes of these abnormal states are discussed below.

In the clinical setting, changes in osmolality are described in terms of the sodium content of plasma. Sodium is used as the reference for classification because this ion is the principal extracellular solute. (Recall that plasma sodium content ranges from 135 to 145 mEq/L.) In most cases, the total osmolality of plasma is about 2 times the osmolality of sodium. That is, total plasma osmolality usually ranges from 280 to 300 mOsm/kg water.

Volume Contraction

Isotonic Contraction

Definition and Causes. Isotonic contraction is defined as volume contraction in which *sodium and water are lost in isotonic proportions*. Hence, although there is a decrease in the total volume of extracellular fluid, there is no change in osmolality. Causes of isotonic contraction include vomiting, diarrhea, kidney disease, and misuse of diuretics. Isotonic contraction is characteristic of cholera, an infection that produces vomiting and severe diarrhea.

Treatment. Lost volume should be replaced with fluids that are isotonic to plasma. This can be accomplished by infusing isotonic (0.9%) sodium chloride in sterile water, a solution in which both sodium and chloride are present at a concentration of 145 mEq/L. Volume should be replenished slowly to avoid pulmonary edema.

Hypertonic Contraction

Definition and Causes. Hypertonic contraction is defined as volume contraction in which *loss of water exceeds loss of sodium*. Hence, there is a reduction in extracellular fluid volume coupled with an increase in osmolality. Because of extracellular hypertonicity, water is drawn out of cells, thereby producing intracellular dehydration and partial compensation for lost extracellular volume.

Causes of hypertonic contraction include excessive sweating, osmotic diuresis, and feeding excessively concentrated foods to infants. Hypertonic contraction may also develop secondary to extensive burns or disorders of the central nervous system (CNS) that render the patient unable to experience or report thirst.

Treatment. Volume replacement in hypertonic contraction should be accomplished with hypotonic fluids (eg, 0.11% sodium chloride) or with fluids that contain no solutes at all. Initial therapy may consist simply of drinking water. Alternatively, 5% dextrose can be infused intravenously. (Since dextrose is rapidly metabolized to carbon dioxide and water, dextrose solutions can be viewed as the osmotic equivalent of water alone.) Volume replenishment should be done in stages. About 50% of the estimated loss should be replaced during the first few hours of treatment. The remainder should be replenished over 1 to 2 days.

Hypotonic Contraction

Definition and Causes. Hypotonic contraction is defined as volume contraction in which *loss of sodium exceeds loss of water*. Hence, both the volume and osmolality of extracellular fluid are reduced. Because intracellular osmolality now exceeds extracellular osmolality, extracellular volume becomes diminished further by movement of water into cells.

The principal cause of hypotonic contraction is excessive loss of sodium through the kidneys. This may occur because of diuretic therapy, chronic renal insufficiency, or lack of aldosterone (the adrenocortical hormone that promotes renal retention of sodium).

Treatment. If hyponatremia is mild, and if renal function is adequate, hypotonic contraction can be corrected by infusing *isotonic* sodium chloride solution for injection. When this is done, plasma tonicity will be adjusted by the kidneys. However, if the sodium loss is severe, a *hypertonic* (eg, 3%) solution of sodium chloride should be infused. Administration should continue until plasma sodium concentration has been raised to about 130 mEq/L. Patients should be monitored for signs of fluid overload (distention of neck veins, peripheral or pulmonary edema). When hypotonic contraction is due to aldosterone insufficiency, patients should receive hormone replacement therapy along with intravenous infusion of isotonic sodium chloride.

Volume Expansion

Volume expansion is defined as an *increase in the total volume of body fluid*. As with volume contraction, volume expansion may be *isotonic*, *hypertonic*, or *hypotonic*. Volume expansion may result from an overdose with therapeutic fluids (eg, sodium chloride infusion) or may be associated with disease states, such as heart failure, nephrotic syndrome, or cirrhosis of the liver with ascites. The principal drugs employed to correct volume expansion are *diuretics* and the *agents used for heart failure*. These drugs are discussed in Chapters 41 and 48, respectively. A specific form of volume expansion, known as hypervolemic hyponatremia, can be treated with a vasopressin antagonist, such as conivaptan or tolvaptan (see Chapter 59).

ACID-BASE DISTURBANCES

Maintenance of acid-base balance is a complex process, the full discussion of which is beyond the scope of this text. Hence, discussion here is condensed.

Acid-base status is regulated by multiple systems. The most important are (1) the bicarbonate-carbonic acid buffer

system, (2) the respiratory system, and (3) the kidneys. The respiratory system influences pH through control of CO₂ exhalation. Because CO₂ represents volatile carbonic acid, exhalation of CO₂ tends to elevate pH (reduce acidity), whereas retention of CO₂ (secondary to respiratory slowing) tends to lower pH. The kidneys influence pH by regulating bicarbonate excretion. By *retaining* bicarbonate, the kidneys can raise pH. Conversely, by increasing bicarbonate *excretion*, the kidneys can lower pH, and thereby compensate for alkalosis.

There are four principal types of acid-base imbalance: (1) respiratory alkalosis, (2) respiratory acidosis, (3) metabolic alkalosis, and (4) metabolic acidosis. Causes and treatments are discussed below.

Respiratory Alkalosis

Causes. Respiratory alkalosis is produced by hyperventilation. Deep and rapid breathing increases CO₂ loss, which in turn lowers the pCO₂* of blood, and thereby increases pH. Mild hyperventilation may result from a number of causes, including hypoxia, pulmonary disease, and drugs (especially aspirin and other salicylates). Severe hyperventilation can be caused by CNS injury and hysteria.

Treatment. Management of respiratory alkalosis is dictated by the severity of pH elevation. When alkalosis is mild, no specific treatment is indicated. Severe respiratory alkalosis resulting from hysteria can be controlled by having the patient rebreathe his or her CO₂-laden expired breath. This can be accomplished by holding a paper bag over the nose and mouth. A similar effect can be achieved by having the patient inhale a gas mixture containing 5% CO₂. A sedative (eg, diazepam [Valium]) can help suppress the hysteria.

Respiratory Acidosis

Causes. Respiratory acidosis results from retention of CO₂ secondary to hypoventilation. Reduced CO₂ exhalation raises plasma pCO₂, which in turn causes plasma pH to fall. Primary causes of impaired ventilation are (1) depression of the medullary respiratory center, and (2) pathologic changes in the lungs (eg, status asthmaticus, airway obstruction). Over time, the kidneys compensate for respiratory acidosis by excreting less bicarbonate.

Treatment. Primary treatment of respiratory acidosis is directed at correcting respiratory impairment. The patient may also need oxygen and ventilatory assistance. Infusion of sodium bicarbonate may be indicated if acidosis is severe.

Metabolic Alkalosis

Causes. Metabolic alkalosis is characterized by increases in both the pH and bicarbonate content of plasma. Causes include excessive loss of gastric acid (through vomiting or suctioning) and administration of alkalinizing salts (eg, sodium bicarbonate). The body compensates for metabolic alkalosis by (1) hypoventilation (which causes retention of CO₂), (2) increased renal excretion of bicarbonate, and (3) accumulation of organic acids.

*pCO₂ is the partial pressure of carbon dioxide in blood.

Treatment. In most cases, metabolic alkalosis can be corrected by infusing a solution of *sodium chloride plus potassium chloride*. This facilitates renal excretion of bicarbonate, and thereby promotes normalization of plasma pH. When alkalosis is severe, direct correction of pH is indicated. This can be accomplished by infusing dilute (0.1 N) *hydrochloric acid* through a central venous catheter or by administering an acid-forming salt, such as *ammonium chloride*. However, ammonium chloride must not be given to patients with liver failure, because the drug is likely to cause hepatic encephalopathy.

Metabolic Acidosis

Causes. Principal causes of metabolic acidosis are chronic renal failure, loss of bicarbonate during severe diarrhea, and metabolic disorders that result in overproduction of lactic acid (lactic acidosis) or ketoacids (ketoacidosis). Metabolic acidosis may also result from poisoning by methanol and certain medications (eg, aspirin and other salicylates).

Treatment. Treatment consists of correcting the underlying cause of acidosis, and, if the acidosis is severe, administering an alkalinizing salt (eg, sodium bicarbonate, sodium carbonate).

When an alkalinizing salt is indicated, *sodium bicarbonate* is generally preferred. Administration may be oral or intravenous. If acidosis is mild, oral administration is preferred. Intravenous infusion is usually reserved for severe reductions of pH. When sodium bicarbonate is given IV to treat acute, severe acidosis, caution must be exercised to avoid excessive elevation of plasma pH. Why? Because rapid conversion from acidosis to alkalosis can be hazardous. Also, because of the sodium content of sodium bicarbonate, care should be taken to avoid hypernatremia.

POTASSIUM IMBALANCES

Potassium is the most abundant *intracellular* cation, having a concentration within cells of about 150 mEq/L. In contrast, *extracellular* concentrations are low (4 to 5 mEq/L). Potassium plays a major role in conducting nerve impulses and maintaining the electrical excitability of muscle. Potassium also helps regulate acid-base balance.

Regulation of Potassium Levels

Serum levels of potassium are regulated primarily by the kidneys. Under steady-state conditions, urinary output of potassium equals intake. Renal excretion of potassium is increased by aldosterone, an adrenal steroid that promotes conservation of sodium while increasing potassium loss. Potassium excretion is also increased by most diuretics. Potassium-sparing diuretics (eg, spironolactone) are the exception.

Potassium levels are influenced by extracellular pH. In the presence of extracellular *alkalosis*, potassium uptake by cells is *enhanced*, causing a *reduction* in extracellular potassium levels. Conversely, extracellular *acidosis* promotes the exit of potassium from cells, thereby causing extracellular *hyperkalemia*.

Insulin has a profound effect on potassium: In high doses, insulin stimulates potassium uptake by cells. This ability has been exploited to treat hyperkalemia.

Hypokalemia

Causes and Consequences

Hypokalemia is defined as a deficiency of potassium in the blood. By definition, hypokalemia exists when serum potassium levels fall below 3.5 mEq/L. The most common cause is treatment with a thiazide or loop diuretic (see Chapter 41). Other causes include insufficient potassium intake; alkalosis and excessive insulin (both of which decrease extracellular potassium levels by driving potassium into cells); increased renal excretion of potassium (eg, as caused by aldosterone); and potassium loss associated with vomiting, diarrhea, and abuse of laxatives. Hypokalemia may also occur because of excessive potassium loss in sweat. As a rule, potassium depletion is accompanied by loss of chloride. Insufficiency of both ions produces *hypokalemic alkalosis*.

Hypokalemia has adverse effects on skeletal muscle, smooth muscle, blood pressure, and the heart. Symptoms include weakness or paralysis of skeletal muscle, a risk of fatal dysrhythmias, and intestinal dilation and ileus. In patients taking digoxin (a cardiac drug), hypokalemia is the principal cause of digoxin toxicity. For all people, hypokalemia increases the risk of hypertension and stroke.

Prevention and Treatment

Potassium depletion can be treated with three potassium salts: potassium chloride, potassium phosphate, and potassium bicarbonate. These may also be used for prophylaxis against potassium insufficiency. For either treatment or prophylaxis, the preferred salt is *potassium chloride*. Why? Because chloride deficiency frequently coexists with potassium deficiency.

Potassium chloride may be administered PO or IV. Oral therapy is preferred for prophylaxis and for treating mild deficiency. Intravenous therapy is reserved for severe deficiency and for patients who cannot take potassium by mouth.

Oral Potassium Chloride. Uses, Dosage, and Preparations. Oral potassium chloride may be used for both prevention and treatment of potassium deficiency. Dosages for prevention range from 16 to 24 mEq/day. Dosages for deficiency range from 40 to 100 mEq/day.

Oral potassium chloride is available in solution and in solid formulations: immediate-release tablets, sustained-release tablets, effervescent tablets, and powders. *The sustained-release tablets (eg, Klor-Con, Micro-K) are preferred.* Why? Because they are more convenient and better tolerated than the other formulations, and hence offer the best chance of patient adherence.

Adverse Effects. Potassium chloride irritates the GI tract, frequently causing abdominal discomfort, nausea, vomiting, and diarrhea. With the exception of the sustained-release tablets, solid formulations can produce high local concentrations of potassium, resulting in severe intestinal injury (ulcerative lesions, bleeding, perforation); death has occurred. To minimize GI effects, oral potassium chloride should be taken with meals or a full glass of water. If symp-

toms of irritation occur, dosing should be discontinued. Rarely, oral potassium chloride produces hyperkalemia. This dangerous development is much more likely with IV therapy.

Intravenous Potassium Chloride. Intravenous potassium chloride is indicated for prevention and treatment of hypokalemia. Intravenous solutions must be diluted (preferably to 40 mEq/L or less) and infused slowly (generally no faster than 10 mEq/hr in adults).

The principal complication is hyperkalemia, which can prove fatal. To reduce the risk of hyperkalemia, serum potassium levels should be measured prior to the infusion and periodically throughout the treatment interval. Also, renal function should be assessed before and during treatment to ensure adequate output of urine. If renal failure develops, the infusion should be stopped immediately. Changes in the electrocardiogram (ECG) can be an early indication that potassium toxicity is developing.

Contraindications to Potassium Use. Potassium should be avoided under conditions that predispose to hyperkalemia (eg, severe renal impairment, use of potassium-sparing diuretics, hypoaldosteronism). Potassium must also be avoided when hyperkalemia already exists.

Hyperkalemia

Causes. Hyperkalemia (excessive elevation of serum potassium) can result from a number of causes. These include severe tissue trauma, untreated Addison's disease, acute acidosis (which draws potassium out of cells), misuse of potassium-sparing diuretics, and overdose with IV potassium.

Consequences. The most serious consequence of hyperkalemia is disruption of the electrical activity of the heart. Because hyperkalemia alters the generation and conduction of cardiac impulses, alterations in the ECG and cardiac rhythm are usually the earliest signs that potassium levels are growing dangerously high. With mild elevation of serum potassium (5 to 7 mEq/L), the T wave heightens and the PR interval becomes prolonged. When serum potassium reaches 8 to 9 mEq/L, cardiac arrest can occur, possibly preceded by ventricular tachycardia or fibrillation.

Effects of hyperkalemia are not limited to the heart. Non-cardiac effects include confusion, anxiety, dyspnea, weakness or heaviness of the legs, and numbness or tingling of the hands, feet, and lips.

Treatment. Treatment is begun by withholding any foods that contain potassium and any medicines that promote potassium accumulation (eg, potassium-sparing diuretics, potassium supplements). After this, management consists of measures that (1) counteract potassium-induced cardiotoxicity and (2) lower extracellular levels of potassium. Specific steps include (1) infusion of a calcium salt (eg, calcium gluconate) to offset effects of hyperkalemia on the heart; (2) infusion of glucose and insulin to promote uptake of potassium by cells and thereby decrease extracellular potassium levels; and (3) if acidosis is present (which is likely), infusion of sodium bicarbonate to move pH toward alkalinity, and thereby increase cellular uptake of potassium. If these measures prove inadequate, steps can be taken to remove potassium. These include (1) oral or rectal administration of sodium polystyrene sulfonate [Kayexalate,

Kionex, Marlexate], an exchange resin that absorbs potassium; and (2) peritoneal or extracorporeal dialysis.

MAGNESIUM IMBALANCES

Magnesium is required for the activity of many enzymes and for binding of messenger RNA to ribosomes. In addition, magnesium helps regulate neurochemical transmission and the excitability of muscle. The concentration of magnesium within cells is about 40 mEq/L, much higher than its concentration outside cells (about 2 mEq/L).

Hypomagnesemia

Causes and Consequences

Low levels of magnesium may result from a variety of causes, including diarrhea, hemodialysis, kidney disease, and prolonged intravenous feeding with magnesium-free solutions. Hypomagnesemia may also be seen in chronic alcoholics and in people with diabetes or pancreatitis. Frequently, patients with magnesium deficiency also present with hypocalcemia and hypokalemia.

Prominent symptoms of hypomagnesemia involve cardiac and skeletal muscle. In the presence of low levels of magnesium, release of acetylcholine at the neuromuscular junction is enhanced. This can increase muscle excitability to the point of tetany. Hypomagnesemia also increases excitability of neurons in the CNS, causing disorientation, psychoses, and seizures.

In the kidneys, hypomagnesemia may lead to nephrocalcinosis (formation of minuscule calcium stones within nephrons). Renal injury occurs when the stones become large enough to block the flow of tubular urine.

Prevention and Treatment

Frank hypomagnesemia is treated with parenteral magnesium sulfate. For prophylaxis against magnesium deficiency, an oral preparation (magnesium hydroxide) may be used.

Magnesium Hydroxide. Tablets of magnesium hydroxide may be taken as supplements to dietary magnesium to help prevent hypomagnesemia. Milk of magnesia (a liquid formulation of magnesium hydroxide) may also be used for prophylaxis. With any oral magnesium preparation, excessive doses may cause diarrhea. The adult and pediatric dosage for preventing deficiency is 5 mg/kg/day.

Magnesium Sulfate. Uses, Administration, and Dosage. Magnesium sulfate (IM or IV) is the preferred treatment for severe hypomagnesemia. The IM dosage is 0.5 to 1 gm 4 times a day. For IV therapy, a 10% solution can be used, infused at a rate of 1.5 mL/min or less.

Adverse Effects. Excessive levels of magnesium cause neuromuscular blockade. Paralysis of the respiratory muscles is of particular concern. By suppressing neuromuscular transmission, magnesium excess can intensify the effects of neuromuscular blocking agents (eg, succinylcholine, atracurium). Hence, caution must be exercised in patients receiving these drugs. The neuromuscular blocking actions of magnesium can be counteracted with calcium. Accordingly, when parenteral magnesium is being employed, an inject-

able form of calcium (eg, calcium gluconate) should be immediately available.

In the heart, excessive magnesium can suppress impulse conduction through the atrioventricular (AV) node. Accordingly, magnesium sulfate is contraindicated for patients with AV heart block.

To minimize the risk of toxicity, serum magnesium levels should be monitored. Respiratory paralysis occurs at 12 to 15 mEq/L. When magnesium levels exceed 25 mEq/L, cardiac arrest may set in.

Hypermagnesemia

Toxic elevation of magnesium levels is most common in patients with renal insufficiency, especially when magnesium-containing antacids or cathartics are being used. Symptoms of mild intoxication include muscle weakness (resulting from inhibition of acetylcholine release), hypotension, sedation, and ECG changes. As noted, respiratory paralysis is likely when plasma levels reach 12 to 15 mEq/L. At higher magnesium concentrations, there is a risk of cardiac arrest. Muscle weakness and paralysis can be counteracted with intravenous calcium.

KEY POINTS

- Treat isotonic volume contraction with isotonic (0.9%) sodium chloride.
- Treat hypertonic volume contraction with hypotonic (eg, 0.11%) sodium chloride.
- Treat hypotonic volume contraction with hypertonic (eg, 3%) sodium chloride.
- Treat volume expansion with diuretics.
- Treat respiratory or metabolic acidosis with sodium bicarbonate.
- Treat respiratory alkalosis by having patients inhale 5% CO₂ or rebreathe their expired air.
- Treat metabolic alkalosis with an infusion of sodium chloride plus potassium chloride. For severe cases, infuse 0.1% hydrochloric acid or ammonium chloride.
- Treat moderate hypokalemia with potassium chloride in sustained-release tablets.
- Treat severe hypokalemia with IV potassium chloride.
- To treat hyperkalemia, begin by withdrawing potassium-containing foods and drugs that promote potassium accumulation (eg, potassium supplements, potassium-sparing diuretics). Subsequent measures include (1) infusing a calcium salt to offset the cardiac effects of potassium, (2) infusing glucose and insulin to promote potassium uptake by cells, and (3) infusing sodium bicarbonate if acidosis is present.
- Treat hypomagnesemia with IM or IV magnesium sulfate. For prophylaxis, give oral magnesium (eg, magnesium hydroxide).

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Review of Hemodynamics

Overview of the Circulatory System

Components of the Circulatory System

Distribution of Blood

What Makes Blood Flow?

How Does Blood Get Back to the Heart?

Regulation of Cardiac Output

Determinants of Cardiac Output

Control of Stroke Volume by Venous Return

Starling's Law and Maintenance of Systemic-Pulmonary Balance

Regulation of Arterial Pressure

Overview of Control Systems

Steady-State Control by the ANS

Rapid Control by the ANS: The Baroreceptor Reflex

The Renin-Angiotensin-Aldosterone System

Renal Retention of Water

Postural Hypotension

Natriuretic Peptides

Hemodynamics is the study of the movement of blood throughout the circulatory system, along with the regulatory mechanisms and driving forces involved. Concepts introduced here reappear throughout the chapters on cardiovascular drugs. Accordingly, I urge you to review these now. Because this is a pharmacology text, and not a physiology text, discussion is limited to hemodynamic factors that have particular relevance to the actions of drugs.

OVERVIEW OF THE CIRCULATORY SYSTEM

The circulatory system has two primary functions: (1) delivery of oxygen, nutrients, hormones, electrolytes, and other essentials to cells; and (2) removal of carbon dioxide, metabolic wastes, and other detritus from cells. In addition, the system helps fight infection.

The circulatory system has two major divisions: the *pulmonary circulation* and the *systemic circulation*. The pulmonary circulation delivers blood to the lungs. The systemic circulation delivers blood to all other organs and tissues. The systemic circulation is also known as the *greater circulation* or *peripheral circulation*.

Components of the Circulatory System

The circulatory system is composed of the *heart* and *blood vessels*. The heart is the pump that moves blood through the arterial tree. The blood vessels have several functions:

- *Arteries* transport blood under high pressure to tissues.
- *Arterioles* are control valves that regulate local blood flow.
- *Capillaries* are the sites for exchange of fluid, oxygen, carbon dioxide, nutrients, hormones, wastes, and so forth.
- *Venules* collect blood from the capillaries.
- *Veins* transport blood back to the heart. In addition, veins serve as a major reservoir for blood.

Arteries and veins differ with respect to distensibility (elasticity). Arteries are very muscular, and hence do not readily stretch. As a result, large increases in arterial pressure (AP) cause only small increases in arterial diameter. Veins are much less muscular, and hence are 6 to 10 times more distensible. As a result, small increases in venous pressure cause large increases in vessel diameter, which produces a large increase in venous volume.

Distribution of Blood

The adult circulatory system contains about 5 L of blood, which is distributed throughout the system. As indicated in Figure 43-1, 9% is in the pulmonary circulation, 7% is in the heart, and 84% is in the systemic circulation. Within the systemic circulation, however, distribution is uneven: most (64%) of the blood is in veins, venules, and venous sinuses; the remaining 20% is in arteries (13%) and arterioles or capillaries (7%). The large volume of blood in the venous system serves as a reservoir.

What Makes Blood Flow?

Blood moves within vessels because the force that drives flow is greater than the resistance to flow. As indicated in Figure 43-2, the force that drives blood flow is the pressure gradient between two points in a vessel. Obviously, blood will flow from the point where pressure is higher toward the point where pressure is lower. Resistance to flow is determined by the diameter and length of the vessel, and by blood viscosity. From a pharmacologic viewpoint, the most important determinant of resistance is vessel diameter: The larger the vessel, the smaller the resistance. Accordingly, when vessels dilate, resistance declines, causing blood flow to increase—and when vessels constrict, resistance rises, causing blood flow to decline. In order to maintain adequate flow when resistance rises, blood pressure must rise as well.

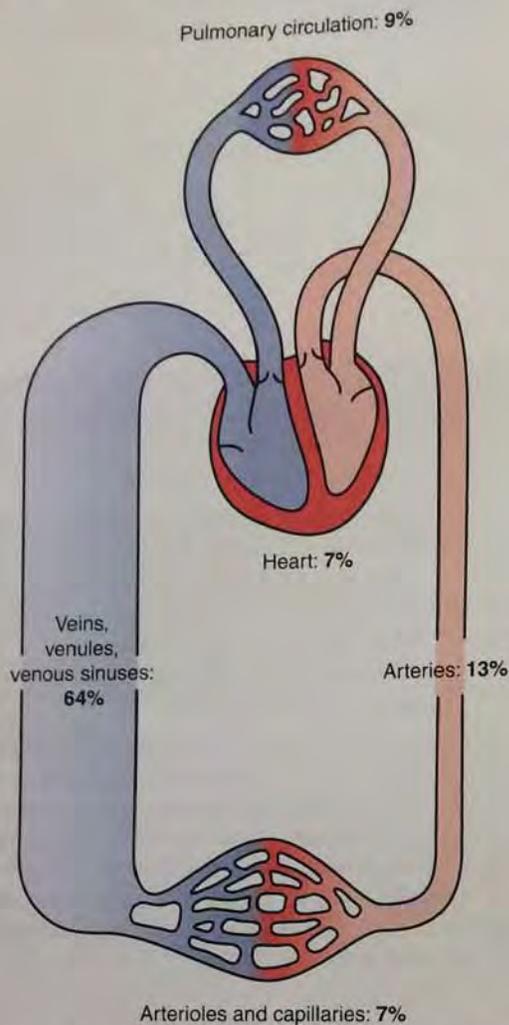


Figure 43-1 = Distribution of blood in the circulatory system.

Note that a large percentage of the blood resides in the venous system.

How Does Blood Get Back to the Heart?

As indicated in Figure 43-3, pressure falls progressively as blood moves through the systemic circulation. Pressure is 120 mm Hg when blood enters the aorta, 30 mm Hg when blood enters capillaries, and only 18 mm Hg when blood leaves capillaries, and then drops to negative values (0 to -5 mm Hg) in the right atrium. (Negative atrial pressure is generated by expansion of the chest during inspiration.)

Given that pressure is only 18 mm Hg when blood leaves capillaries, we must ask, "How does blood get back to the heart? After all, a pressure of 18 mm Hg does not seem adequate to move blood from the feet all the way up to the thorax." The answer is that, in addition to the small pressure head in venules, three mechanisms help ensure venous return. First, negative pressure in the right atrium helps "suck" blood toward the heart. Second, constriction of smooth muscle in the venous wall increases venous pressure, which helps drive blood toward the heart. Third, and most important, the combination of venous valves and skeletal muscle contraction constitutes an auxiliary "venous pump." As indicated in Figure 43-4A, the veins are equipped with a system of one-way valves. When skeletal

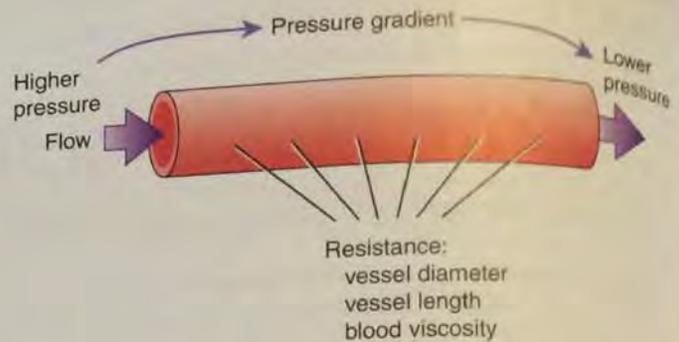


Figure 43-2 = Forces that promote and impede flow of blood.

Blood flows from the point of higher pressure toward the point of lower pressure. Resistance to flow is determined by vessel diameter, vessel length, and blood viscosity.

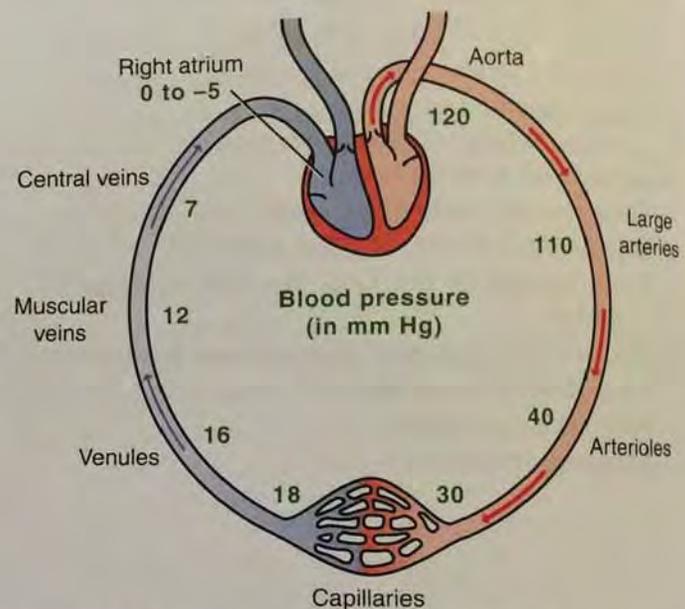


Figure 43-3 = Distribution of pressure within the systemic circulation.

Note that pressure is highest when blood leaves the left ventricle, falls to only 18 mm Hg as blood exits capillaries, and reaches negative values within the right atrium.

muscles contract (Fig. 43-4B), venous blood is squeezed toward the heart—the only direction the valves will permit.

REGULATION OF CARDIAC OUTPUT

In the average adult, cardiac output is about 5 L/min. Hence, every minute the heart pumps the equivalent of all the blood in the body. In this section, we consider the major factors that determine how much blood the heart pumps.

Determinants of Cardiac Output

The basic equation for cardiac output is

$$CO = HR \times SV$$

where CO is cardiac output, HR is heart rate, and SV is stroke volume. According to the equation, an increase in HR or SV

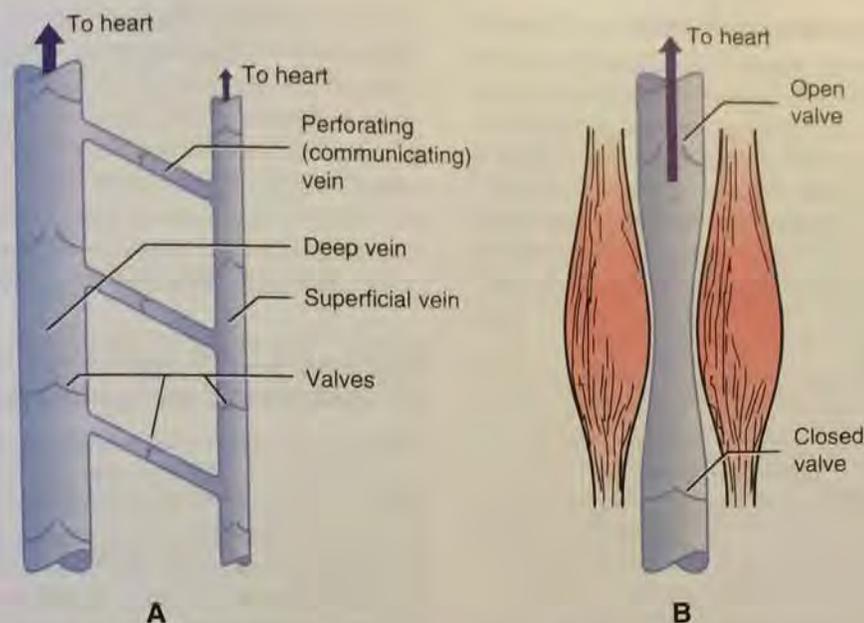


Figure 43-4 • Venous valves and the auxiliary venous “pump.”

A, Veins and their one-way valves in the leg. Note that the configuration of these valves ensures that blood will move toward the heart. **B**, Contraction of skeletal muscle pumps venous blood toward the heart.

will increase CO, whereas a decrease in HR or SV will decrease CO. For the average person, heart rate is about 70 beats/min and stroke volume is about 70 mL. Multiplying these, we get 4.9 L/min—the average value for CO.

Heart Rate. Heart rate is controlled primarily by the autonomic nervous system (ANS). Rate is increased by the sympathetic branch acting through β_1 -adrenergic receptors in the sinoatrial (SA) node. Rate is decreased by the parasympathetic branch acting through muscarinic receptors in the SA node. Parasympathetic impulses reach the heart via the vagus nerve.

Stroke Volume. Stroke volume is determined largely by three factors: (1) myocardial contractility, (2) cardiac afterload, and (3) cardiac preload. *Myocardial contractility* is defined as the force with which the ventricles contract. Contractility is determined primarily by the degree of cardiac dilation, which in turn is determined by the amount of venous return. The importance of venous return in regulating contractility and stroke volume is discussed separately below. In addition to regulation by venous return, contractility can be increased by the sympathetic nervous system, acting through β_1 -adrenergic receptors in the myocardium.

Preload. Preload is formally defined as the amount of tension (stretch) applied to a muscle prior to contraction. In the heart, stretch is determined by ventricular filling pressure, that is, the *force of venous return*. The greater filling pressure is, the more the ventricles will stretch. Cardiac preload can be expressed as either *end-diastolic volume* or *end-diastolic pressure*. As discussed below, an increase in preload will increase stroke volume, whereas a decrease in preload will reduce stroke volume. Frequently, the terms *preload* and *force of venous return* are used interchangeably—although they are not truly equivalent.

Afterload. Afterload is formally defined as the load against which a muscle exerts its force (ie, the load a muscle must overcome in order to contract). For the heart, afterload is the *arterial pressure* that the left ventricle must overcome

to eject blood. Common sense tells us that, if afterload increases, stroke volume will decrease. Conversely, if afterload falls, stroke volume will rise. Cardiac afterload is determined primarily by the degree of peripheral resistance, which in turn is determined by constriction and dilation of arterioles. That is, when arterioles constrict, peripheral resistance rises, causing AP (afterload) to rise as well. Conversely, when arterioles dilate, peripheral resistance falls, causing AP to decline.

Control of Stroke Volume by Venous Return

Q: How much blood does the heart pump with each stroke?
A: Exactly the amount delivered to it by the veins!

Starling's Law of the Heart

Starling's law states that the force of ventricular contraction is proportional to muscle fiber length (up to a point). Accordingly, as fiber length (ventricular diameter) increases, there is a corresponding increase in contractile force (Fig. 43-5). Because of this built-in mechanism, when more blood enters the heart, more is pumped out. As a result, the healthy heart is able to precisely match its output with the volume of blood delivered by veins. That is, when venous return increases, cardiac output increases correspondingly. Conversely, when venous return declines, cardiac output declines to precisely the same extent. Hence, under normal, nonstressed conditions, stroke volume is determined by factors that regulate venous return.

Why does contractile force change as a function of fiber length (ventricular diameter)? Recall that muscle contraction results from the interaction of two proteins: actin and myosin. As the heart stretches in response to increased ventricular filling, actin and myosin are brought into a more optimal alignment with each other, which allows them to interact with greater force.

Factors That Determine Venous Return

Having established that venous return is the primary determinant of stroke volume (and hence cardiac output), we need to understand the factors that determine venous return. With regard to pharmacology, the most important factor is *systemic filling pressure* (ie, the force that returns blood to the heart). The normal value for filling pressure is 7 mm Hg. This value can be raised to 17 mm Hg by constriction of veins. Filling pressure can also be raised by an increase in blood volume.

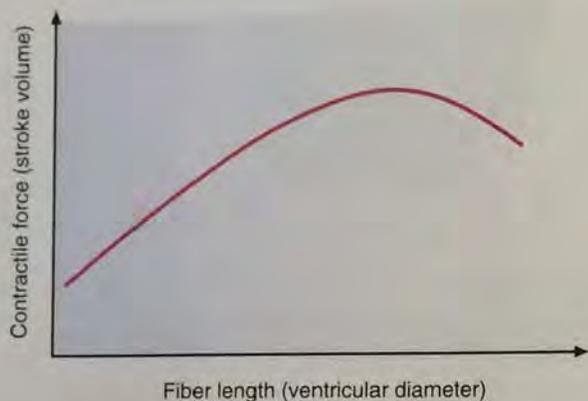


Figure 43-5 ■ The Starling relationship between myocardial fiber length and contractile force.

Note that an increase in fiber length produces a corresponding increase in contractile force. Fiber length increases as the ventricles enlarge during filling. Increased contractile force is reflected by increased stroke volume.

Conversely, filling pressure, and hence venous return, can be lowered by venodilation or by reducing blood volume. Blood volume and venous tone can both be altered with drugs.

In addition to systemic filling pressure, three other factors influence venous return: (1) the auxiliary muscle pumps discussed above, (2) resistance to flow between peripheral vessels and the right atrium, and (3) right atrial pressure, elevation of which will impede venous return. None of these factors can be directly influenced with drugs.

Starling's Law and Maintenance of Systemic-Pulmonary Balance

Because the myocardium operates in accord with Starling's law, the right and left ventricles always pump exactly the same amount of blood. When venous return increases, stroke volume of the right ventricle increases, thereby increasing delivery of blood to the pulmonary circulation, which in turn delivers more blood to the left ventricle; this increases filling of the left ventricle, which causes *its* stroke volume to increase. Because an increase in venous return causes the output of *both* ventricles to increase, blood flow through the systemic and pulmonary circulations is always in balance, as long as the heart is healthy.

In the failing heart, Starling's law breaks down. That is, force of contraction no longer increases in proportion to increased ventricular filling. As a result, blood backs up behind the failing ventricle. The deadly consequence is illustrated in Figure 43-6. In this example, output of the left ventricle is 1% less than the output of the right ventricle, which causes blood to back up in the pulmonary circulation. In only 20 minutes,

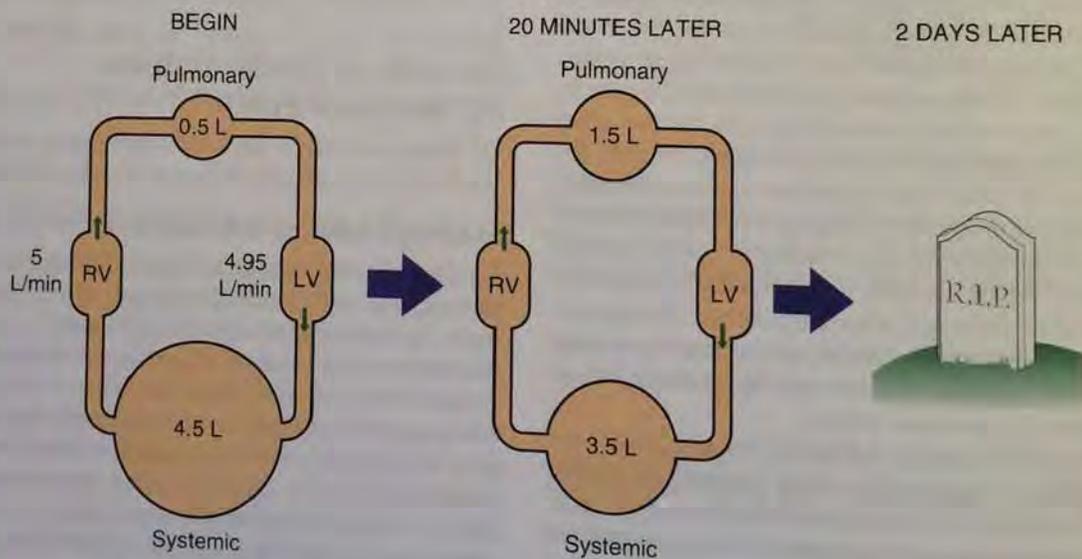


Figure 43-6 ■ Systemic-pulmonary imbalance that develops when the output of the left and right ventricles is not identical.

In this example, the output of the left ventricle (LV) is 1% less than the output of the right ventricle (RV). Hence, while the right ventricle pumps 5000 mL/min, the left pumps only 4950 mL/min—50 mL/min less than the right side. This causes blood to back up in the pulmonary circulation. After 20 minutes, 1000 mL of blood has shifted from the systemic circulation to the pulmonary circulation. Death would ensue in less than 40 minutes. (The 2 days are an allowance for the blood undertaker and clergy.) Numbers in the pulmonary and systemic circulations indicate volume of blood in liters. (Adapted from Burton AC: *Physiology and Biophysics of the Circulation*. Chicago: Year Book Medical Publishers, 1968:144.)

this small imbalance between left and right ventricular output shifts a liter of blood from the systemic circulation to the pulmonary circulation. In less than 40 minutes, death from pulmonary congestion would ensue. This example underscores the importance of systemic-pulmonary balance, and the critical role of Starling's mechanism in maintaining it.

REGULATION OF ARTERIAL PRESSURE

AP is the driving force that moves blood through the arterial side of the systemic circulation. The general formula for arterial pressure is

$$AP = PR \times CO$$

where AP is arterial pressure, PR is peripheral resistance, and CO is cardiac output. Accordingly, an increase in PR or CO will increase AP, whereas a decrease in PR or CO will decrease AP. Peripheral resistance is regulated primarily through constriction and dilation of arterioles. Cardiac output is regulated by the mechanisms discussed above. Regulation of AP through processes that alter PR and CO is discussed below.

Overview of Control Systems

Under normal circumstances, AP is regulated primarily by three systems: the ANS, the renin-angiotensin-aldosterone system (RAAS), and the kidneys. These systems differ greatly with regard to time frame of response. The ANS acts in two ways: (1) it responds rapidly (in seconds or minutes) to acute changes in blood pressure, and (2) it provides steady-state control. The RAAS responds more slowly, taking hours or days to influence AP. The kidneys are responsible for long-term control, and hence may take days or weeks to adjust AP.

Arterial pressure is also regulated by a fourth system: a family of natriuretic peptides. These peptides come into play primarily under conditions of volume overload.

Steady-State Control by the ANS

The ANS regulates AP by adjusting CO and peripheral resistance. Sympathetic tone to the heart increases heart rate and contractility, thereby increasing CO. In contrast, parasympathetic tone slows the heart, and thereby reduces CO. As discussed in Chapter 13, constriction of blood vessels is regulated exclusively by the sympathetic branch of the ANS; blood vessels have no parasympathetic innervation. Steady-state sympathetic tone provides a moderate level of vasoconstriction. The resultant resistance to blood flow maintains AP. Complete elimination of sympathetic tone would cause AP to fall by 50%.

Rapid Control by the ANS: The Baroreceptor Reflex

The baroreceptor reflex serves to maintain AP at a predetermined level. When AP changes, the reflex immediately attempts to restore AP to the preset value.

The reflex works as follows. Baroreceptors (pressure sensors) in the aortic arch and carotid sinus sense AP and relay this information to the vasoconstrictor center of the medulla. When AP changes, the vasoconstrictor center compensates by

sending appropriate instructions to arterioles, veins, and the heart. For example, when AP drops, the vasoconstrictor center causes (1) constriction of nearly all arterioles, thereby increasing peripheral resistance; (2) constriction of veins, thereby increasing venous return; and (3) acceleration of heart rate (by increasing sympathetic impulses to the heart and decreasing parasympathetic impulses). The combined effect of these responses is to restore AP to the preset level. When AP rises too high, opposite responses occur: The reflex dilates arterioles and veins and slows the heart.

The baroreceptor reflex is poised for rapid action—but not for sustained action. When AP falls or rises, the reflex acts within seconds to restore the preset pressure. However, when AP remains elevated or lowered, the system resets to the new pressure within 1 to 2 days. After this, the system perceives the new (elevated or reduced) pressure as “normal,” and hence ceases to respond.

Drugs that lower AP will trigger the baroreceptor reflex. For example, if we administer a drug that dilates arterioles, the resultant drop in peripheral resistance will reduce AP, causing the baroreceptor reflex to activate. The most noticeable response is *reflex tachycardia*. The baroreceptor reflex can temporarily negate efforts to lower AP with drugs.

The Renin-Angiotensin-Aldosterone System

The RAAS supports AP by causing (1) constriction of arterioles and veins, and (2) retention of water by the kidneys. Vasoconstriction is mediated by a hormone named *angiotensin II*. Water retention is mediated in part by *aldosterone*. Responses develop in hours (vasoconstriction) to days (water retention). The RAAS and its role in controlling blood pressure are discussed at length in Chapter 44.

Renal Retention of Water

When AP remains low for a long time, the kidneys respond by retaining water, which in turn causes AP to rise. Pressure rises because fluid retention increases blood volume, which increases venous pressure, which increases venous return, which increases CO, which increases AP. Water retention is a mechanism for maintaining AP over long periods (weeks, months, years).

Why does a reduction in AP cause the kidneys to retain water? First, low AP reduces renal blood flow (RBF), which in turn reduces glomerular filtration rate (GFR). Because less fluid is filtered, less urine is produced, and therefore more water is retained. Second, low AP activates the RAAS, causing levels of angiotensin II and aldosterone to rise. Angiotensin II causes constriction of renal blood vessels, and thereby further decreases RBF and GFR. Aldosterone promotes renal retention of sodium, which causes water to be retained along with it.

Postural Hypotension

Postural hypotension, also known as *orthostatic hypotension*, is a reduction in AP that can occur when we move from a supine or seated position to an upright position. The cause of hypotension is pooling of blood in veins, which decreases venous return, which in turn decreases CO. Between 300 and

800 mL of blood can pool in veins when we stand, causing CO to drop by as much as 2 L/min. Why does blood collect in veins? When we stand, gravity increases the pressure that blood exerts on veins. Since veins are not very muscular, they are unable to retain their shape when pressure increases, and hence they stretch. The resultant increase in venous volume allows blood to pool.

Two mechanisms help overcome postural hypotension. One is the system of auxiliary venous pumps, which promote venous return. In fact, in healthy individuals, these auxiliary pumps usually prevent postural hypotension from occurring in the first place. When postural hypotension does occur, the baroreceptor reflex can restore AP by (1) constricting veins and arterioles and (2) increasing heart rate.

What would happen if we gave a drug that promoted dilation of veins (or prevented them from constricting)? In patients taking drugs that interfere with venoconstriction, postural hypotension is more intense and more prolonged. Hypotension is more intense because venous pooling is greater. Hypotension is more prolonged because there is no venoconstriction to help reverse venous pooling. As with drugs that reduce AP by dilating arterioles, drugs that reduce AP by relaxing veins can trigger the baroreceptor reflex, and can thereby cause reflex tachycardia.

Natriuretic Peptides

Natriuretic peptides serve to protect the cardiovascular system in the event of volume overload, a condition that increases preload, and thereby increases CO and AP. Volume overload is

caused by excessive retention of sodium and water. Natriuretic peptides work primarily by (1) reducing blood volume and (2) promoting dilation of arterioles and veins. Both actions lower AP.

The family of natriuretic peptides has three principal members: *atrial natriuretic peptide* (ANP), *B- or brain natriuretic peptide* (BNP), and *C-natriuretic peptide* (CNP). ANP is produced by myocytes of the atria; BNP is produced by myocytes of the ventricles (and to a lesser extent by cells in the brain, where BNP was discovered); and CNP is produced by cells of the vascular endothelium. When blood volume is excessive, all three peptides are released (Release of ANP and BNP is triggered by stretching of the atria and ventricles, which occurs because of increased preload.)

ANP and BNP have similar actions. Both peptides reduce blood volume and increase venous capacitance, and thereby reduce cardiac preload. Three processes are involved. First, ANP and BNP shift fluid from the vascular system to the extravascular compartment; the underlying mechanism is increased vascular permeability. Second, these peptides act on the kidney to cause diuresis (loss of water) and natriuresis (loss of sodium). Third, they promote dilation of arterioles and veins, in part by suppressing sympathetic outflow from the central nervous system. In addition to these actions, ANP and BNP help protect the heart during the early phase of heart failure. How? By suppressing both the RAAS and sympathetic outflow, and by inhibiting proliferation of myocytes. Although CNP shares some actions of ANP and BNP, its primary action is to promote vasodilation.

KEY POINTS*

- Arterioles serve as control valves to regulate local blood flow.
- Veins are a reservoir for blood.
- Arteries are not very distensible. As a result, large increases in AP cause only small increases in arterial diameter.
- Veins are highly distensible. As a result, small increases in venous pressure cause large increases in venous diameter.
- The adult circulatory system contains 5 L of blood, 64% of which is in systemic veins.
- Vasodilation reduces resistance to blood flow, whereas vasoconstriction increases resistance to flow.
- In addition to the small pressure head in venules, three mechanisms help ensure venous return to the heart: (1) negative pressure in the right atrium sucks blood toward the heart; (2) constriction of veins increases venous pressure, and thereby drives blood toward the heart; and (3) contraction of skeletal muscles, in conjunction with one-way venous valves, pumps blood toward the heart.
- Heart rate is increased by sympathetic nerve impulses and decreased by parasympathetic impulses.
- Stroke volume is determined by myocardial contractility, cardiac preload, and cardiac afterload.
- Preload is defined as the amount of tension (stretch) applied to a muscle prior to contraction. In the heart, preload is determined by the force of venous return.
- Afterload is defined as the load against which a muscle exerts its force. For the heart, afterload is the arterial pressure (AP) that the left ventricle must overcome to eject blood.
- Cardiac afterload is determined primarily by peripheral resistance, which in turn is determined by the degree of constriction in arterioles.
- Starling's law states that the force of ventricular contraction is proportional to myocardial fiber length. Because of this relationship, when more blood enters the heart, more is pumped out. As a result, the healthy heart is able to precisely match output with venous return.
- The most important determinant of venous return is systemic filling pressure, which can be raised by constricting veins and increasing blood volume.
- Because cardiac muscle operates under Starling's law, the right and left ventricles always pump exactly the same

*Key points are limited to concepts that might not have been stressed when you studied physiology (eg, veins serve as a blood reservoir). Important but obvious concepts (eg, the heart is a pump, arteries deliver blood to tissues under pressure) are not included in this summary.

amount of blood (assuming the heart is healthy). Hence, balance between the pulmonary and systemic circulations is maintained.

- Arterial pressure is regulated by the ANS, the RAAS, the kidneys, and natriuretic peptides.
- The ANS regulates AP (1) through tonic control of heart rate and peripheral resistance and (2) through the baroreceptor reflex.
- The baroreceptor reflex is useful only for short-term control of AP. When pressure remains elevated or lowered, the system resets to the new pressure within 1 to 2 days, and hence ceases to respond.
- Drugs that lower AP trigger the baroreceptor reflex, and thereby cause reflex tachycardia. Hence, the baroreceptor reflex can temporarily negate efforts to lower AP with drugs.
- The RAAS supports AP by causing (1) constriction of arterioles and veins and (2) retention of water by the kid-

neys. Vasoconstriction is mediated by angiotensin II; water retention is mediated in part by aldosterone.

- The kidneys provide long-term control of blood pressure by regulating blood volume.
- Postural (orthostatic) hypotension is caused by decreased venous return secondary to pooling of blood in veins, which can occur when we assume an erect posture.
- Drugs that dilate veins intensify and prolong postural hypotension. As with other drugs that reduce AP, venodilators can trigger the baroreceptor reflex, and can thereby cause reflex tachycardia.
- Natriuretic peptides defend the cardiovascular system from volume overload—primarily by reducing blood volume and promoting vasodilation.

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Drugs Acting on the Renin-Angiotensin-Aldosterone System

Physiology of the Renin-Angiotensin-Aldosterone System

Types of Angiotensin

Actions of Angiotensin II

Actions of Aldosterone

Formation of Angiotensin II by Renin and Angiotensin-Converting Enzyme

Regulation of Blood Pressure by the Renin-Angiotensin-Aldosterone System

Tissue (Local) Angiotensin II Production

Angiotensin-Converting Enzyme Inhibitors

Angiotensin II Receptor Blockers

Aliskiren, a Direct Renin Inhibitor

Aldosterone Antagonists

Eplerenone

Spironolactone

In this chapter we consider four families of drugs: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), direct renin inhibitors (DRIs), and aldosterone antagonists. With all four groups, effects result from interfering with the renin-angiotensin-aldosterone system (RAAS). The ACE inhibitors, available for more than three decades, have established roles in the treatment of hypertension, heart failure, and diabetic nephropathy; in addition, these drugs are indicated for myocardial infarction and prevention of cardiovascular events in patients at risk. Indications for ARBs are limited to hypertension, heart failure, diabetic nephropathy, and prevention of cardiovascular events in patients at risk. The aldosterone antagonists have only two indications: hypertension and heart failure. Current indications for DRIs are limited to hypertension. We begin the chapter by reviewing the physiology of the RAAS. After that, we discuss the drugs that affect it.

PHYSIOLOGY OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The RAAS plays an important role in regulating blood pressure, blood volume, and fluid and electrolyte balance. In addition, the system appears to mediate certain pathophysiologic changes associated with hypertension, heart failure, and myocardial infarction. The RAAS exerts its effects through angiotensin II and aldosterone.

Types of Angiotensin

Before considering the physiology of the RAAS, we need to introduce the angiotensin family, which consists of angiotensin I, angiotensin II, and angiotensin III. All three compounds are small polypeptides. Angiotensin I is the precursor of angiotensin II (Fig. 44-1) and has only weak biologic activity. In contrast, angiotensin II has strong biologic activity. And angiotensin III, which is formed by degradation of angiotensin II, has moderate biologic activity.

Actions of Angiotensin II

Angiotensin II participates in all processes regulated by the RAAS. The most prominent actions of angiotensin II are vasoconstriction and stimulation of aldosterone release. Both actions raise blood pressure. In addition, angiotensin II (as well as aldosterone) can act on the heart and blood vessels to cause pathologic changes in their structure and function.

Vasoconstriction. Angiotensin II is a powerful vasoconstrictor. The compound acts directly on vascular smooth muscle (VSM) to cause contraction. Vasoconstriction is prominent in arterioles and less so in veins. As a result of angiotensin-induced vasoconstriction, blood pressure rises. In addition to its direct action on blood vessels, angiotensin II can cause vasoconstriction indirectly by acting on (1) sympathetic neurons to promote norepinephrine release, (2) the adrenal medulla to promote epinephrine release, and (3) the central nervous system to increase sympathetic outflow to blood vessels.

Release of Aldosterone. Angiotensin II acts on the adrenal cortex to promote synthesis and secretion of aldosterone, whose actions are discussed below. The adrenal cortex is highly sensitive to angiotensin II, and hence angiotensin II can stimulate aldosterone release even when angiotensin II levels are too low to induce vasoconstriction. Aldosterone secretion is enhanced when sodium levels are low and when potassium levels are high.

Alteration of Cardiac and Vascular Structure. Angiotensin II may cause pathologic structural changes in the heart and blood vessels. In the heart, it may cause *hypertrophy* (increased cardiac mass) and *remodeling* (redistribution of mass within the heart). In hypertension, angiotensin II may be responsible for increasing the thickness of blood vessel walls. In atherosclerosis, it may be responsible for thickening the intimal surface of blood vessels. And in heart failure and myocardial infarction, it may be responsible for causing cardiac hypertrophy and fibrosis. Known effects of

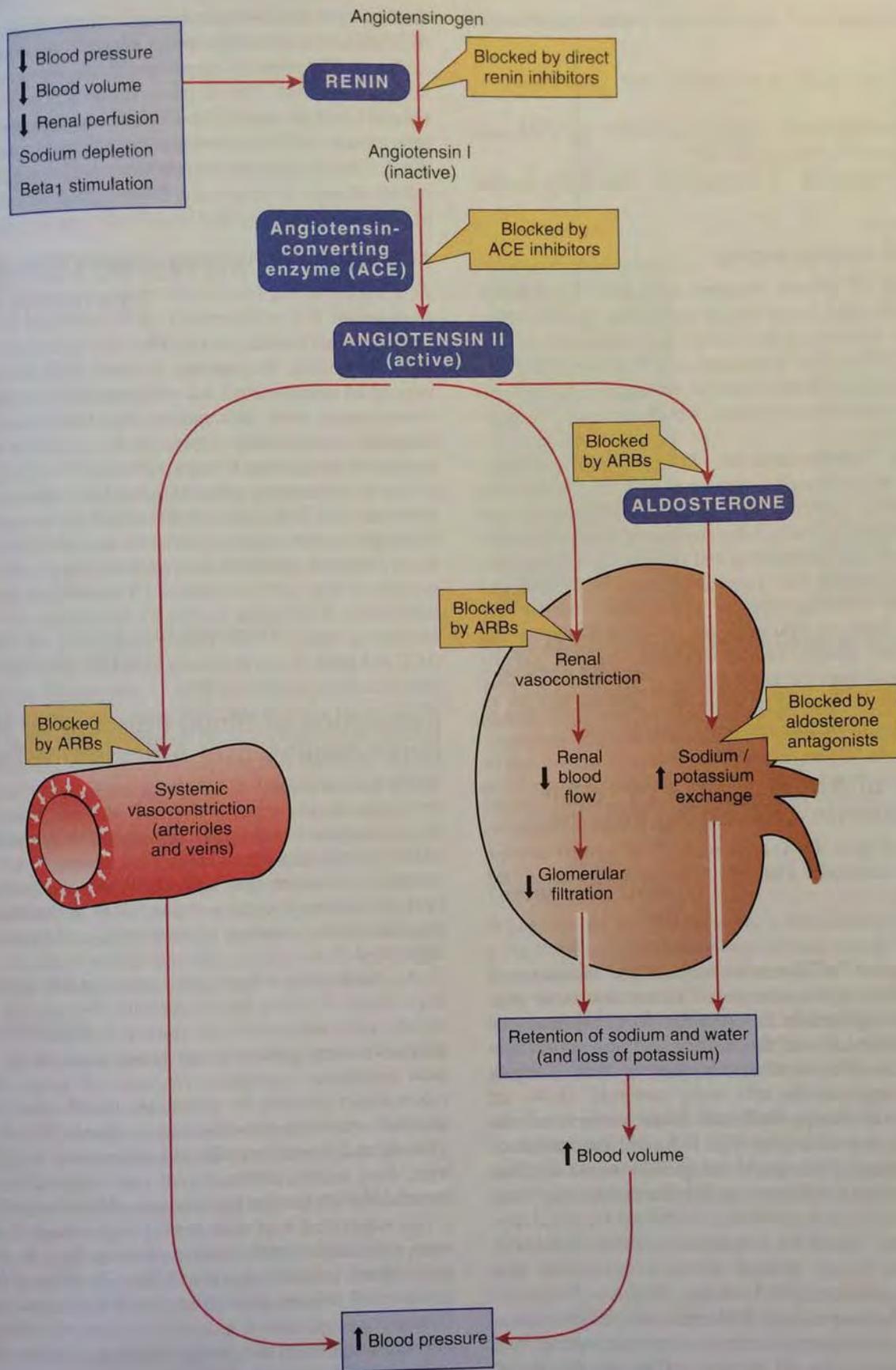


Figure 44-1 • Regulation of blood pressure by the renin-angiotensin-aldosterone system. In addition to the mechanisms depicted, angiotensin II can raise blood pressure by (1) acting on the distal nephron to promote reabsorption of sodium and (2) increasing vasoconstriction by three mechanisms: promoting release of norepinephrine from sympathetic nerves; promoting release of epinephrine from the adrenal medulla; and acting in the central nervous system to increase sympathetic outflow to blood vessels. (ARBs = angiotensin receptor blockers.)

angiotensin II that could underlie these pathologic changes include

- Increased migration, proliferation, and hypertrophy of VSM cells
- Increased production of extracellular matrix by VSM cells
- Hypertrophy of cardiac myocytes
- Increased production of extracellular matrix by cardiac fibroblasts

Actions of Aldosterone

Regulation of Blood Volume and Blood Pressure. After being released from the adrenal cortex, aldosterone acts on distal tubules of the kidney to cause retention of sodium and excretion of potassium and hydrogen. Because retention of sodium causes water to be retained as well, aldosterone increases blood volume, which causes blood pressure to rise.

Pathologic Cardiovascular Effects. Until recently, knowledge of aldosterone's actions was limited to effects on the kidney. Now, however, we know that aldosterone can cause more harmful effects. Like angiotensin II, aldosterone can promote cardiac remodeling and fibrosis. In addition, aldosterone can activate the sympathetic nervous system and suppress uptake of norepinephrine in the heart, thereby predisposing the heart to dysrhythmias. Also, aldosterone can promote vascular fibrosis (which decreases arterial compliance) and it can disrupt the baroreceptor reflex. These adverse effects appear to be limited to states such as heart failure, in which levels of aldosterone can be extremely high.

Formation of Angiotensin II by Renin and Angiotensin-Converting Enzyme

As indicated in Figure 44-1, angiotensin II is formed through two sequential reactions. The first is catalyzed by renin, the second by ACE.

Renin

Renin (pronounced "REE-nin") catalyzes the formation of *angiotensin I* from *angiotensinogen*. This reaction is the rate-limiting step in angiotensin II formation. Renin is produced by juxtaglomerular cells of the kidney and undergoes controlled release into the bloodstream, where it cleaves angiotensinogen into angiotensin I.

Regulation of Renin Release. Since renin catalyzes the rate-limiting step in angiotensin II formation, and since renin must be released into the blood in order to act, the factors that regulate renin release regulate the rate of angiotensin II formation.

As indicated in Figure 44-1, release of renin can be triggered by multiple factors. Release *increases* in response to a *decline* in blood pressure, blood volume, plasma sodium content, or renal perfusion pressure. Reduced renal perfusion pressure is an especially important stimulus for renin release, and can occur in response to (1) stenosis of the renal arteries, (2) reduced systemic blood pressure, and (3) reduced plasma volume (brought on by dehydration, hemorrhage, or chronic sodium depletion). For the most part, these factors increase renin release through effects exerted locally in the kidney. However, some of these factors may also promote renin release through activation of the sympathetic nervous system. (Sympa-

thetic nerves increase secretion of renin by causing stimulation of beta₁-adrenergic receptors on juxtaglomerular cells.)

Release of renin is *suppressed* by factors opposite to those that cause release. That is, renin secretion is inhibited by elevation of blood pressure, blood volume, and plasma sodium content. Hence, as blood pressure, blood volume, and plasma sodium content increase in response to renin release, further release of renin is suppressed. In this regard, we can view release of renin as being regulated by a classic negative feedback loop.

Angiotensin-Converting Enzyme (Kinase II)

ACE catalyzes the conversion of angiotensin I (inactive) into angiotensin II (highly active). ACE is located on the luminal surface of all blood vessels. The vasculature of the lungs is especially rich in the enzyme. Because ACE is abundant, conversion of angiotensin I into angiotensin II occurs almost instantaneously after angiotensin I has been formed. ACE is a relatively nonspecific enzyme that can act on a variety of substrates in addition to angiotensin I.

Nomenclature regarding ACE can be confusing and requires comment. As just noted, ACE can act on several substrates. When the substrate is angiotensin I, we refer to the enzyme as ACE. However, when the enzyme is acting on other substrates, we refer to it by different names. Of importance to us, when the substrate is a hormone known as *bradykinin*, we refer to the enzyme as *kinase II*. So, please remember, whether we call it ACE or kinase II, we're talking about the same enzyme.

Regulation of Blood Pressure by the Renin-Angiotensin-Aldosterone System

The RAAS is poised to help regulate blood pressure. Factors that lower blood pressure turn the RAAS on; factors that raise blood pressure turn it off. However, although the RAAS does indeed contribute to blood pressure control, its role in *normovolemic, sodium-replete* individuals is only modest. In contrast, the system can be a major factor in maintaining blood pressure in the presence of *hemorrhage, dehydration, or sodium depletion*.

As depicted in Figure 44-1, the RAAS, acting through angiotensin II, raises blood pressure through two basic processes: vasoconstriction and renal retention of water and sodium. Vasoconstriction raises blood pressure by increasing total peripheral resistance; retention of water and sodium raises blood pressure by increasing blood volume. Vasoconstriction occurs within minutes to hours of activating the system, and hence can raise blood pressure quickly. In contrast, days, weeks, or even months are required for the kidney to raise blood pressure by increasing blood volume.

As suggested by Figure 44-1, angiotensin II acts in two ways to promote renal retention of water. First, by constricting renal blood vessels, angiotensin II reduces renal blood flow, and thereby reduces glomerular filtration. Second, angiotensin II stimulates release of aldosterone from the adrenal cortex. Aldosterone then acts on renal tubules to promote retention of sodium and water and excretion of potassium.

Tissue (Local) Angiotensin II Production

In addition to the traditional RAAS that we've been discussing, in which angiotensin II is produced in the blood and then carried to target tissues, angiotensin II is produced in indi-

vidual tissues. This permits discrete, local effects of angiotensin II independent of the main system. Interference with local production of angiotensin II may underlie some effects of the ACE inhibitors.

It is important to note that some angiotensin II is produced by pathways that *do not involve* ACE. As a result, drugs that inhibit ACE cannot completely block angiotensin II production.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The ACE inhibitors are important drugs for *treating* hypertension, heart failure, diabetic nephropathy, and myocardial infarction (MI). In addition, they are used to *prevent* adverse cardiovascular events in patients at risk. Their most prominent adverse effects are cough, angioedema, first-dose hypotension, and hyperkalemia. For all of these agents, beneficial effects result largely from suppressing formation of angiotensin II. Because the similarities among ACE inhibitors are much more striking than their differences, we will discuss these drugs as a group, rather than selecting a prototype to represent them.

Mechanism of Action and Overview of Pharmacologic Effects

As indicated in Figure 44–2, ACE inhibitors produce their beneficial effects and adverse effects by (1) reducing levels of angiotensin II (through inhibition of ACE) and (2) increasing levels of bradykinin (through inhibition of kinase II). By reducing levels of angiotensin II, ACE inhibitors can dilate blood vessels (primarily arterioles and to a lesser extent veins), reduce blood volume (through effects on the kidney), and, importantly, prevent or reverse pathologic changes in the heart and blood vessels mediated by angiotensin II and aldosterone. Inhibition of ACE can also cause hyperkalemia and fetal injury. Elevation of bradykinin causes vasodilation (secondary to increased production of prostaglandins and nitric oxide), and can also promote cough and angioedema.

Pharmacokinetics

Regarding pharmacokinetics, the following generalizations apply:

- Nearly all ACE inhibitors are administered *orally*. The only exception is enalaprilat (the active form of enalapril), which is given IV.
- Except for captopril and moexipril, all oral ACE inhibitors can be administered with food.
- With the exception of captopril, all ACE inhibitors have prolonged half-lives, and hence can be administered just once or twice a day. Captopril is administered 2 or 3 times a day.
- With the exception of lisinopril, all ACE inhibitors are *prodrugs* that must undergo conversion to their active form in the small intestine and liver. Lisinopril is active as given.
- All ACE inhibitors are *excreted by the kidneys*. As a result, nearly all can accumulate to dangerous levels in patients with kidney disease, and hence *dosages must be reduced in these patients*. Only one agent—fosinopril—does not require a dosage reduction.

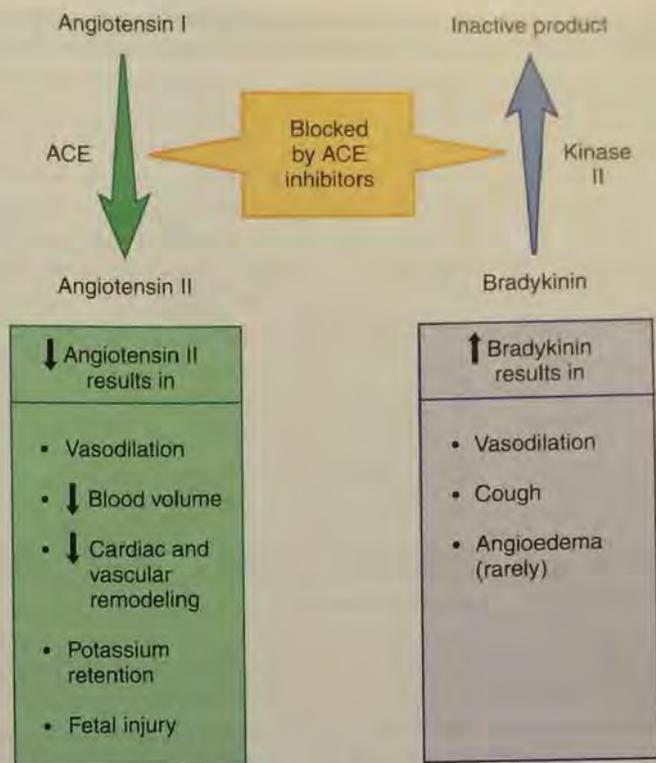


Figure 44–2 • Overview of ACE inhibitor actions and pharmacologic effects.

Angiotensin-converting enzyme (ACE) and *kinase II* are two names for the same enzyme. When angiotensin II is the substrate, we call the enzyme ACE; when bradykinin is the substrate, we call it kinase II. Inhibition of this enzyme decreases production of angiotensin II (thereby *reducing* angiotensin II levels), and decreases breakdown of bradykinin (thereby *increasing* bradykinin levels).

Therapeutic Uses

When the ACE inhibitors were introduced (over 30 years ago), their only indication was hypertension. Today, they are also used for heart failure, acute MI, left ventricular dysfunction, and diabetic and nondiabetic nephropathy. In addition, they can help prevent MI, stroke, and death in patients at high risk for cardiovascular events. It should be noted that no single ACE inhibitor is approved for all of these conditions (Table 44–1). However, given that all ACE inhibitors are very similar, it seems likely that all may produce similar benefits.

Hypertension. All ACE inhibitors are approved for hypertension. These drugs are especially effective against malignant hypertension and hypertension secondary to renal arterial stenosis. They are also useful against essential hypertension of mild to moderate intensity—although maximal benefits may take several weeks to develop.

In patients with essential hypertension, the mechanism underlying blood pressure reduction is not fully understood. Initial responses are proportional to circulating angiotensin II levels and are clearly related to reduced formation of that compound. (By lowering angiotensin II levels, ACE inhibitors dilate blood vessels and reduce blood volume; both actions help lower blood pressure.) However, with *prolonged* therapy, blood pressure often undergoes additional decline. During this phase, there is no correspondence between reductions in blood pressure and reductions in *circulating* angiotensin II. It

TABLE 44-1 ■ ACE Inhibitors: Approved Indications and Adult Dosages

Generic Name	Trade Name	Approved Indications*	Starting Dosage†	Usual Maintenance Dosage‡
Benazepril	Lotensin	Hypertension	10 mg once/day	20–40 mg/day in 1 or 2 doses
Captopril	Capoten	Hypertension	25 mg 2 or 3 times/day	25–50 mg 2 or 3 times/day
		Heart failure	6.25 mg 3 times/day	50–100 mg 3 times/day
		LVD after MI	12.5 mg 3 times/day	50 mg 3 times/day
		Diabetic nephropathy	25 mg 3 times/day	25 mg 3 times/day
Enalapril	Vasotec	Hypertension	5 mg once/day	10–40 mg/day in 1 or 2 doses
		Heart failure	2.5 mg twice/day	10–20 mg twice/day
		Asymptomatic LVD	2.5 mg twice/day	10 mg twice/day
Enalaprilat	Vasotec	Hypertension	1.25 mg every 6 hr	Not used for maintenance
Fosinopril	Monopril	Hypertension	10 mg once/day	20–40 mg/day in 1 or 2 doses
		Heart failure	5–10 mg once/day	20–40 mg once/day
Lisinopril	Prinivil, Zestril	Hypertension	10 mg once/day	20–40 mg once/day
		Heart failure	2.5–5 mg once/day	20–40 mg once/day
		Acute MI	5 mg once/day	10 mg once/day
Moexipril	Univasc	Hypertension	7.5 mg once/day	7.5–30 mg/day in 1 or 2 doses
Perindopril	Aceon, Coversyl*	Hypertension	4 mg once/day	4–8 mg/day in 1 or 2 doses
		Stable CAD	4 mg once/day	8 mg once/day
Quinapril	Accupril	Hypertension	10–20 mg/day	20–80 mg/day in 1 or 2 doses
		Heart failure	5 mg twice/day	20–40 mg twice/day
Ramipril	Altace	Hypertension	2.5 mg once/day	2.5–20 mg/day in 1 or 2 doses
		Heart failure after MI	1.25–2.5 mg twice/day	5 mg twice/day
		Prevention of MI, stroke, and death in people at high risk for CVD	2.5 mg/day for 1 wk	5 mg once/day for 3 wk
Trandolapril	Mavik	Hypertension	1 mg once/day	2–4 mg once/day
		Heart failure after MI	1 mg once/day	4 mg once/day
		LVD after MI	1 mg once/day	4 mg once/day

*CAD = coronary artery disease, CVD = cardiovascular disease, LVD = left ventricular dysfunction, MI = myocardial infarction.

†For all ACE inhibitors except fosinopril, dosage must be reduced in patients with significant renal impairment.

may be that the delayed response is due to reductions in *local* angiotensin II levels—reductions that would not be revealed by measuring angiotensin II in the blood.

ACE inhibitors offer several advantages over most other antihypertensive drugs. In contrast to the sympatholytic agents, ACE inhibitors do not interfere with cardiovascular reflexes. Hence, exercise capacity is not impaired and orthostatic hypotension is minimal. In addition, these drugs can be used safely in patients with bronchial asthma, a condition that precludes the use of beta₂-adrenergic antagonists. ACE inhibitors do not promote hypokalemia, hyperuricemia, or hyperglycemia—side effects seen with thiazide diuretics. Furthermore, they do not induce lethargy, weakness, or sexual dysfunction—responses that are common with other antihypertensive agents. Most importantly, *ACE inhibitors reduce the risk of cardiovascular mortality caused by hypertension*. The only other drugs proved to reduce hypertension-associated mortality are beta blockers and diuretics (see Chapter 47).

Heart Failure. ACE inhibitors produce multiple benefits in heart failure. By lowering arteriolar tone, these drugs improve regional blood flow, and, by reducing cardiac afterload, they increase cardiac output. By causing venous dilation, they reduce pulmonary congestion and peripheral edema. By dilating blood vessels in the kidney, they increase renal blood flow, and thereby promote excretion of sodium and water. This loss of fluid has two beneficial effects: (1) it helps reduce edema and (2) by lowering blood volume, it decreases venous return

to the heart, and thereby reduces right-heart size. Lastly, by suppressing aldosterone and reducing local production of angiotensin II in the heart, ACE inhibitors may prevent or reverse pathologic changes in cardiac structure. Although only seven ACE inhibitors are approved for heart failure (see Table 44-1), both the American Heart Association and the American College of Cardiology have concluded that the ability to improve symptoms and prolong survival is a class effect. The use of ACE inhibitors in heart failure is discussed further in Chapter 48.

Myocardial Infarction. ACE inhibitors can reduce mortality following acute MI (heart attack). In addition, they decrease the chance of developing overt heart failure. Treatment should begin as soon as possible after infarction and should continue for at least 6 weeks. In patients who develop overt heart failure, treatment should continue long term. As for patients who do not develop heart failure, there are no data to indicate whether continued treatment would be beneficial or not. At this time, only three ACE inhibitors—captopril, lisinopril, and trandolapril—are approved for patients with MI.

Diabetic and Nondiabetic Nephropathy. ACE inhibitors can benefit patients with diabetic nephropathy, the leading cause of end-stage renal disease in the United States. In patients with overt nephropathy, as indicated by proteinuria of more than 500 mg/day, ACE inhibitors can slow progression of renal disease. In patients with less advanced nephropathy (30 to 300 mg proteinuria/day), ACE inhibitors can delay onset of overt

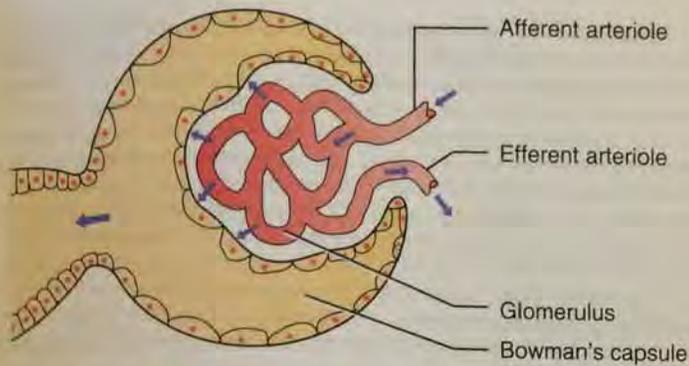


Figure 44-3 = Elevation of glomerular filtration pressure by angiotensin II.

Angiotensin II increases filtration pressure by (1) increasing pressure in the afferent arteriole (secondary to increasing systemic arterial pressure), and by (2) constricting the efferent arteriole, thereby generating back-pressure in the glomerulus.

nephropathy. These benefits were first demonstrated in patients with type 1 diabetes (insulin-dependent diabetes mellitus) and were later demonstrated in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus). More recently, ACE inhibitors have been shown to provide similar benefits in patients with nephropathy unrelated to diabetes.

The principal protective mechanism appears to be reduction of glomerular filtration pressure. ACE inhibitors lower filtration pressure by reducing levels of angiotensin II, a compound that can raise filtration pressure by two mechanisms. First, angiotensin II raises systemic blood pressure, which raises pressure in the afferent arteriole of the glomerulus (Fig. 44-3). Second, it constricts the efferent arteriole, thereby generating back-pressure in the glomerulus. The resultant increase in filtration pressure promotes injury. By reducing levels of angiotensin II, ACE inhibitors lower glomerular filtration pressure, and thereby slow development of renal injury.

At this time, the only ACE inhibitor approved for nephropathy is captopril. However, the American Diabetes Association considers benefits in diabetic nephropathy to be a class effect, and hence recommends choosing an ACE inhibitor based on its cost and likelihood of patient adherence.

Can ACE inhibitors be used for *primary prevention* of diabetic nephropathy? No. This conclusion is based on the *Renin-Angiotensin System Study* (RASS), which evaluated the effects of an ACE inhibitor—*enalapril* [Vasotec]—and an ARB—*losartan* [Cozaar]—in patients with type 1 diabetes who did not have hypertension or any signs of early kidney disease. The result? Both drugs failed to protect the kidney: Compared with patients receiving placebo, those receiving enalapril or losartan developed the same degree of microalbuminuria (an early sign of kidney damage), the same decline in kidney function, and the same changes in glomerular structure (as shown by microscopic analysis of kidney biopsy samples). Hence, although ACE inhibitors may slow progression of established nephropathy, they do not protect against early kidney damage.

Prevention of MI, Stroke, and Death in Patients at High Cardiovascular Risk. One ACE inhibitor—*ramipril* [Altace]—is approved for reducing the risk of MI, stroke, and death (from cardiovascular causes) in patients at *high risk* for a major cardiovascular event—high risk being defined by

(1) a history of stroke, coronary artery disease, peripheral vascular disease, or diabetes, combined with (2) at least one other risk factor, such as hypertension, high LDL cholesterol, low HDL cholesterol, or cigarette smoking. Ramipril was approved for this use based on results of the *Heart Outcomes Prevention Evaluation* (HOPE) trial, a large study in which patients at high cardiovascular risk took either ramipril (10 mg/day) or placebo. Follow-up time was 5 years. The result? The combined endpoint of MI, stroke, or death from cardiovascular causes was significantly lower in the ramipril group (14% vs. 18%)—a 22% reduction in risk. Possible mechanisms underlying benefits include reduced vascular resistance and protection of the heart, blood vessels, and kidneys from the damage that angiotensin II and aldosterone can cause over time.

Like ramipril, *perindopril* [Aceon, Coversyl*] can reduce morbidity and mortality in patients at risk for major cardiovascular events. However, the drug is not yet approved for this use. Benefits were demonstrated in the *EUROPEAN trial On reduction of cardiac events with Perindopril in stable coronary Artery disease* (EUROPA). Patients in EUROPA were at lower risk than those in HOPE.

Can ACE inhibitors other than ramipril and perindopril also reduce cardiovascular risk? Possibly. However, at this time there is insufficient evidence to say for sure.

Diabetic Retinopathy. The RASS trial showed that at least one ACE inhibitor—*enalapril*—can reduce the risk of diabetic retinopathy in *some* patients. Specifically, in patients with *type 1 diabetes*, who do not have hypertension, nephropathy, or established retinopathy, enalapril prevented or slowed development of retinal change. However, in patients with *type 1 diabetes* and *established* retinopathy, enalapril had no benefit. In patients with *type 2 diabetes*, enalapril had no benefit, regardless of retinopathy status.

Adverse Effects

ACE inhibitors are generally well tolerated. Some adverse effects (eg, first-dose hypotension, hyperkalemia) are due to a reduction in angiotensin II, whereas others (cough, angioedema) are due to elevation of bradykinin.

First-Dose Hypotension. A precipitous drop in blood pressure may occur following the first dose of an ACE inhibitor. This reaction is caused by widespread vasodilation secondary to abrupt lowering of angiotensin II levels. First-dose hypotension is most likely in patients with severe hypertension, in patients taking diuretics, and in patients who are sodium depleted or volume depleted. To minimize the first-dose effect, initial doses should be low. Also, diuretics should be temporarily discontinued, starting 2 to 3 days before starting an ACE inhibitor. Blood pressure should be monitored for several hours following the first dose of an ACE inhibitor. If hypotension develops, the patient should assume a supine position. If necessary, blood pressure can be raised with an infusion of normal saline.

Cough. All ACE inhibitors can cause persistent, dry, irritating, nonproductive cough. Severity can range from a scratchy throat to severe hacking cough. The underlying cause is accumulation of bradykinin secondary to inhibition of kinase II (another name for ACE). Cough occurs in about 10% of patients and is the most common reason for discontinuing therapy. Factors that increase the risk of cough include advanced age, female sex, and Asian ancestry. Cough begins to

subside 3 days after discontinuing an ACE inhibitor and is gone within 10 days.

Hyperkalemia. Inhibition of aldosterone release (secondary to inhibition of angiotensin II production) can cause potassium retention by the kidney. As a rule, significant potassium accumulation is limited to patients taking potassium supplements, salt substitutes (which contain potassium), or a potassium-sparing diuretic. For most other patients, hyperkalemia is rare. Patients should be instructed to avoid potassium supplements and potassium-containing salt substitutes unless they are prescribed.

Renal Failure. ACE inhibitors can cause severe renal insufficiency in patients with *bilateral renal artery stenosis or stenosis in the artery to a single remaining kidney*. In patients with renal artery stenosis, the kidneys release large amounts of renin. The resulting high levels of angiotensin II serve to maintain glomerular filtration by two mechanisms: elevation of blood pressure and constriction of efferent glomerular arterioles (see Fig. 44-3). When ACE is inhibited, causing angiotensin II levels to fall, the mechanisms that had been supporting glomerular filtration fail, causing urine production to drop precipitously. Not surprisingly, *ACE inhibitors are contraindicated for patients with bilateral renal artery stenosis (or stenosis in the artery to a single remaining kidney)*.

Fetal Injury. For a long time, we have known that use of ACE inhibitors during the *second and third trimesters* of pregnancy can injure the developing fetus. Specific effects include hypotension, hyperkalemia, skull hypoplasia, pulmonary hypoplasia, anuria, renal failure (reversible and irreversible), and death. Women who become pregnant while using ACE inhibitors should discontinue treatment as soon as possible. Infants who have been exposed to ACE inhibitors during the second or third trimester should be closely monitored for hypotension, oliguria, and hyperkalemia.

Are ACE inhibitors safe *early* in pregnancy? Maybe. Maybe not. Until recently, there were no data indicating risk, and hence first-trimester exposure was considered safe. However, in 2006, an article in the *New England Journal of Medicine* reported that, among 209 children exposed to ACE inhibitors during the first trimester, 18 (8.7%) had major congenital malformations, compared with 3.2% of controls. These data contrast with animal studies, which suggest that such malformations are not likely. Furthermore, no mechanism by which ACE inhibitors might disrupt early embryogenesis is known. Nonetheless, given the new human data, it would seem that early exposure to ACE inhibitors can no longer be considered safe, and hence should be avoided.

Angioedema. Angioedema is a potentially fatal reaction that develops in up to 1% of patients. Symptoms, which result from increased capillary permeability, include giant wheals and edema of the tongue, glottis, and pharynx. Severe reactions should be treated with subcutaneous epinephrine. If angioedema develops, ACE inhibitors should be discontinued and never used again. Angioedema is caused by accumulation of bradykinin secondary to inhibition of kinase II.

Dysgeusia and Rash. Dysgeusia (impaired or distorted sense of taste) and rash are relatively common with captopril, but can occur with other ACE inhibitors as well. For some patients, dysgeusia may result in anorexia and weight loss. If these complications arise, the ACE inhibitor should be withdrawn. Both reactions resolve following cessation of treatment. At one time, researchers believed rash and dysgeusia were related to the sulfhydryl group found in the structure of captopril and some other ACE inhibitors. However, this appears to be untrue. Why? Because ACE inhibitors that lack a sulfhydryl group also cause these reactions.

Neutropenia. Neutropenia, with its associated risk of infection, is a rare but serious complication. Neutropenia is most likely in patients with renal impairment and in those with collagen vascular diseases (eg, systemic lupus erythematosus, scleroderma). These patients should be followed closely. Fortunately, neutropenia is reversible when detected early. To promote early detection, a white blood cell count with differential should be obtained every 2 weeks during the first 3 months of therapy and periodically thereafter. If neutropenia develops, ACE inhibitors should be withdrawn immediately. Neutrophil counts should normalize in approximately 2 weeks. In the absence of early detection, neutropenia may progress to fatal agranulocytosis. Patients should be informed about early signs of infection (eg, fever, sore throat) and instructed to report them immediately. As with dysgeusia and rash, neutropenia is more common with captopril than with other ACE inhibitors.

Drug Interactions

Diuretics. Diuretics may intensify first-dose hypotension. To prevent this interaction, diuretics should be withdrawn 1 week prior to giving an ACE inhibitor. Diuretic therapy can be resumed later if needed.

Antihypertensive Agents. The hypotensive effects of ACE inhibitors are often additive with those of other antihypertensive drugs (eg, diuretics, sympatholytics, vasodilators, calcium channel blockers). When an ACE inhibitor is added to an antihypertensive regimen, dosages of other drugs may require reduction.

Drugs That Raise Potassium Levels. ACE inhibitors increase the risk of hyperkalemia caused by *potassium supplements and potassium-sparing diuretics*. The risk of hyperkalemia is increased because, by suppressing aldosterone secretion, ACE inhibitors can reduce excretion of potassium. To minimize the risk of hyperkalemia, potassium supplements and potassium-sparing diuretics should be employed only when clearly indicated.

Lithium. ACE inhibitors can make lithium accumulate to toxic levels. Lithium levels should be monitored frequently.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs). Aspirin, ibuprofen, and other NSAIDs may reduce the antihypertensive effects of ACE inhibitors.

Preparations, Dosage, and Administration

Except for enalaprilat, all ACE inhibitors are administered orally. Of the oral products, all are available in single-drug formulations, and most are also available in fixed-dose combinations with hydrochlorothiazide, a thiazide diuretic; one agent—benazepril—is available combined with amlodipine, a calcium channel blocker. Except for captopril and moexipril, all oral formulations may be administered without regard to meals; captopril and moexipril should be administered 1 hour before meals. Dosages for all ACE inhibitors (except fosinopril) should be reduced in patients with renal impairment. Dosages for specific indications are summarized in Table 44-1. Formulations are described below.

- Benazepril is available alone (5-, 10-, 20-, and 40-mg tablets) as *Lotensin*, combined with hydrochlorothiazide as *Lotensin HCT*, and combined with amlodipine as *Lotrel*.
- Captopril is available alone (12.5-, 25-, 50-, and 100-mg tablets) as *Capoten*, and combined with hydrochlorothiazide as *Capozide*.
- Enalapril is available alone (2.5-, 5-, 10-, and 20-mg tablets) as *Vasotec*, combined with hydrochlorothiazide as *Vasoretic* and combined with amlodipine as *Lexxel*.
- Enalaprilat [Vasotec], the active form of enalapril, is available in solution (1.25 mg/mL) for IV therapy of severe hypertension. Enalaprilat is the only ACE inhibitor that is not given PO.
- Fosinopril is available alone (10-, 20-, and 40-mg tablets) as *Monopril*.

- and combined with hydrochlorothiazide as *Monopril-HCT*.
- Lisinopril is available alone (2.5-, 5-, 10-, 20-, 30-, and 40-mg tablets) as *Prinivil* and *Zestril*, and combined with hydrochlorothiazide as *Prinzide*.
- Moexipril is available alone (7.5- and 15-mg tablets) as *Univasc*, and combined with hydrochlorothiazide as *Uniretic*.
- Perindopril is available in tablets (2, 4, and 8 mg) as *Aceon* and *Coversyl*♣. The drug is not available in combination with hydrochlorothiazide.
- Quinapril is available alone (5-, 10-, 20-, and 40-mg tablets) as *Accupril*, and combined with hydrochlorothiazide as *Accuretic*.
- Ramipril is available in capsules (1.25, 2.5, 5, and 10 mg) as *Altace*. The drug is not available in combination with hydrochlorothiazide.
- Trandolapril is available in tablets (1, 2, and 4 mg) as *Mavik*. The drug is not available in combination with hydrochlorothiazide.

ANGIOTENSIN II RECEPTOR BLOCKERS

The angiotensin II receptor blockers (ARBs) are relatively new, and their indications are evolving. Initially, ARBs were approved only for hypertension. Today, they also are approved for treating heart failure, diabetic nephropathy, and myocardial infarction (MI), and for prevention of MI, stroke, and death in people at high risk for cardiovascular events.

Like the ACE inhibitors, ARBs decrease the influence of angiotensin II. However, the mechanisms involved differ: Whereas ACE inhibitors block *production* of angiotensin II, ARBs block the *actions* of angiotensin II. Because both groups interfere with angiotensin II, they both have similar effects. They differ primarily in that ARBs do not cause cough or hyperkalemia, but may increase the risk of cancer.

Given that ACE inhibitors and ARBs have very similar effects, are these drugs clinically interchangeable? No. We have clear and extensive evidence that ACE inhibitors decrease cardiovascular morbidity and mortality. The evidence for ARBs is less convincing. Accordingly, until more is known, ACE inhibitors are preferred. For patients who cannot tolerate ACE inhibitors, ARBs are an appropriate second choice.

Eight ARBs are available. All eight are very similar, hence we will discuss them as a group, rather than choosing one as a prototype.

Mechanism of Action and Overview of Pharmacologic Effects

ARBs block access of angiotensin II to its receptors in blood vessels, the adrenals, and all other tissues. As a result, ARBs have effects much like those of the ACE inhibitors. By blocking angiotensin II receptors on blood vessels, ARBs cause dilation of arterioles and veins. By blocking angiotensin II receptors in the heart, ARBs can prevent angiotensin II from inducing pathologic changes in cardiac structure. By blocking angiotensin II receptors in the adrenals, ARBs decrease release of aldosterone, and can thereby increase renal excretion of sodium and water. Sodium and water excretion is further increased through dilation of renal blood vessels.

In contrast to the ACE inhibitors, ARBs do *not* inhibit kinase II, and hence do not increase levels of bradykinin in the lung. As a result, ARBs do not promote cough, the most common reason for stopping ACE inhibitors.

Therapeutic Uses

Hypertension. All ARBs are approved for hypertension. Reductions in blood pressure equal those seen with ACE inhibitors. Whether ARBs share the ability of ACE inhibitors to reduce mortality has not been established.

Heart Failure. Currently, only two ARBs—*valsartan* [Diovan] and *candesartan* [Atacand]—are approved for heart failure. In clinical trials, these drugs reduced symptoms, decreased hospitalizations, improved functional capacity, and increased left ventricular (LV) ejection fraction. More importantly, they prolonged survival. Because experience with these drugs is limited, they should be reserved for patients who cannot tolerate ACE inhibitors (because of cough). Although the other ARBs are not yet approved for heart failure, most authorities believe they are effective.

Diabetic Nephropathy. Two ARBs—*irbesartan* [Avapro] and *losartan* [Cozaar]—are approved for managing nephropathy in hypertensive patients with type 2 diabetes. In clinical trials, these drugs delayed development of overt nephropathy, and slowed progression of established nephropathy. Benefits are due in part to reductions in blood pressure, and in part to mechanisms that have not been determined. How do ARBs compare with ACE inhibitors? Although both groups of drugs can retard progression of nephropathy, only the ACE inhibitors have been shown to reduce mortality. As noted above, neither ARBs nor ACE inhibitors are effective for primary prevention of diabetic nephropathy.

Myocardial Infarction. One ARB—*valsartan* [Diovan]—is approved for reducing cardiovascular mortality in post-MI patients with heart failure or LV dysfunction. Approval was based on the results of a major trial—the *Valsartan in Acute Myocardial Infarction Trial* (VALIANT)—that showed that valsartan was as effective as captopril at reducing short-term and long-term mortality in these patients.

Stroke Prevention. One ARB—*losartan* [Cozaar]—is approved for reducing the risk of stroke in patients with hypertension and LV hypertrophy. In clinical studies, stroke prevention with losartan was better than with atenolol (a beta blocker), even though both drugs produced an equivalent decrease in blood pressure. This observation indicates that the benefits of losartan cannot be explained on the basis of reduced blood pressure alone.

Prevention of MI, Stroke, and Death in Patients at High Cardiovascular Risk. One ARB—*telmisartan* [Micardis]—is approved for reducing the risk of MI, stroke, and death from cardiovascular causes in patients age 55 and over, but only if they are intolerant of ACE inhibitors. (Recall that ramipril, an ACE inhibitor, is also approved for preventing MI, stroke, and death in high-risk patients.) Approval of telmisartan was based on the ONTARGET study, which showed that telmisartan was similar to ramipril with regard to reducing cardiovascular morbidity and mortality. Of note, combining telmisartan with ramipril was no more effective than either agent alone, but did increase the risk of adverse events. Can other ARBs reduce cardiovascular risk? Possibly. But proof is lacking.

Diabetic Retinopathy. In the RASS study mentioned above, benefits of the ARB *losartan* [Cozaar] were like those of enalapril: In patients with type 1 diabetes without established retinopathy, losartan slowed the development and progression of retinopathy—but had no benefit in patients with established retinopathy. In patients with type 2 diabetes, the drug offered no benefit at all, regardless of retinopathy status.

Migraine Headache. As discussed in Chapter 30, prophylactic therapy with *candesartan* [Atacand] can reduce the incidence and duration of migraine attacks.

TABLE 44-2 ■ Angiotensin II Receptor Blockers: Approved Indications and Adult Dosages

Generic Name	Trade Name	Approved Indications	Initial Dosage	Maintenance Dosage
Azilsartan	Edarbi	Hypertension	40 mg once/day	40–80 mg once/day
Candesartan	Atacand	Hypertension Heart failure	16 mg once/day 4 mg once/day	8–32 mg/day in 1 or 2 doses 32 mg once/day
Eprosartan	Teveten	Hypertension	600 mg once/day	400–800 mg/day in 1 or 2 doses
Irbesartan	Avapro	Hypertension Diabetic nephropathy*	150 mg once/day 300 mg once/day	150–300 mg once/day 300 mg once/day
Losartan	Cozaar	Hypertension Stroke prevention† Diabetic nephropathy*	25–50 mg once/day 50 mg once/day 50 mg once/day	25–100 mg/day in 1 or 2 doses 50–100 mg once/day 100 mg once/day
Olmесartan	Benicar, Olmetec‡	Hypertension	20 mg once/day	20–40 mg once/day
Telmisartan	Micardis	Hypertension Prevention of MI, stroke, and death in people at high risk for CVD but who can't take an ACE inhibitor	40 mg once/day 80 mg once/day	20–80 mg once/day 80 mg once/day
Valsartan	Diovan	Hypertension Heart failure Myocardial infarction	80–160 mg once/day 40 mg twice/day 20 mg twice/day	80–320 mg once/day 40–160 mg twice/day 20–160 mg twice/day

ACE = angiotensin-converting enzyme, CVD = cardiovascular disease, MI = myocardial infarction.

*In patients with type 2 diabetes.

†In patients with hypertension and left ventricular hypertrophy.

Adverse Effects

All of the ARBs are well tolerated. In contrast to ACE inhibitors, ARBs do not cause clinically significant hyperkalemia. Furthermore, because ARBs do not promote accumulation of bradykinin in the lung, they do not induce cough. However, there is concern that ARBs may promote cancer.

Angioedema. Like the ACE inhibitors, ARBs can cause angioedema, although the incidence may be lower with ARBs. If angioedema occurs, ARBs should be withdrawn immediately and never used again. Severe reactions are treated with subcutaneous epinephrine.

How do ARBs cause angioedema? Possibly by increasing bradykinin availability. Unlike ACE inhibitors, ARBs do not inhibit bradykinin breakdown. However, through an indirect mechanism, ARBs may be able to increase local bradykinin synthesis.

Is it reasonable to give an ARB to a patient who developed angioedema with an ACE inhibitor? Sometimes. About 8% of patients who experience angioedema with an ACE inhibitor will also develop angioedema if given an ARB. Nonetheless, switching to an ARB may be worth the risk for specific patients, namely, those with a disorder for which ARBs are known to improve outcomes (ie, heart failure, diabetes, and myocardial infarction).

Fetal Harm. Like the ACE inhibitors, ARBs can injure the developing fetus if taken during the second or third trimester of pregnancy, and hence are contraindicated during this period. Also, there is concern that ARBs and ACE inhibitors may harm the fetus earlier in pregnancy, and hence should be discontinued as soon as pregnancy is discovered.

Renal Failure. Like the ACE inhibitors, ARBs can cause renal failure in patients with bilateral renal artery stenosis or stenosis in the artery to a single remaining kidney. Accordingly, ARBs are contraindicated for patients with these conditions.

Cancer. Do ARBs increase cancer risk? Probably not. Concern arose in 2010, when a meta-analysis of 5 randomized

trials revealed a small, but statistically significant increase in cancer cases among patients who used ARBs. In response, the FDA conducted a more extensive meta-analysis of its own. Specifically, the FDA analyzed data from 31 randomized trials involving 155,816 patients, 84,461 of whom received an ARB, and 71,355 of whom received a nonARB comparator treatment. The results, published in 2011, showed no association between ARBs and the overall incidence of cancer: For every 100 patient-years, there were 1.82 cases among the ARB recipients, and 1.84 cases among the nonARB recipients. Furthermore, there was no association between use of ARBs and three specific cancers: cancer of the breast, lung, and prostate. These results led the FDA to conclude that treatment with an ARB does not increase the risk of cancer. Three other studies, also published in 2011, reached the same conclusion. The bottom line? In all likelihood, ARBs do not increase cancer risk—and if they do increase risk, the increase is small.

Drug Interactions

The hypotensive effects of ARBs are additive with those of other antihypertensive drugs. When an ARB is added to an antihypertensive regimen, dosages of the other drugs may require reduction.

Preparations, Dosage, and Administration

All ARBs are administered PO, and all may be taken with or without food. All are available alone, and all but azilsartan are also available in fixed-dose combinations with hydrochlorothiazide, a thiazide diuretic. Dosages for specific indications are summarized in Table 44-2. Formulations are described below.

- Azilsartan is available in tablets (40 and 80 mg) as *Edarbi*. Unlike other ARBs, the drug is not available combined with hydrochlorothiazide.
- Candesartan is available alone (4-, 8-, 16-, and 32-mg tablets) as *Atacand* and combined with hydrochlorothiazide as *Atacand HCT*.

- Eprosartan is available alone (400- and 600-mg tablets) as *Teveten*, and combined with hydrochlorothiazide as *Teveten HCT*.
- Irbesartan is available alone (75-, 150-, and 300-mg tablets) as *Avapro*, and combined with hydrochlorothiazide as *Avalide*.
- Losartan is available alone (25-, 50-, and 100-mg tablets) as *Cozaar*, and combined with hydrochlorothiazide as *Hyzaar*.
- Olmesartan is available alone (5-, 20-, and 40-mg tablets) as *Benicar* and *Olmetec* ♣, combined with hydrochlorothiazide as *Benicar HCT* and *Olmetec Plus* ♣ combined with amlodipine as *Azor*, and combined with amlodipine plus hydrochlorothiazide as *Tribenzor*.
- Telmisartan is available alone (20-, 40-, and 80-mg tablets) as *Micardis*, combined with hydrochlorothiazide as *Micardis HCT*, and combined with amlodipine as *Twynsta*.
- Valsartan is available alone (40-, 80-, 160-, and 320-mg tablets) as *Diovan*, combined with hydrochlorothiazide as *Diovan HCT*, combined with amlodipine as *Exforge*, combined amlodipine plus hydrochlorothiazide as *Exforge HCT*, and combined with aliskiren as *Valturna*.

ALISKIREN, A DIRECT RENIN INHIBITOR

Direct renin inhibitors (DRIs) are drugs that act on renin to inhibit the conversion of angiotensinogen into angiotensin I. By decreasing production of angiotensin I, DRIs can suppress the entire RAAS. Currently, only one DRI is available.

Aliskiren [Tekturna, Rasilez ♣], approved for hypertension in 2007, was the first DRI on the market. Blood pressure reduction equals that seen with ACE inhibitors. Aliskiren causes less cough and angioedema than the ACE inhibitors, but poses similar risks to the developing fetus.

Mechanism of Action

Aliskiren binds tightly with renin, and thereby inhibits the cleavage of angiotensinogen into angiotensin I. Since this reaction is the first and rate-limiting step in the production of angiotensin II and aldosterone, aliskiren can reduce the influence of the entire RAAS. In clinical trials, the drug decreased plasma renin activity by 50% to 80%. Although aliskiren works at an earlier step than either the ACE inhibitors or ARBs, there is no proof that doing so results in superior clinical outcomes.

Therapeutic Use

Aliskiren is approved only for *hypertension*. It may be used alone or in combination with other antihypertensives. In clinical trials, aliskiren reduced blood pressure to the same extent as did ACE inhibitors, ARBs, or calcium channel blockers. Maximal effects developed within 2 weeks. Although aliskiren can reduce blood pressure in hypertensive patients, we don't know if the drug also reduces negative outcomes (ie, blindness, stroke, kidney disease, death). In contrast, the ability of ACE inhibitors and ARBs to improve outcomes is well established. Until the long-term benefits and safety of aliskiren are known, older antihypertensives should be considered first. In addition to its use in hypertension, aliskiren is under investigation for treating heart failure, and renal failure associated with diabetes.

Pharmacokinetics

Aliskiren is administered orally, and bioavailability is low (only 2.5%). Dosing with a *high-fat meal* makes availability much lower (about 0.8%). Aliskiren undergoes some metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450), but the extent of metabolism is not known. About 25% of the drug is eliminated unchanged in the urine. The half-life is about 24 hours.

Adverse Effects

Aliskiren is generally well tolerated. At usual doses, the risk of angioedema, cough, or hyperkalemia is low. At high therapeutic doses, some patients experience diarrhea. Like other drugs that affect the RAAS, aliskiren should be avoided during pregnancy.

Angioedema and Cough. With ACE inhibitors, angioedema and cough result from inhibition of kinase II. Since aliskiren does not inhibit kinase II, the risk of these effects is low. In clinical trials, the incidence of cough was 1.1% with aliskiren, versus about 10% with an ACE inhibitor. Similarly, the incidence of angioedema was 0.06% with aliskiren, versus 1% with an ACE inhibitor. If angioedema does occur, aliskiren should be discontinued immediately.

Gastrointestinal Effects. Aliskiren causes dose-dependent diarrhea, seen in 2.3% of patients taking 300 mg/day. Women and the elderly are most susceptible. Excessive doses (600 mg/day) are associated with abdominal pain and dyspepsia.

Hyperkalemia. Like the ACE inhibitors, aliskiren rarely causes hyperkalemia when used alone. However, hyperkalemia might be expected if aliskiren were combined with an ACE inhibitor, a potassium-sparing diuretic, or potassium supplements.

Fetal Injury and Death. Although aliskiren has not been studied in pregnant women, the drug is likely to pose a risk of major congenital malformations and fetal death. Why? Because the risk of these events is well established with other drugs that suppress the RAAS. Therefore, like the ACE inhibitors and ARBs, aliskiren is contraindicated during the second and third trimesters, and should be discontinued as soon as possible when pregnancy occurs.

Drug Interactions

Aliskiren undergoes some metabolism by CYP3A4, but it neither induces nor inhibits the P450 system. In clinical trials, aliskiren had no significant interactions with atenolol, digoxin, amlodipine, valsartan, ramipril, or hydrochlorothiazide. However, levels of aliskiren were significantly raised by atorvastatin and ketoconazole (a P450 inhibitor), and significantly lowered by irbesartan. Levels of furosemide were lowered by aliskiren.

Preparations, Dosage, and Administration

Aliskiren is available alone as *Tekturna* and *Rasilez* ♣, in combination with hydrochlorothiazide as *Tekturna HCT* and *Rasilez HCT* ♣ in combination with amlodipine as *Tekamlo* and in combination with valsartan as *Valturna*. All four formulations are indicated for hypertension.

Aliskiren alone [Tekturna, Rasilez ♣] is available in 150- and 300-mg tablets. The initial dosage is 150 mg once a day. If control of blood pressure is inadequate, dosage may be increased to 300 mg once a day. Daily doses above 300 mg will not increase benefits, but will increase the risk of diarrhea. Since high-fat meals decrease absorption substantially, each daily dose should be taken at the same time with respect to meals (eg, 1 hour before dinner), so as to achieve a consistent response.

Aliskiren/hydrochlorothiazide [Tekturna HCT, Rasilez HCT ♣] tablets are available in four strengths—150 mg/12.5 mg, 150 mg/25 mg, 300 mg/12.5 mg, and 300 mg/25 mg—for once-daily dosing. As with Tekturna, each daily dose should be taken at the same time with respect to meals.

Aliskiren/amlodipine [Tekamlo] tablets are available in four strengths—150 mg/5 mg, 150 mg/10 mg, 300 mg/5 mg, and 300 mg/10 mg—for once-daily dosing. As with Tekturna and Tekturna HCT, each daily dose should be taken at the same time with respect to meals.

Aliskiren/valsartan [Valturna] tablets are available in two strengths—150 mg/320 mg and 300 mg/320 mg—for once-daily dosing. As with Tekturna, each daily dose should be taken at the same time with respect to meals.

ALDOSTERONE ANTAGONISTS

Aldosterone antagonists are drugs that block receptors for aldosterone. Two such agents are available: eplerenone and spironolactone. Both drugs have similar structures and ac-

tions, and both are used for the same disorders: hypertension and heart failure. They differ, however, in that spironolactone is less selective than eplerenone. As a result, spironolactone causes more side effects.

Eplerenone

Eplerenone [Inspra], approved in September 2002, is a first-in-class *selective aldosterone receptor blocker*. The drug is used for hypertension and heart failure, and has one significant side effect: hyperkalemia.

Mechanism of Action

Eplerenone produces selective blockade of aldosterone receptors, having little or no effect on receptors for other steroid hormones (eg, glucocorticoids, progesterone, androgens). In the kidney, activation of aldosterone receptors promotes excretion of potassium and retention of sodium and water. Receptor blockade has the opposite effect: retention of potassium and increased excretion of sodium and water. Loss of sodium and water reduces blood volume, and hence blood pressure. Blockade of aldosterone receptors at nonrenal sites may prevent or reverse pathologic effects of aldosterone on cardiovascular structure and function.

Therapeutic Use

Hypertension. For treatment of hypertension, eplerenone may be used alone or in combination with other antihypertensive agents. Maximal reductions in blood pressure take about 4 weeks to develop. In clinical trials, reductions in blood pressure were equivalent to those produced by spironolactone, and superior to those produced by losartan (an ARB). In patients already using an ACE inhibitor or an ARB, adding eplerenone produced a further reduction in blood pressure.

Although it is clear that eplerenone can lower blood pressure, we have no information on what really matters: the drug's ability to reduce morbidity and mortality. Until more is known, eplerenone should be reserved for patients who have not responded to traditional antihypertensive drugs.

Heart Failure. In patients with heart failure, eplerenone can improve symptoms, reduce hospitalizations, and prolong life. Benefits appear to derive from blocking the adverse effects of aldosterone on cardiovascular structure and function. Use of eplerenone in heart failure is discussed in Chapter 48.

Pharmacokinetics

Eplerenone is administered orally, and absorption is not affected by food. Plasma levels peak about 1.5 hours after dosing. Absolute bioavailability is unknown. Eplerenone undergoes metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450), followed by excretion in the urine (67%) and feces (32%). The elimination half-life is 4 to 6 hours.

Adverse Effects

Eplerenone is generally well tolerated. The incidence of adverse effects is nearly identical to that of placebo. A few adverse effects—diarrhea, abdominal pain, cough, fatigue, gy-

necomastia, flu-like syndrome—occur slightly (1% to 2%) more often with eplerenone than with placebo.

Hyperkalemia. The greatest concern is hyperkalemia, which can occur secondary to potassium retention. Because of this risk, combined use with potassium supplements, salt substitutes, or potassium-sparing diuretics (eg, spironolactone, triamterene) is contraindicated. Combined use with ACE inhibitors or ARBs is permissible, but should be done with caution. Eplerenone is contraindicated for patients with high serum potassium (above 5.5 mEq/L), and for patients with impaired renal function or type 2 diabetes with microalbuminuria, both of which can promote hyperkalemia. Monitoring potassium levels is recommended for patients at risk (eg, those taking ACE inhibitors or ARBs).

Drug Interactions

Inhibitors of CYP3A4 can increase levels of eplerenone, thereby posing a risk of toxicity. Weak inhibitors (eg, erythromycin, saquinavir, verapamil, fluconazole) can double eplerenone levels. Strong inhibitors (eg, ketoconazole, itraconazole) can increase levels fivefold. If eplerenone is combined with a weak inhibitor, eplerenone dosage should be reduced. Eplerenone should not be combined with a strong inhibitor.

Drugs that raise potassium levels can increase the risk of hyperkalemia. Eplerenone should not be combined with potassium supplements, salt substitutes, or potassium-sparing diuretics. Combining eplerenone with ACE inhibitors or ARBs should be done with caution.

Drugs similar to eplerenone (eg, ACE inhibitors and diuretics) are known to increase levels of *lithium*. Although the combination of eplerenone and lithium has not been studied, caution is nonetheless advised. Lithium levels should be measured frequently.

Preparations, Dosage, and Administration

Eplerenone [Inspra] is available in 25- and 50-mg tablets. The usual starting dosage is 50 mg once a day, taken with or without food. After 4 weeks, dosage can be increased to 50 mg twice daily (if the hypotensive response has been inadequate). Raising the dosage above 100 mg/day is not recommended. Why? Because doing so is unlikely to increase the therapeutic response, but *will* increase the risk of hyperkalemia. In patients taking weak inhibitors of CYP3A4, the initial dosage should be reduced by 50% (to 25 mg once a day).

Spironolactone

Spironolactone [Aldactone], a much older drug than eplerenone, blocks receptors for aldosterone, but also binds with receptors for other steroid hormones (eg, glucocorticoids, progesterone, androgens). Blockade of aldosterone receptors underlies beneficial effects in hypertension and heart failure, as well as the drug's major adverse effect: hyperkalemia. Binding with receptors for other steroid hormones underlies additional adverse effects: gynecomastia, menstrual irregularities, impotence, hirsutism, and deepening of the voice. The basic pharmacology of spironolactone and its use in heart failure are discussed in Chapters 41 and 48, respectively.

KEY POINTS

- The RAAS helps regulate blood pressure, blood volume, and fluid and electrolyte balance. The system can promote cardiovascular pathology.
- The RAAS acts through production of angiotensin II and aldosterone.
- Angiotensin II has much greater biologic activity than angiotensin I or angiotensin III.
- Angiotensin II is formed by the actions of two enzymes: renin and ACE.
- Angiotensin II causes vasoconstriction (primarily in arterioles) and release of aldosterone. In addition, angiotensin II can promote pathologic changes in the heart and blood vessels.
- Aldosterone acts on the kidneys to promote retention of sodium and water. In addition, aldosterone can also mediate pathologic changes in cardiovascular function.
- The RAAS raises blood pressure by causing vasoconstriction and by increasing blood volume (secondary to aldosterone-mediated retention of sodium and water).
- In addition to the traditional RAAS, in which angiotensin II is produced in the blood and then carried to target tissues, angiotensin II can be produced locally by individual tissues.
- Beneficial effects of ACE inhibitors result largely from inhibition of ACE and partly from inhibition of kinase II (the name for ACE when the substrate is bradykinin).
- By inhibiting ACE, ACE inhibitors decrease production of angiotensin II. The result is vasodilation, decreased blood volume, and prevention or reversal of pathologic changes in the heart and blood vessels mediated by angiotensin II and aldosterone.
- ACE inhibitors (and ARBs) are used to treat patients with hypertension, heart failure, myocardial infarction (MI), and established diabetic nephropathy. In addition, they are used to prevent MI, stroke, and death from cardiovascular causes in patients at high risk for a cardiovascular event. Of note, ACE inhibitors (and ARBs) are *not* effective for primary prevention of diabetic nephropathy.
- Preliminary data indicate that ACE inhibitors (and ARBs) can reduce the risk of developing diabetic retinopathy, although they can't slow the progression of established retinopathy.
- ACE inhibitors can produce significant first-dose hypotension by causing a sharp drop in circulating angiotensin II.
- Cough, secondary to accumulation of bradykinin, is the most common reason for discontinuing ACE inhibitors.
- By suppressing aldosterone release, ACE inhibitors can cause hyperkalemia. Exercise caution in patients taking potassium supplements, salt substitutes, or potassium-sparing diuretics.
- ACE inhibitors can cause major fetal malformations, and should be avoided during pregnancy. Until recently, we thought that risk was limited to exposure during the second and third trimesters. However, new data indicate that exposure during the first trimester may be dangerous as well.
- ACE inhibitors can cause a precipitous drop in blood pressure in patients with bilateral renal artery stenosis (or stenosis in the artery to a single remaining kidney).
- Angiotensin II receptor blockers (ARBs) block the actions of angiotensin II in blood vessels, the adrenals, and all other tissues.
- ARBs are similar to ACE inhibitors in that they cause vasodilation, suppress aldosterone release, promote excretion of sodium and water, reduce blood pressure, and cause birth defects and angioedema.
- ARBs differ from ACE inhibitors in that they do not cause hyperkalemia or cough.
- Aliskiren, a DRI, binds tightly with renin and thereby inhibits cleavage of angiotensinogen into angiotensin I. As a result, the drug suppresses the entire RAAS.
- Like the ACE inhibitors and ARBs, aliskiren causes vasodilation, suppresses aldosterone release, promotes excretion of sodium and water, reduces blood pressure, and causes birth defects and angioedema.
- Despite their similarities, aliskiren, ARBs, and ACE inhibitors are not clinically interchangeable.
- Aldosterone antagonists (spironolactone, eplerenone) block receptors for aldosterone.
- By blocking aldosterone receptors, aldosterone antagonists can (1) promote renal excretion of sodium and water (and can thereby reduce blood volume and blood pressure) and (2) prevent or reverse pathologic effects of aldosterone on cardiovascular structure and function.

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Summary of Major Nursing Implications*

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Benazepril
Captopril
Enalapril
Enalaprilat
Fosinopril
Lisinopril
Moexipril
Perindopril
Quinapril
Ramipril
Trandolapril

Unless indicated otherwise, the implications summarized below pertain to all of the ACE inhibitors.

Preadministration Assessment

Therapeutic Goal

ACE inhibitors are used to:

- Reduce blood pressure in patients with hypertension (*all ACE inhibitors*).
- Improve hemodynamics in patients with heart failure (*captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril*).
- Slow progression of established diabetic nephropathy (*captopril*).
- Reduce mortality following acute MI (*lisinopril*).
- Treat heart failure after MI (*ramipril, trandolapril*).
- Reduce risk of MI, stroke, or death from cardiovascular causes in patients at high risk (*ramipril*).
- Reduce cardiovascular mortality or nonfatal MI in patients with stable coronary artery disease (*perindopril*).

Baseline Data

Determine blood pressure and obtain a white blood cell count and differential.

Identifying High-Risk Patients

ACE inhibitors are *contraindicated* during the second and third trimesters of pregnancy and for patients with (1) bilateral renal artery stenosis (or stenosis in the artery to a single remaining kidney) or (2) a history of hypersensitivity reactions (especially angioedema) to ACE inhibitors.

Exercise *caution* in patients with salt or volume depletion, renal impairment, or collagen vascular disease, and in those taking potassium supplements, salt substitutes, potassium-sparing diuretics, ARBs, aliskiren, or lithium.

Implementation: Administration

Routes

Oral. All ACE inhibitors (except enalaprilat).
Intravenous. Enalaprilat.

Dosage and Administration

Dosage is low initially and then gradually increased.

Instruct patients to administer captopril and moexipril at least 1 hour before meals. All other oral ACE inhibitors can be administered with food.

Ongoing Evaluation and Interventions

Monitoring Summary

Monitor blood pressure closely for 2 hours after the first dose and periodically thereafter. Obtain a white blood cell count and differential every 2 weeks for the first 3 months of therapy and periodically thereafter.

Evaluating Therapeutic Effects

Hypertension. Monitor for reduced blood pressure. The usual target pressure is systolic/diastolic of 140/90 mm Hg.

Heart Failure. Monitor for lessening of signs and symptoms (eg, dyspnea, cyanosis, jugular vein distention, edema).

Diabetic Nephropathy. Monitor for proteinuria and altered glomerular filtration rate.

Minimizing Adverse Effects

First-Dose Hypotension. Severe hypotension can occur with the first dose. Minimize hypotension by (1) withdrawing diuretics 1 week before initiating ACE inhibitors and (2) using low initial doses. Monitor blood pressure for 2 hours following the first dose. **Instruct patients to lie down if hypotension develops.** If necessary, infuse normal saline to restore pressure.

Cough. Warn patients about the possibility of persistent, dry, irritating, nonproductive cough. **Instruct them to consult the prescriber if cough is bothersome.** Stopping the ACE inhibitor may be indicated.

Hyperkalemia. ACE inhibitors may increase potassium levels. **Instruct patients to avoid potassium supplements and potassium-containing salt substitutes unless they are prescribed by the provider.** Potassium-sparing diuretics must also be avoided.

Fetal Injury. Warn women of child-bearing age that taking ACE inhibitors during the second and third trimesters of pregnancy can cause major fetal injury (hypotension, hyperkalemia, skull hypoplasia, anuria, reversible and irreversible renal failure, death), and that taking these drugs earlier in pregnancy may pose a risk as well. If the patient becomes pregnant, withdraw ACE inhibitors as soon as possible. Closely monitor infants who have been exposed to ACE inhibitors during the second or third trimester for hypotension, oliguria, and hyperkalemia. **Reassure women who took ACE inhibitors during the first trimester that risk to the fetus is probably low.**

Angioedema. This rare and potentially fatal reaction is characterized by giant wheals and edema of the tongue, glottis, and pharynx. **Instruct patients to seek immediate medical attention if these symptoms develop.** If angioedema is diagnosed, ACE inhibitors should be discontinued and never used again. Treat severe reactions with subcutaneous epinephrine.

*Patient education information is highlighted as **blue text**.

Summary of Major Nursing Implications*—cont'd

Renal Failure. Renal failure is a risk for patients with bilateral renal artery stenosis or stenosis in the artery to a single remaining kidney. ACE inhibitors are contraindicated for these people.

Dysgeusia and Rash (Mainly with Captopril). Minimize these reactions by avoiding high doses. **Instruct patients to notify the prescriber if rash or dysgeusia persist.** If dysgeusia results in anorexia and weight loss, withdraw the drug. Rash and dysgeusia resolve with cessation of treatment.

Neutropenia (Mainly with Captopril). Neutropenia poses a high risk of infection. **Inform patients about early signs of infection (fever, sore throat, mouth sores) and instruct them to notify the prescriber if these occur.** Obtain white blood cell counts and differentials every 2 weeks during the first 3 months of therapy and periodically thereafter. If neutropenia develops, withdraw the drug immediately; neutrophil counts should normalize in approximately 2 weeks. Neutropenia is most likely in patients with renal impairment and collagen vascular diseases (eg, systemic lupus erythematosus, scleroderma); monitor these patients closely.

Minimizing Adverse Interactions

Diuretics. Diuretics may intensify first-dose hypotension. Withdraw diuretics 1 week prior to beginning an ACE inhibitor. Diuretics may be resumed later if needed.

Antihypertensive Agents. The antihypertensive effects of ACE inhibitors are additive with those of other antihypertensive drugs (eg, ARBs, diuretics, sympatholytics, vasodilators, calcium channel blockers). When an ACE inhibitor is added to an antihypertensive regimen, dosages of the other drugs may require reduction.

Drugs That Elevate Potassium Levels. ACE inhibitors increase the risk of hyperkalemia associated with *potassium supplements*, *potassium-sparing diuretics*, and possibly *aliskiren*. Risk can be minimized by avoiding potassium supplements and potassium-sparing diuretics except when they are clearly indicated.

Lithium. ACE inhibitors can increase serum levels of lithium, causing toxicity. Monitor lithium levels frequently.

Nonsteroidal Anti-inflammatory Drugs. NSAIDs (eg, aspirin, ibuprofen) can interfere with the antihypertensive effects of ACE inhibitors. **Advise patients to minimize NSAID use.**

ANGIOTENSIN II RECEPTOR BLOCKERS

Azilsartan
Candesartan
Eprosartan
Irbesartan
Losartan
Olmesartan
Telmisartan
Valsartan

Unless indicated otherwise, the implications summarized below pertain to all of the ARBs.

*Patient education information is highlighted as **blue text**.

Preadministration Assessment

Therapeutic Goal

ARBs are used to:

- Reduce blood pressure in patients with hypertension (*all ARBs*).
- Treat heart failure (*candesartan, valsartan*).
- Slow progression of established diabetic nephropathy (*irbesartan, losartan*).
- Prevent stroke in patients with hypertension and LV hypertrophy (*losartan*).
- Protect against MI, stroke, and death from cardiovascular causes in high-risk patients, but only if they can't tolerate ACE inhibitors (*telmisartan*).

Baseline Data

Determine blood pressure.

Identifying High-Risk Patients

ARBs are *contraindicated* during the second and third trimesters of pregnancy and for patients with either (1) bilateral renal artery stenosis (or stenosis in the artery to a single remaining kidney) or (2) a history of hypersensitivity reactions (especially angioedema) to ARBs.

Implementation: Administration

Route

Oral.

Dosage and Administration

Inform patients that ARBs may be taken with or without food.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Hypertension. Monitor for reduced blood pressure. The usual target pressure is systolic/diastolic of 140/90 mm Hg.

Heart Failure. Monitor for lessening of signs and symptoms (eg, dyspnea, cyanosis, jugular vein distention, edema).

Diabetic Nephropathy. Monitor for proteinuria and altered glomerular filtration rate.

Minimizing Adverse Effects

Angioedema. This rare and potentially fatal reaction is characterized by giant wheals and edema of the tongue, glottis, and pharynx. **Instruct patients to seek immediate medical attention if these symptoms develop.** If angioedema is diagnosed, ARBs should be discontinued and never used again. Treat severe reactions with subcutaneous epinephrine.

Fetal Injury. Warn women of child-bearing age that ARBs can cause fetal injury during the second and third trimesters of pregnancy, and may pose a risk earlier in pregnancy as well. If the patient becomes pregnant, withdraw ARBs as soon as possible. Closely monitor infants who have been exposed to ARBs during the second or third trimester for hypotension, oliguria, and hyperkalemia. **Reassure women who took ARBs during the first trimester that risk to the fetus is low.**

Summary of Major Nursing Implications*—cont'd

Renal Failure. Renal failure is a risk for patients with bilateral renal artery stenosis or stenosis in the artery to a single remaining kidney. ARB inhibitors are contraindicated for these people.

Cancer. ARBs may (or may not) pose a small risk of cancer. To reduce any risk that might exist, reserve ARBs for patients who cannot tolerate ACE inhibitors.

Minimizing Adverse Interactions

Antihypertensive Agents. The antihypertensive effects of ARBs are additive with those of other antihypertensive drugs (eg, diuretics, sympatholytics, vasodilators, calcium channel blockers). When an ARB is added to an antihypertensive regimen, dosages of the other drugs may require reduction.

ALISKIREN, A DIRECT RENIN INHIBITOR

Preadministration Assessment

Therapeutic Goal

Reduction of blood pressure in patients with hypertension.

Baseline Data

Determine blood pressure.

Identifying High-Risk Patients

Aliskiren is *contraindicated* during the second and third trimesters of pregnancy.

Exercise *caution* in patients taking potassium supplements, salt substitutes, potassium-sparing diuretics, or ACE inhibitors.

Implementation: Administration

Route

Oral.

Dosage and Administration

Advise patients to take each daily dose at the same time with respect to meals (eg, 1 hour before dinner). Dosage should be low (150 mg/day) initially, and increased to a maximum of 300 mg/day, if needed.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hyperkalemia. Aliskiren may increase potassium levels. **Instruct patients to avoid potassium supplements and potassium-containing salt substitutes unless they are prescribed by the provider.** Potassium-sparing diuretics must also be avoided. Exercise caution in patients taking an ACE inhibitor.

Fetal Injury. Warn women of child-bearing age that aliskiren taken during the second and third trimesters of pregnancy can cause fetal injury (hypotension, hyperkalemia, skull hypoplasia, anuria, reversible and irreversible renal failure, death). If the patient becomes pregnant, withdraw aliskiren as soon as possible. Closely monitor infants who have been exposed to aliskiren during the second or third trimester for hypotension, oliguria, and hyperkalemia. Reassure women who took aliskiren during the first trimester that this does not represent a risk to the fetus.

Angioedema. This rare and potentially fatal reaction is characterized by giant wheals and edema of the tongue, glottis, and pharynx. **Instruct patients to seek immediate medical attention if these symptoms develop.** If angioedema is diagnosed, aliskiren should be discontinued and never used again. Treat severe reactions with subcutaneous epinephrine.

Minimizing Adverse Interactions

Drugs That Elevate Potassium Levels. Aliskiren increases the risk of hyperkalemia associated with *ACE inhibitors, potassium supplements, and potassium-sparing diuretics.* Risk can be minimized by avoiding ACE inhibitors, potassium supplements, and potassium-sparing diuretics except when they are clearly indicated.

Antihypertensive Agents. The antihypertensive effects of aliskiren are additive with those of other antihypertensive drugs (eg, diuretics, sympatholytics, vasodilators, calcium channel blockers). When aliskiren is added to an antihypertensive regimen, dosages of the other drugs may require reduction.

*Patient education information is highlighted as blue text.

Calcium Channel Blockers

Calcium Channels: Physiologic Functions and Consequences of Blockade

Vascular Smooth Muscle

Heart

Calcium Channel Blockers: Classification and Sites of Action

Verapamil and Diltiazem: Agents That Act on Vascular Smooth Muscle and the Heart

Verapamil

Diltiazem

Dihydropyridines: Agents That Act Mainly on Vascular Smooth Muscle

Nifedipine

Other Dihydropyridines

Calcium channel blockers (CCBs) are drugs that prevent calcium ions from entering cells. These agents have their greatest effects on the heart and blood vessels. CCBs are used widely to treat hypertension, angina pectoris, and cardiac dysrhythmias. Since 1995, there has been controversy about the safety of CCBs, especially in patients with hypertension and diabetes. Alternative names for CCBs are *calcium antagonists* and *slow channel blockers*.

CALCIUM CHANNELS: PHYSIOLOGIC FUNCTIONS AND CONSEQUENCES OF BLOCKADE

Calcium channels are gated pores in the cytoplasmic membrane that regulate entry of calcium ions into cells. Calcium entry plays a critical role in the function of vascular smooth muscle (VSM) and the heart.

Vascular Smooth Muscle

In VSM, calcium channels regulate contraction. When an action potential travels down the surface of a smooth muscle cell, calcium channels open and calcium ions flow inward, thereby initiating the contractile process. If calcium channels are blocked, contraction will be prevented and vasodilation will result.

At therapeutic doses, CCBs act selectively on *peripheral arterioles and arteries and arterioles of the heart*. CCBs have no significant effect on veins.

Heart

In the heart, calcium channels help regulate the myocardium, the sinoatrial (SA) node, and the atrioventricular (AV) node. Calcium channels at all three sites are coupled to beta₁-adrenergic receptors.

Myocardium. In cardiac muscle, calcium entry has a positive inotropic effect. That is, calcium increases force of contraction. If calcium channels in atrial and ventricular muscle are blocked, contractile force will diminish.

SA Node. Pacemaker activity of the SA node is regulated by calcium influx. When calcium channels are open, spontaneous discharge of the SA node increases. Conversely, when calcium channels close, pacemaker activity declines. Hence, the effect of calcium channel blockade is to reduce heart rate.

AV Node. Impulses that originate in the SA node must pass through the AV node on their way to the ventricles. Because of this arrangement, regulation of AV conduction plays a critical role in coordinating contraction of the ventricles with contraction of the atria.

The excitability of AV nodal cells is regulated by calcium entry. When calcium channels are open, calcium entry increases, and cells of the AV node discharge more readily. Conversely, when calcium channels are closed, discharge of AV nodal cells is suppressed. Hence, the effect of calcium channel blockade is to decrease velocity of conduction through the AV node.

Coupling of Cardiac Calcium Channels to Beta₁-Adrenergic Receptors. In the heart, calcium channels are coupled to beta₁-adrenergic receptors (Fig. 45-1). As a result, when cardiac beta₁ receptors are activated, calcium influx is enhanced. Conversely, when beta₁ receptors are blocked, calcium influx is suppressed. Because of this relationship, CCBs and beta blockers have identical effects on the heart. That is, they both reduce force of contraction, slow heart rate, and suppress conduction through the AV node.

CALCIUM CHANNEL BLOCKERS: CLASSIFICATION AND SITES OF ACTION

Classification

The CCBs used in the United States belong to three chemical families (Table 45-1). The largest family is the *dihydropyridines*, for which *nifedipine* is the prototype. This family name is encountered frequently and hence the name is worth remembering. The other two families consist of orphans: *verapamil* is the only *phenylalkylamine*, and *diltiazem* is the only *benzothiazepine*. The drug names are important; the family names are not.

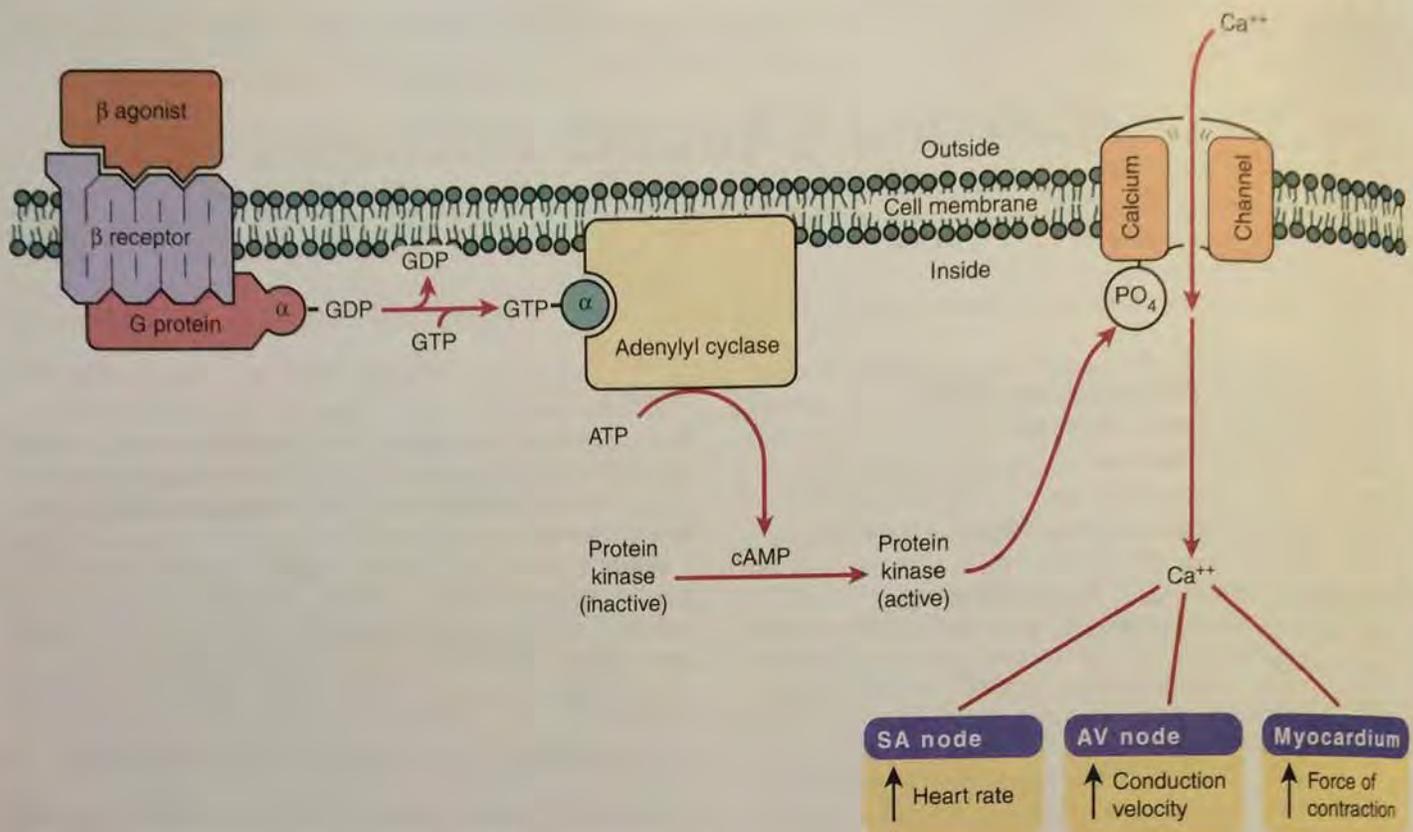


Figure 45-1 ■ Coupling of cardiac calcium channels with β_1 -adrenergic receptors.

In the heart, β_1 receptors are coupled to calcium channels. As a result, when cardiac β_1 receptors are activated, calcium influx is enhanced. The process works as follows. Binding of an agonist (eg, norepinephrine) causes a conformational change in the beta receptor, which in turn causes a change in G protein, converting it from an inactive state (in which GDP is bound to the alpha subunit) to an active state (in which GTP is bound to the alpha subunit). (G protein is so named because it binds guanine nucleotides: GDP and GTP.) Following activation, the alpha subunit dissociates from the rest of G protein and activates adenylyl cyclase, an enzyme that converts ATP to cyclic AMP (cAMP). cAMP then activates protein kinase, an enzyme that phosphorylates proteins—in this case, the calcium channel. Phosphorylation changes the channel such that calcium entry is enhanced when the channel opens. (Opening of the channel is triggered by a change in membrane voltage [ie, by passage of an action potential].)

The effect of calcium entry on cardiac function is determined by the type of cell involved. If the cell is in the SA node, heart rate increases; if the cell is in the AV node, impulse conduction through the node accelerates; and if the cell is part of the myocardium, force of contraction is increased.

Because binding of a single agonist molecule to a single beta receptor stimulates the synthesis of many cAMP molecules, with the subsequent activation of many protein kinase molecules, causing the phosphorylation of many calcium channels, this system can greatly amplify the signal initiated by the agonist.

Sites of Action

At therapeutic doses, the dihydropyridines act primarily on arterioles; in contrast, verapamil and diltiazem act on arterioles *and* the heart (see Table 45-1). However, although dihydropyridines don't affect the heart at *therapeutic* doses, *toxic* doses can produce dangerous cardiac suppression (just like verapamil and diltiazem can). The differences in selectivity among CCBs are based on structural differences among the drugs themselves and structural differences among calcium channels.

VERAPAMIL AND DILTIAZEM: AGENTS THAT ACT ON VASCULAR SMOOTH MUSCLE AND THE HEART

Verapamil

Verapamil [Calan, Covera-HS, Isoptin SR, Verelan] blocks calcium channels in blood vessels and in the heart. Major indications are angina pectoris, essential hypertension, and cardiac dysrhythmias. Verapamil was the first CCB available and will serve as our prototype for the group.

TABLE 45-1 • Calcium Channel Blockers: Classification, Sites of Action, and Indications

Classification	Sites of Action	Indications				
		Hypertension	Angina	Dysrhythmias	Migraine*	Others
Dihydropyridines						
Nifedipine [Adalat CC, Nifediac, Nifedical, Procardia]	Arterioles	✓	✓		✓	†
Amlodipine [Norvase]	Arterioles	✓	✓			
Clevidipine [Cleviprex]	Arterioles	✓‡				
Felodipine [Plendil♦, Renedil♦]	Arterioles	✓				
Isradipine [DynaCirc CR]	Arterioles	✓				
Nicardipine [Cardene SR, Cardene I.V.]	Arterioles	✓	✓			
Nimodipine [Nimotop]	Arterioles				✓	‡
Nisoldipine [Sular]	Arterioles	✓				
Phenylalkylamines						
Verapamil [Calan, Covera-HS, Isoptin SR, Verelan]	Arterioles/ heart	✓	✓	✓	✓	
Benzothiazepines						
Diltiazem [Cardizem, Dilacor XR, Tiazac, others]	Arterioles/ heart	✓	✓	✓		

*Investigational use.

†Suppression of preterm labor (investigational use).

‡Only for IV treatment of severe hypertension.

§Prophylaxis of neurologic injury after rupture of an intracranial aneurysm.

Hemodynamic Effects

The overall hemodynamic response to verapamil is the net result of (1) direct effects on the heart and blood vessels and (2) reflex responses.

Direct Effects. By blocking calcium channels in the heart and blood vessels, verapamil has five direct effects:

- Blockade at peripheral arterioles causes dilation, and thereby reduces arterial pressure.
- Blockade at arteries and arterioles of the heart increases coronary perfusion.
- Blockade at the SA node reduces heart rate.
- Blockade at the AV node decreases AV nodal conduction.
- Blockade in the myocardium decreases force of contraction.

Of the direct effects on the heart, reduced AV conduction is the most important.

Indirect (Reflex) Effects. Verapamil-induced lowering of blood pressure activates the baroreceptor reflex, causing increased firing of sympathetic nerves to the heart. Norepinephrine released from these nerves acts to increase heart rate, AV conduction, and force of contraction. However, since these same three parameters are suppressed by the direct actions of verapamil, the direct and indirect effects tend to neutralize each other.

Net Effect. Because the direct effects of verapamil on the heart are counterbalanced by indirect effects, the drug has little or no net effect on cardiac performance: For most patients, heart rate, AV conduction, and contractility are not noticeably altered. Consequently, the overall cardiovascular effect of verapamil is simply vasodilation accompanied by reduced arterial pressure and increased coronary perfusion.

Pharmacokinetics

Verapamil may be administered orally or IV. The drug is well absorbed following oral administration, but undergoes extensive metabolism on its first pass through the liver. Consequently, only about 20% of an oral dose reaches the systemic circulation. Effects begin 30 minutes after dosing and peak within 5 hours. Elimination is primarily by hepatic metabolism. Because the drug is eliminated by the liver, doses must be reduced substantially in patients with hepatic impairment.

Therapeutic Uses

Angina Pectoris. Verapamil is used widely to treat angina pectoris. The drug is approved for vasospastic angina and angina of effort. Benefits in both disorders derive from vasodilation. The role of verapamil in angina is discussed in Chapter 51.

Essential Hypertension. Verapamil is a first-line agent for chronic hypertension. The drug lowers blood pressure by dilating arterioles. The role of verapamil and other CCBs in hypertension is discussed in Chapter 47.

Cardiac Dysrhythmias. Verapamil, administered IV, is used to slow ventricular rate in patients with atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia. Benefits derive from suppressing impulse conduction through the AV node, thereby preventing the atria from driving the ventricles at an excessive rate. Antidysrhythmic applications are discussed in Chapter 49.

Migraine. Verapamil can help prevent migraine headache. This investigational use is discussed in Chapter 30.

Adverse Effects

Common Effects. Verapamil is generally well tolerated. Constipation occurs frequently and is the most common complaint. This problem, which can be especially severe in the elderly, can be minimized by increasing dietary fluids and fiber. Constipation results from blockade of calcium channels in smooth muscle of the intestine. Other common effects—*dizziness, facial flushing, headache, and edema of the ankles and feet*—occur secondary to vasodilation.

Cardiac Effects. Blockade of calcium channels in the heart can compromise cardiac function. In the SA node, calcium channel blockade can cause bradycardia; in the AV node, blockade can cause partial or complete AV block; and in the myocardium, blockade can decrease contractility. When the heart is healthy, these effects rarely have clinical significance. However, in patients with certain cardiac diseases, verapamil can seriously exacerbate dysfunction. Accordingly, the drug must be used with special caution in patients with cardiac failure, and must not be used at all in patients with sick sinus syndrome or second-degree or third-degree AV block.

Other Effects. In older patients, CCBs have been associated with *chronic eczematous eruptions*, typically starting 3 to 6 months after treatment onset. If the reaction is mild, switching to a different CCB may help. If the condition is severe, use of verapamil and other CCBs should stop.

Gingival hyperplasia (overgrowth of gum tissue) has been reported.

Drug and Food Interactions

Digoxin. Like verapamil, digoxin suppresses impulse conduction through the AV node. Accordingly, when these drugs are used concurrently, the risk of AV block is increased. Patients receiving the combination should be monitored closely.

Verapamil increases plasma levels of digoxin by about 60%, thereby increasing the risk of digoxin toxicity. If signs of toxicity appear, digoxin dosage should be reduced.

Beta-Adrenergic Blocking Agents. Beta blockers and verapamil have the same effects on the heart: They decrease heart rate, AV conduction, and contractility. Hence, when a beta blocker and verapamil are used together, there is a risk of excessive cardiodepression. To minimize risk, beta blockers and IV verapamil should be administered several hours apart.

Grapefruit Juice. As discussed in Chapter 6, grapefruit juice can inhibit the intestinal and hepatic metabolism of many drugs, and can thereby raise their levels. In a case report on verapamil toxicity, consumption of grapefruit juice and verapamil (360 mg over 24 hours) led to a verapamil blood level of 2772 ng/mL—approximately 8 to 24 times higher than would have been achieved without grapefruit juice.

Toxicity

Clinical Manifestations. Overdose can produce severe hypotension and cardiotoxicity (bradycardia, AV block, ventricular tachydysrhythmias).

Treatment. General Measures. Verapamil can be removed from the GI tract with gastric lavage followed by a cathartic. Intravenous calcium gluconate can counteract both vasodilation and negative inotropic effects, but will not reverse AV block.

Hypotension. Hypotension can be treated with IV norepinephrine, which promotes vasoconstriction (by activating α_1 receptors on blood vessels) and increases cardiac output (by activating β_1 receptors in the heart). Placing the patient in modified Trendelenburg's position (legs elevated) and administering IV fluids may also help.

Bradycardia and AV Block. Bradycardia and AV block can be treated with isoproterenol (a beta-adrenergic agonist) and with atropine (an anticholinergic drug that blocks parasympathetic influences on the heart). If pharmacologic measures are inadequate, electronic pacing may be required.

Ventricular Tachydysrhythmias. The preferred treatment is direct-current (DC) cardioversion. Antidysrhythmic drugs (procainamide, lidocaine) may also be tried.

Preparations, Dosage, and Administration

Oral. Verapamil is available in immediate-release (IR) tablets (40, 80, and 120 mg) as *Calan*; sustained-release (SR) tablets (120, 180, and 240 mg) as *Calan SR*, *Covera-HS*, and *Isoptin SR*; and sustained-release capsules (120, 180, 240, and 360 mg) as *Verelan*. In addition, verapamil is available as *Verelan PM* (100-, 200-, and 300-mg capsules), a timed-release formulation that, when administered at bedtime, produces maximum verapamil levels in the morning. The sustained-, timed-, and extended-release formulations are approved only for hypertension. Instruct patients to swallow these products intact, without crushing or chewing. A fixed-dose combination withtrandolapril (an angiotensin-converting enzyme [ACE] inhibitor) is available under the trade name *Tarka*.

The usual initial dosage for *angina pectoris* is 80 to 120 mg 3 times a day. The usual initial dosage for *essential hypertension* is 80 mg 3 times a day (using IR tablets), 240 mg of a SR formulation (administered once a day in the morning with food), or 200 mg of *Verelan PM* (administered once a day at bedtime). Dosages should be reduced for elderly patients and for patients with advanced renal or liver disease. Dosages for dysrhythmias are presented in Chapter 49.

Intravenous. Intravenous verapamil is used for dysrhythmias. Because IV verapamil can cause severe adverse cardiovascular effects, blood pressure and the electrocardiogram (ECG) should be monitored and equipment for resuscitation should be immediately available. Intravenous dosages for dysrhythmias are presented in Chapter 49.

Diltiazem

Actions and Uses. Like verapamil, diltiazem [Cardizem, Dilacor XR, Tiazac, others] blocks calcium channels in the heart and blood vessels. As a result, the actions and applications of verapamil and diltiazem are very similar. Diltiazem has the same effects on cardiovascular function as verapamil. Both drugs lower blood pressure through arteriolar dilation and, because their direct suppressant actions are balanced by reflex cardiac stimulation, both have little *net* effect on the heart. Like verapamil, diltiazem is used for *angina pectoris*, *essential hypertension*, and *cardiac dysrhythmias* (atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia).

Pharmacokinetics. Oral diltiazem is well absorbed and then extensively metabolized on its first pass through the liver. As a result, bioavailability is only about 50%. Effects begin rapidly (within a few minutes) and peak within half an hour. The drug undergoes nearly complete metabolism prior to elimination in the urine and feces.

Adverse Effects. Adverse effects are like those of verapamil, except that diltiazem causes less constipation. The most common effects are *dizziness, flushing, headache, and edema of the ankles and feet*. Like verapamil, diltiazem can exacerbate cardiac dysfunction in patients with *bradycardia*, *sick sinus syndrome*, *heart failure*, or *second-degree or third-degree AV block*. Like other CCBs, diltiazem may cause *chronic eczematous rash* in the elderly.

Drug and Food Interactions. Like verapamil, diltiazem can exacerbate digoxin-induced suppression of AV conduction, and can intensify the cardiodepressant effects of beta blockers. Patients receiving diltiazem concurrently with digoxin or a beta blocker should be monitored closely for cardiac status. As with verapamil, grapefruit juice can significantly increase levels of diltiazem.

Preparations, Dosage, and Administration. Oral diltiazem is available in IR tablets (30, 60, 90, and 120 mg) as *Cardizem*, extended-release (ER) tablets (120, 180, 240, 300, 360, and 420 mg) as *Cardizem LA* and SR capsules (60, 90, 120, 180, 240, 300, 360, and 420 mg) as *Cardizem CD*, *Cartia XT*, *Dilacor XR*, *Dilt-CD*, *Dilt-XR*, *Diltia XT*, *Taztia XT*, and *Tiazac*. The drug is also available in solution (5 mg/mL) for IV administration under the trade name *Cardizem*. The usual initial dosage for hypertension is 180 mg once a day with *Cardizem CD*, 60 to 120 mg twice a day with *Cardizem CD* or *Dilacor XR*, and 180 to 240 mg once a day with *Cardizem LA*. *Angina pectoris* can be treated with IR tablets (30 mg 4 times a day initially and 60 mg 4 times a day for maintenance). Intravenous diltiazem is reserved for dysrhythmias.

DIHYDROPYRIDINES: AGENTS THAT ACT MAINLY ON VASCULAR SMOOTH MUSCLE

All of the drugs discussed in this section belong to the *dihydropyridine* family. At therapeutic doses, these drugs produce significant blockade of calcium channels in blood vessels and minimal blockade of calcium channels in the heart. The dihydropyridines are similar to verapamil in some respects, but quite different in others.

Nifedipine

Nifedipine [Adalat CC, Nifedical XL, Nifediac CC, Procardia, Procardia XL] was the first dihydropyridine available and will serve as our prototype for the group. Like verapamil, nifedipine blocks calcium channels in VSM and thereby promotes vasodilation. However, in contrast to verapamil, nifedipine produces very little blockade of calcium channels in the heart. As a result, nifedipine cannot be used to treat dysrhythmias, does not cause cardiac suppression, and is less likely than verapamil to exacerbate pre-existing cardiac disorders. Nifedipine also differs from verapamil in that nifedipine is more likely to cause reflex tachycardia. Contrasts between nifedipine and verapamil are summarized in Table 45-2.

Hemodynamic Effects

Direct Effects. The direct effects of nifedipine on the cardiovascular system are limited to blockade of calcium channels in VSM. Blockade of calcium channels in peripheral arterioles causes vasodilation, and thereby lowers arterial pressure. Calcium channel blockade in arteries and arterioles of the heart increases coronary perfusion. Because nifedipine does not block cardiac calcium channels at usual therapeutic doses, the drug has no *direct* suppressant effects on automaticity, AV conduction, or contractile force.

Indirect (Reflex) Effects. By lowering blood pressure, nifedipine activates the baroreceptor reflex, thereby causing sympathetic stimulation of the heart. Because nifedipine lacks direct cardiosuppressant actions, cardiac stimulation is unopposed, and hence heart rate and contractile force increase.

It is important to note that reflex effects occur primarily with the *fast-acting* formulation of nifedipine, not with the sustained-release formulation. Why? Because the baroreceptor reflex is turned on only by a *rapid* fall in blood pressure; a gradual decline will not activate the reflex. With the fast-acting formulation, blood levels of nifedipine rise quickly, and hence blood pressure drops quickly and the reflex is turned on. Conversely, with the sustained-release formulation,

TABLE 45-2 ■ Comparisons and Contrasts Between Nifedipine and Verapamil

Property	Drug	
	Nifedipine	Verapamil
Direct Effects on the Heart and Arterioles		
Arteriolar dilation	Yes	Yes
<i>Effects on the heart</i>		
Reduced automaticity	No	Yes
Reduced AV conduction	No	Yes
Reduced contractile force	No	Yes
Major Indications		
Hypertension	Yes	Yes
Angina pectoris (classic and variant)	Yes	Yes
Dysrhythmias	No	Yes
Adverse Effects		
<i>Exacerbation of</i>		
AV block	No	Yes
Sick sinus syndrome	No	Yes
Heart failure	No	Yes
<i>Effects secondary to vasodilation</i>		
Edema (ankles and feet)	Yes	Yes
Flushing	Yes	Yes
Headaches	Yes	Yes
Dizziness	Yes	Yes
Reflex tachycardia	Yes	No
Constipation	No	Yes
Drug Interactions		
Intensifies digoxin-induced AV block	No	Yes
Intensifies cardiosuppressant effects of beta blockers	No	Yes
Often combined with a beta blocker to suppress reflex tachycardia	Yes	No

AV = atrioventricular.

blood levels of nifedipine rise slowly, and hence blood pressure falls slowly and the reflex is blunted.

Net Effect. The overall hemodynamic response to nifedipine is simply the sum of its direct effect (vasodilation) and indirect effect (reflex cardiac stimulation). Accordingly, nifedipine (1) lowers blood pressure, (2) increases heart rate, and (3) increases contractile force. Please note, however, that the reflex increases in heart rate and contractile force are transient and occur primarily with the rapid-acting formulation.

Pharmacokinetics

Nifedipine is well absorbed following oral administration, but undergoes extensive first-pass metabolism. As a result, only about 50% of an oral dose reaches the systemic circulation. With the fast-acting formulation, effects begin rapidly and peak in 30 minutes; with the sustained-release formulation, effects begin in 20 minutes and peak in 6 hours. Nifedipine is fully metabolized prior to excretion in the urine.

Therapeutic Uses

Angina Pectoris. Nifedipine is indicated for vasospastic angina and angina of effort. The drug is usually combined with a beta blocker to prevent reflex stimulation of the heart, which could intensify anginal pain. Long-term use reduces the rates of overt heart failure, coronary angiography, and coronary bypass surgery—but not rates of stroke, myocardial infarction, or death. The role of nifedipine in angina is discussed in Chapter 51.

Hypertension. Nifedipine is used widely to treat *essential hypertension*. Only the sustained-release formulation should be used. In the past, nifedipine was used for *hypertensive emergencies*, but has largely been replaced by drugs that are safer. The use of CCBs in essential hypertension is discussed in Chapter 47.

Investigational Uses. Nifedipine has been used on an investigational basis to *suppress preterm labor* (see Chapter 64).

Adverse Effects

Some adverse effects are like those of verapamil; others are quite different. Like verapamil, nifedipine can cause *flushing, dizziness, headache, peripheral edema, and gingival hyperplasia*, and may pose a risk of *chronic eczematous rash* in older patients. In contrast to verapamil, nifedipine causes very little constipation. Also, since nifedipine causes minimal blockade of calcium channels in the heart, the drug is not likely to exacerbate AV block, heart failure, bradycardia, or sick sinus syndrome. Accordingly, nifedipine is preferred to verapamil for patients with these disorders.

A response that occurs with nifedipine that does not occur with verapamil is *reflex tachycardia*. This response is problematic in that it increases cardiac oxygen demand and can thereby increase pain in patients with angina. To prevent reflex tachycardia, nifedipine can be combined with a beta blocker (eg, propranolol).

Rapid-acting nifedipine has been associated with increased mortality in patients with myocardial infarction and unstable angina. Other rapid-acting CCBs have been associated with an increased risk of myocardial infarction in patients with hypertension. However, in both cases, a causal relationship has not been established. Nonetheless, the National Heart, Lung, and Blood Institute has recommended that *rapid-acting nifedipine*, especially in higher doses, be used with great caution, if at all. It is important to note that these adverse effects

have not been associated with *sustained-release nifedipine* or with any other long-acting CCB.

Drug Interactions

Beta-Adrenergic Blockers. Beta blockers are combined with nifedipine to prevent reflex tachycardia. It is important to note that, whereas beta blockers can *decrease* the adverse cardiac effects of *nifedipine*, they can *intensify* the adverse cardiac effects of *verapamil* and *diltiazem*.

Toxicity

When taken in excessive dosage, nifedipine loses selectivity. Hence, toxic doses affect the heart in addition to blood vessels. Consequently, the manifestations and treatment of nifedipine overdose are the same as described above for verapamil.

Preparations, Dosage, and Administration

Nifedipine is available in capsules (10 and 20 mg) as *Procardia* and SR tablets (30, 60, and 90 mg) as *Adalat CC*, *Nifedical XL*, *Nifediac CC*, and *Procardia XL*. Instruct patients to swallow SR tablets whole, without crushing or chewing.

For treatment of *angina pectoris*, the usual initial dosage is 10 mg 3 times a day. The usual maintenance dosage is 10 to 20 mg 3 times a day. The maximum recommended dosage is 180 mg/day.

For *essential hypertension*, only the SR tablets are approved. The usual initial dosage is 30 mg once a day.

Other Dihydropyridines

In addition to nifedipine, seven other dihydropyridines are available. All are similar to nifedipine. Like nifedipine, these drugs produce greater blockade of calcium channels in VSM than in the heart.

Nicardipine. At therapeutic doses, nicardipine [Cardene SR, Cardene I.V.] produces selective blockade of calcium channels in blood vessels and has minimal direct effects on the heart. The drug has two indications: *essential hypertension* and *effort-induced angina pectoris*. The most common adverse effects are flushing, headache, asthenia (weakness), dizziness, palpitations, and edema of the ankles and feet. As with other CCBs, eczematous rash may develop in older patients. Gingival hyperplasia (overgrowth of gum tissue) has been reported. Like nifedipine, nicardipine can be combined with a beta blocker to promote therapeutic effects and suppress reflex tachycardia. Nicardipine is available in 20- and 30-mg IR capsules (generic only), SR capsules (30, 45, and 60 mg) sold as Cardene SR, and an IV formulation (0.1 and 0.2 mg/mL) sold as Cardene I.V. The usual initial dosage for *angina pectoris* is 20 mg 3 times a day using the IR capsules. The usual initial dosage for *essential hypertension* is 20 mg 3 times a day (using IR capsules) or 30 mg twice a day (using SR capsules).

Amlodipine. At therapeutic doses, amlodipine [Norvasc] produces selective blockade of calcium channels in blood vessels, having minimal direct effects on the heart. Approved indications are *essential hypertension* and *angina pectoris* (effort induced and vasospastic). Amlodipine is administered orally and absorbed slowly; peak levels develop in 6 to 12 hours. The drug has a long half-life (30 to 50 hours) and therefore is effective with once-a-day dosing. Principal adverse effects are peripheral and facial edema. Flushing, dizziness, and headache may also occur, as may eczematous rash in older patients. In contrast to other dihydropyridines, amlodipine causes little reflex tachycardia. Amlodipine is available in 2.5-, 5-, and 10-mg tablets. The usual initial dosage for hypertension or angina pectoris is 5 mg once a day. Three fixed-dose combinations are also available: amlodipine/benazepril (an ACE inhibitor), sold as *Lotrel*, amlodipine/telmisartan (an angiotensin receptor blocker), sold as *Twynsta*, and amlodipine/hydrochlorothiazide/olmesartan, sold as *Tribenzor*.

Isradipine. Like nifedipine, isradipine [DynaCirc CR] produces relatively selective blockade of calcium channels in blood vessels. In the United States, the drug is approved only for hypertension. Isradipine is rapidly absorbed following oral administration, but undergoes extensive first-pass metabolism. Parent drug and metabolites are excreted in the urine. The most common side effects are facial flushing (11%), headache (14%), dizziness (7%), and ankle edema (7%). Eczematous rash may develop in older patients. In contrast to nifedipine, isradipine causes minimal reflex tachycardia. The

drug is available in capsules (2.5 and 5 mg) and controlled-release tablets (5 and 10 mg). The usual antihypertensive dosage is 2.5 to 5 mg twice a day.

Felodipine. Felodipine [Plendil[®], Renedil[®], generic only in the United States], produces selective blockade of calcium channels in blood vessels. In the United States, the drug is approved only for hypertension. Felodipine is well absorbed following oral administration but undergoes extensive first-pass metabolism. As a result, bioavailability is low—only 20%. Plasma levels peak in 2.5 to 5 hours and then decay with a half-life of 24 hours. Because of its prolonged half-life, felodipine is effective with once-a-day dosing. Characteristic adverse effects are reflex tachycardia, peripheral edema, headache, facial flushing, and dizziness. Eczematous rash may develop in older patients. Gingival hyperplasia has been reported. Felodipine is available in extended-release tablets (2.5, 5, and 10 mg). The usual dosage for hypertension is 5 to 10 mg once a day. A fixed-dose combination with enalapril (an ACE inhibitor) is available under the trade name *Lexxel*.

Nimodipine. Nimodipine [*Nimotop*] produces selective blockade of calcium channels in *cerebral blood vessels*. The only approved application is prophylaxis of neurologic injury following rupture of an intracranial aneurysm. Benefits derive from preventing cerebral arterial spasm that follows subarachnoid hemorrhage (SAH) and can result in ischemic neurologic injury. Dosing (60 mg every 4 hours) should begin within 96 hours of SAH and continue for 21 days. Nimodipine is available in 30-mg liquid-filled capsules for oral administration only. *Nimodipine must never be given intravenously, owing to a risk of potentially fatal cardiovascular events.*

Nisoldipine. Like nifedipine, nisoldipine [*Sular*] produces selective blockade of calcium channels in blood vessels; the drug has minimal direct

effects on the heart. The only approved indication is hypertension. Nisoldipine is well absorbed following oral administration, but the first-pass effect limits bioavailability to 5%. Plasma levels peak 6 hours after administration. The most common side effects are dizziness, headache, and peripheral edema. Reflex tachycardia may also occur. As with other CCBs, eczematous rash may develop in older patients. Nisoldipine is available in extended-release tablets (10, 20, 30, and 40 mg). The dosage for hypertension is 20 to 60 mg once a day.

Clevidipine. Clevidipine [*Cleviprex*], approved in 2008, is indicated only for intravenous therapy of severe hypertension, defined as systolic blood pressure above 180 mm Hg or diastolic pressure above 115 mm Hg. The drug has an ultrashort half-life (about 1 minute), owing to rapid inactivation by plasma esterases. Effects are not altered by impairment of liver or kidney function. Because of IV dosing and rapid inactivation, blood pressure falls quickly and then rises quickly when the infusion is slowed or stopped. As a result, responses can be easily titrated. Clevidipine is formulated in a lipid emulsion made from soybean oil and egg yolk phospholipids, and hence is contraindicated for patients allergic to soybeans or eggs. Clevidipine is supplied in single-dose vials (50 or 100 mL) at a concentration of 0.5 mg/mL. For patients with severe hypertension, the infusion rate is 1 to 2 mg/hr initially, and can be doubled every 3 minutes up to a maximum of 32 mg/hr. In clinical trials, the average time to reach the target blood pressure was 10.9 minutes. The most common side effects are headache, nausea, and vomiting. Like other dihydropyridines, clevidipine can cause hypotension and reflex tachycardia.

KEY POINTS

- Calcium channels are gated pores in the cytoplasmic membrane that regulate calcium entry into cells.
- In blood vessels, calcium entry causes vasoconstriction, and hence calcium channel blockade causes vasodilation.
- In the heart, calcium entry increases heart rate, AV conduction, and myocardial contractility, and hence calcium channel blockade has the opposite effects.
- In the heart, calcium channels are coupled to beta₁ receptors, activation of which enhances calcium entry. As a result, calcium channel blockade and beta blockade have identical effects on cardiac function.
- At therapeutic doses, nifedipine and the other dihydropyridines act primarily on VSM; in contrast, verapamil and diltiazem act on VSM *and* on the heart.
- All CCBs promote vasodilation, and hence are useful in hypertension and angina pectoris.
- Because they suppress AV conduction, verapamil and diltiazem are useful for treating cardiac dysrhythmias (in addition to hypertension and angina pectoris).
- Because of their cardiopressant effects, verapamil and diltiazem can cause bradycardia, partial or complete AV block, and exacerbation of heart failure.
- Beta blockers intensify cardioppression caused by verapamil and diltiazem.
- Nifedipine and other dihydropyridines can cause reflex tachycardia. Tachycardia is most intense with rapid-acting formulations, and much less intense with sustained-release formulations.
- Beta blockers can be used to suppress reflex tachycardia caused by nifedipine and other dihydropyridines.
- Because they cause vasodilation, all CCBs can cause dizziness, headache, and peripheral edema.
- In toxic doses, nifedipine and other dihydropyridines can cause cardioppression, just like verapamil and diltiazem.
- Rapid-acting nifedipine has been associated with increased mortality in patients with myocardial infarction and unstable angina, although a causal relationship has not been established. The National Heart, Lung, and Blood Institute recommends that rapid-acting nifedipine, especially in higher doses, be used with great caution, if at all.

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Summary of Major Nursing Implications*

VERAPAMIL AND DILTIAZEM

Preadministration Assessment

Therapeutic Goal

Verapamil and diltiazem are indicated for *hypertension*, *angina pectoris*, and *cardiac dysrhythmias* (atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia).

Baseline Data

For *all patients*, determine blood pressure and pulse rate, and obtain laboratory evaluations of liver and kidney function. For patients with *angina pectoris*, obtain baseline data on the frequency and severity of anginal attacks. For baseline data relevant to *hypertension*, see Chapter 47.

Identifying High-Risk Patients

Verapamil and diltiazem are *contraindicated* for patients with severe hypotension, sick sinus syndrome (in the absence of electronic pacing), and second-degree or third-degree AV block. Use with *caution* in patients with heart failure or liver impairment and in patients taking digoxin or beta blockers.

Implementation: Administration

Routes

Oral, IV.

Administration

Oral. *Verapamil* and *diltiazem* may be used for angina pectoris and essential hypertension. *Verapamil* may be used with digoxin to control ventricular rate in patients with atrial fibrillation and atrial flutter.

Sustained-release formulations are reserved for essential hypertension. **Instruct patients to swallow sustained-release formulations whole, without crushing or chewing.**

Prior to dosing, measure blood pressure and pulse rate. If hypotension or bradycardia is detected, withhold medication and notify the prescriber.

Intravenous. Intravenous therapy with verapamil or diltiazem is reserved for cardiac dysrhythmias. Perform injections slowly (over 2 to 3 minutes). Monitor the ECG for AV block, sudden reduction in heart rate, and prolongation of the PR or QT interval. Have facilities for cardioversion and cardiac pacing immediately available.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Angina Pectoris. Keep an ongoing record of anginal attacks, noting the time and intensity of each attack and the likely precipitating event. **Teach outpatients to chart the time, intensity, and circumstances of their attacks, and to notify the prescriber if attacks increase.**

Essential Hypertension. Monitor blood pressure periodically. For most patients, the goal is to reduce systolic/diastolic pressure to a value below 140/90 mm Hg. **Teach patients to self-monitor their blood pressure and to maintain a blood pressure record.**

Minimizing Adverse Effects

Cardiosuppression. Verapamil and diltiazem can cause bradycardia, AV block, and heart failure. **Inform patients about manifestations of cardiac effects (eg, slow heartbeat, shortness of breath, weight gain) and instruct them to notify the prescriber if these occur.** If cardiac impairment is severe, drug use should stop.

Peripheral Edema. Inform patients about signs of edema (swelling in ankles or feet) and instruct them to notify the prescriber if these occur. If necessary, edema can be reduced with a diuretic.

Constipation. Constipation occurs primarily with *verapamil*. **Advise patients that constipation can be minimized by increasing dietary fluid and fiber.**

Minimizing Adverse Interactions

Digoxin. The combination of digoxin with verapamil or diltiazem increases the risk of partial or complete AV block. Monitor for indications of impaired AV conduction (missed beats, slowed ventricular rate).

Verapamil (and possibly diltiazem) can increase plasma levels of digoxin. Digoxin dosage should be reduced.

Beta Blockers. Concurrent use of a beta blocker with verapamil or diltiazem can cause bradycardia, AV block, or heart failure. Monitor closely for cardiac suppression. Administer *intravenous verapamil* and beta blockers several hours apart.

Grapefruit Juice. Grapefruit juice can raise levels of verapamil and diltiazem. Toxicity may result. **Advise patients that it may be prudent to minimize grapefruit juice consumption.**

Managing Acute Toxicity

Remove unabsorbed drug with gastric lavage followed by a cathartic. Give intravenous calcium to help counteract excessive vasodilation and reduced myocardial contractility.

To raise blood pressure, give IV norepinephrine. Intravenous fluids and placing the patient in modified Trendelenburg's position can also help.

Bradycardia and AV block can be reversed with isoproterenol and atropine. If these are inadequate, electronic pacing may be required.

Ventricular tachydysrhythmias can be treated with DC cardioversion. Antidysrhythmic drugs (lidocaine or procainamide) may also be used.

DIHYDROPYRIDINES

Amlodipine
Clevipidine
Felodipine
Isradipine
Nicardipine
Nifedipine
Nimodipine
Nisoldipine

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Preadministration Assessment

Therapeutic Goal

Amlodipine, *nifedipine*, and *nicardipine* are approved for essential hypertension and angina pectoris.

Isradipine, *felodipine*, and *nisoldipine* are approved for hypertension only.

Nimodipine is used only for subarachnoid hemorrhage.

Clevidipine is used only for IV therapy of severe hypertension.

Baseline Data

See nursing implications for *Verapamil* and *Diltiazem*.

Identifying High-Risk Patients

Use dihydropyridines with *caution* in patients with hypotension, sick sinus syndrome (in the absence of electronic pacing), angina pectoris (because of reflex tachycardia), heart failure, and second-degree or third-degree AV block.

Implementation: Administration

Route

Oral. All dihydropyridines except *clevidipine*.

Intravenous. *Nicardipine*, *clevidipine*.

Administration

Instruct patients to swallow sustained-release formulations whole, without crushing or chewing.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See nursing implications for *Verapamil* and *Diltiazem*.

Minimizing Adverse Effects

Reflex Tachycardia. Reflex tachycardia can be suppressed with a beta blocker.

Peripheral Edema. Inform patients about signs of edema (swelling in ankles or feet) and instruct them to notify the prescriber if these occur. If necessary, edema can be reduced with a diuretic.

Managing Acute Toxicity

See nursing implications for *Verapamil* and *Diltiazem*.

*Patient education information is highlighted as blue text.

Basic Concepts in Vasodilator Pharmacology**Selectivity of Vasodilatory Effects****Overview of Therapeutic Uses****Adverse Effects Related to Vasodilation****Pharmacology of Individual Vasodilators****Hydralazine****Minoxidil****Sodium Nitroprusside****Drugs Acting on the Renin-Angiotensin-Aldosterone System****Organic Nitrates****Calcium Channel Blockers****Sympatholytic Drugs****Nesiritide****Drugs for Pulmonary Arterial Hypertension**

Vasodilation can be produced with a variety of drugs. The major classes of vasodilators, along with representative agents, are listed in Table 46-1. Some of these drugs act primarily on arterioles, some act primarily on veins, and some act on both types of vessel. The vasodilators are widely used, with indications ranging from hypertension to angina pectoris to heart failure. Many of the vasodilators have been discussed in previous chapters. Three agents—hydralazine, minoxidil, and nitroprusside—are introduced here.

In approaching the vasodilators, we begin by considering concepts that apply to the vasodilators as a group. After that we discuss the pharmacology of individual agents.

BASIC CONCEPTS IN VASODILATOR PHARMACOLOGY**Selectivity of Vasodilatory Effects**

Vasodilators differ from one another with respect to the types of blood vessels they affect. Some agents (eg, hydralazine) produce selective dilation of arterioles. Others (eg, nitroglycerin) produce selective dilation of veins. Still others (eg, prazosin) dilate arterioles *and* veins. The selectivity of some important vasodilators is summarized in Table 46-2.

The selectivity of a vasodilator determines its hemodynamic effects. For example, drugs that dilate *resistance vessels* (arterioles) cause a decrease in cardiac *afterload* (the force the heart works against to pump blood). By decreasing afterload, arteriolar dilators reduce cardiac work while causing cardiac output and tissue perfusion to increase. In contrast, drugs that dilate *capacitance vessels* (veins) reduce the force with which blood is returned to the heart, which reduces ventricular filling. This reduction in filling decreases cardiac

TABLE 46-1 • Types of Vasodilators

Category	Examples
Drugs Acting on the Renin-Angiotensin-Aldosterone System	
Angiotensin-Converting Enzyme Inhibitors	Captopril Enalapril
Angiotensin II Receptor Blockers	Losartan Valsartan
Direct Renin Inhibitors	Aliskiren
Organic Nitrates	Nitroglycerin Isosorbide dinitrate
Calcium Channel Blockers	Diltiazem Verapamil Nifedipine
Sympatholytic Drugs	
Alpha-Adrenergic Blockers	Phentolamine Phenoxybenzamine Prazosin Terazosin
Ganglionic Blockers	Mecamylamine*
Adrenergic Neuron Blockers	Reserpine Guanadrel
Centrally Acting Agents	Clonidine Methyldopa
Drugs for Pulmonary Arterial Hypertension	Bosentan Epoprostenol
Other Important Vasodilators	Hydralazine Minoxidil Nitroprusside Nesiritide

*No longer available in the United States.

preload (the degree of stretch of the ventricular muscle prior to contraction), which in turn decreases the force of ventricular contraction. Hence, by decreasing preload, venous dilators cause a decrease in cardiac work, along with a decrease in cardiac output and tissue perfusion.

Because hemodynamic responses to dilation of arterioles and veins differ, the selectivity of a vasodilator is a major determinant of its effects, both therapeutic and undesired. Undesired effects related to selective dilation of arterioles and veins are discussed below. Therapeutic implications of selective dilation are discussed in Chapters 47, 48, 51, 53, and 107—the chapters in which the primary uses of the vasodilators are presented.

Overview of Therapeutic Uses

The vasodilators, as a group, have a broad spectrum of uses. Principal indications are *essential hypertension*, *hypertensive crisis*, *angina pectoris*, *heart failure*, and *myocardial infarction*.

TABLE 46-2 • Vasodilator Selectivity

Vasodilator	Site of Vasodilation	
	Arterioles	Veins
Hydralazine	+	
Minoxidil	+	
Diltiazem	+	
Nifedipine	+	
Verapamil	+	
Prazosin	+	+
Terazosin	+	+
Phentolamine	+	+
Nitroprusside	+	+
Captopril	+	+
Enalapril	+	+
Losartan	+	+
Aliskiren	+	+
Nesiritide	+	+
Nitroglycerin		+
Isosorbide dinitrate		+

tion. Additional indications include *pheochromocytoma*, *peripheral vascular disease*, *pulmonary arterial hypertension*, and *production of controlled hypotension during surgery*. The specific applications of any particular agent are determined by its pharmacologic profile. Important facets of that profile are route of administration, site of vasodilation (arterioles, veins, or both), and intensity and duration of effects.

Adverse Effects Related to Vasodilation

Postural Hypotension

Postural (orthostatic) hypotension is defined as a fall in blood pressure brought on by moving from a supine or seated position to an upright position. The underlying cause is relaxation of smooth muscle in *veins*. Because of venous relaxation, gravity causes blood to “pool” in veins, thereby decreasing venous return to the heart. Reduced venous return causes a decrease in cardiac output and a corresponding decrease in blood pressure. Hypotension from venous dilation is minimal in recumbent subjects because, when we are lying down, the impact of gravity on venous return is small.

Patients receiving vasodilators should be informed about symptoms of hypotension (lightheadedness, dizziness) and advised to sit or lie down if these occur. Failure to follow this advice may result in fainting. Patients should also be taught that they can minimize hypotension by avoiding abrupt transitions from a supine or seated position to an upright position.

Reflex Tachycardia

Reflex tachycardia can be produced by dilation of arterioles or veins. The mechanism is this: (1a) *arteriolar* dilation causes a direct decrease in arterial pressure or (1b) *venous* dilation reduces cardiac output, which in turn reduces arterial pressure; (2) baroreceptors in the aortic arch and carotid sinus sense the drop in pressure and relay this information to the vasomotor center of the medulla; and (3) in an attempt to bring blood pressure back up, the medulla sends impulses along sympathetic nerves instructing the heart to beat faster.

Reflex tachycardia is undesirable for two reasons. First, tachycardia can put an unacceptable burden on the heart. Second, if the

vasodilator was given to reduce blood pressure, tachycardia would raise pressure and thereby negate the desired effect.

To help prevent vasodilator-induced reflex tachycardia, patients can be pretreated with a beta blocker (eg, propranolol), which will block sympathetic stimulation of the heart.

Expansion of Blood Volume

Prolonged use of *arteriolar* or *venous* dilators can cause an increase in blood volume (secondary to prolonged reduction of blood pressure). The increase in volume represents an attempt by the body to restore blood pressure to pretreatment levels.

Why does blood volume increase? First, reduced blood pressure triggers secretion of aldosterone by the adrenal glands. Aldosterone then acts on the kidney to promote retention of sodium and water, thereby increasing blood volume. Second, by reducing arterial pressure, vasodilators decrease both renal blood flow and glomerular filtration rate; because filtrate volume is decreased, the kidney is able to reabsorb an increased fraction of filtered sodium and water, which causes blood volume to expand.

Increased blood volume can negate the beneficial effects of the vasodilator. For example, if volume increases during the treatment of hypertension, blood pressure will rise and the benefits of therapy will be canceled. To prevent the kidney from neutralizing the beneficial effects of vasodilation, patients often receive concurrent therapy with a diuretic, which prevents fluid retention and volume expansion.

PHARMACOLOGY OF INDIVIDUAL VASODILATORS

In this section we focus on three drugs: hydralazine, minoxidil, and sodium nitroprusside. All of the other vasodilators are discussed at length in other chapters, and hence discussion of them here is brief. Diazoxide [Hyperstat IV], discussed in previous editions of this book, has been withdrawn.

Hydralazine

Cardiovascular Effects

Hydralazine [Apresoline] causes selective dilation of arterioles. The drug has little or no effect on veins. Arteriolar dilation results from a direct action on vascular smooth muscle (VSM). The exact mechanism is unknown. In response to arteriolar dilation, peripheral resistance and arterial blood pressure fall. In addition, heart rate and myocardial contractility increase, largely by reflex mechanisms. Because hydralazine acts selectively on arterioles, postural hypotension is minimal.

Pharmacokinetics

Absorption and Time Course of Action. Hydralazine is readily absorbed following oral administration. Effects begin within 45 minutes and persist for 6 hours or longer. With parenteral administration, effects begin faster (within 10 minutes) and last 2 to 4 hours.

Metabolism. Hydralazine is inactivated by a metabolic process known as *acetylation*. The ability to acetylate drugs is genetically determined. Some people are rapid acetylators; some are slow acetylators. The distinction between rapid and slow acetylators can be clinically significant. Why? Because individuals who acetylate hydralazine slowly are likely to have

higher blood levels of the drug, which can result in excessive vasodilation and other undesired effects. To avoid hydralazine accumulation, dosage should be reduced in slow acetylators.

Therapeutic Uses

Essential Hypertension. Oral hydralazine can be used to lower blood pressure in patients with essential hypertension. The regimen almost always includes a beta blocker, and may include a diuretic as well. Although commonly employed in the past, hydralazine has been largely replaced by newer antihypertensive agents (see Chapter 47).

Hypertensive Crisis. Parenteral hydralazine is used to lower blood pressure rapidly in severe hypertensive episodes. The drug should be administered in small, incremental doses. If dosage is excessive, severe hypotension may replace the hypertension. Treatment of hypertensive emergencies is discussed in Chapter 47.

Heart Failure. As discussed in Chapter 48, hydralazine (usually in combination with isosorbide dinitrate) can be used short term to reduce afterload in patients with heart failure. With prolonged therapy, tolerance to hydralazine develops.

Adverse Effects

Reflex Tachycardia. By lowering arterial blood pressure, hydralazine can trigger reflex stimulation of the heart, thereby causing cardiac work and myocardial oxygen demand to increase. Because hydralazine-induced reflex tachycardia is frequently severe, the drug is usually combined with a beta blocker.

Increased Blood Volume. Hydralazine-induced hypotension can cause sodium and water retention and a corresponding increase in blood volume. A diuretic can prevent volume expansion.

Systemic Lupus Erythematosus-like Syndrome. Hydralazine can cause an acute rheumatoid syndrome that closely resembles systemic lupus erythematosus (SLE). Symptoms include muscle pain, joint pain, fever, nephritis, pericarditis, and the presence of antinuclear antibodies. The syndrome occurs most frequently in slow acetylators and is rare when dosage is kept below 200 mg/day. If an SLE-like reaction occurs, hydralazine should be discontinued. Symptoms are usually reversible but may take 6 or more months to resolve. In some cases, rheumatoid symptoms persist for years.

Other Adverse Effects. Common responses include headache, dizziness, weakness, and fatigue. These reactions are related to hydralazine-induced hypotension.

Drug Interactions

Hydralazine can be combined with a *beta blocker* to protect against reflex tachycardia, and with a *diuretic* to prevent sodium and water retention and expansion of blood volume. Drugs that lower blood pressure will intensify hypotensive responses to hydralazine. Accordingly, if hydralazine is used with other *antihypertensive agents*, care is needed to avoid excessive hypotension. In the treatment of heart failure, hydralazine is usually combined with *isosorbide dinitrate*, a drug that dilates veins.

Preparations, Dosage, and Administration

Preparations. Hydralazine (Apresoline) is available in tablets (10, 25, 50, and 100 mg) for oral use and in solution (20 mg/mL in 1-mL ampules) for parenteral administration. Hydralazine is also available in fixed-dose combination with (1) hydrochlorothiazide (a diuretic) sold generically and (2) isosorbide dinitrate (a vasodilator) sold as *BiDil*. As discussed in Chapters

8 and 48, *BiDil* is the first drug product approved for treating a specific ethnic group—namely, African Americans.

Oral Therapy. Dosage should be low initially (10 mg 4 times a day) and then gradually increased. Rapid increases may produce excessive hypotension. Usual maintenance dosages for adults range from 25 to 100 mg twice a day. Daily doses greater than 200 mg are associated with an increased incidence of adverse effects and should be avoided.

Parenteral Therapy. Parenteral administration (IV and IM) is reserved for hypertensive crises. The usual dose is 20 to 40 mg, repeated as needed. Blood pressure should be monitored frequently to minimize excessive hypotension. In most cases, patients can be switched from parenteral hydralazine to oral therapy within 48 hours.

Minoxidil

Minoxidil produces more intense vasodilation than hydralazine but also causes more severe adverse reactions. Because it is both very effective and very dangerous, minoxidil is reserved for patients with severe hypertension unresponsive to safer drugs.

Cardiovascular Effects

Like hydralazine, minoxidil produces selective dilation of *arterioles*. Little or no venous dilation occurs. Arteriolar dilation decreases peripheral resistance and arterial blood pressure. In response, reflex mechanisms increase heart rate and myocardial contractility. Both responses can increase cardiac oxygen demand, and can thereby exacerbate angina pectoris.

Vasodilation results from a direct action on VSM. In order to relax VSM, minoxidil must first be metabolized to minoxidil sulfate. This metabolite then causes potassium channels in VSM to open. The resultant efflux of potassium hyperpolarizes VSM cells, thereby reducing their ability to contract.

Pharmacokinetics

Minoxidil is rapidly and completely absorbed following oral administration. Vasodilation is maximal within 2 to 3 hours and then gradually declines. Residual effects may persist for 2 days or more. Minoxidil is extensively metabolized. Metabolites and parent drug are eliminated in the urine. The drug's half-life is 4.2 hours.

Therapeutic Uses

The only cardiovascular indication for minoxidil is *severe hypertension*. Because of its serious adverse effects, minoxidil is reserved for patients who have not responded to safer drugs. To minimize adverse responses (reflex tachycardia, expansion of blood volume, pericardial effusion), minoxidil should be used with a beta blocker plus intensive diuretic therapy.

Topical minoxidil [Rogaine, others] is used to promote hair growth in balding men and women (see Chapter 105).

Adverse Effects

Reflex Tachycardia. Blood pressure reduction triggers reflex tachycardia, a serious effect that can be minimized by co-treatment with a beta blocker.

Sodium and Water Retention. Fluid retention is both common and serious. Volume expansion may be so severe as to cause cardiac decompensation. Management of fluid retention requires a high-ceiling diuretic (eg, furosemide) used alone or in combination with a thiazide diuretic. If diuretics are inadequate, dialysis must be employed, or minoxidil must be withdrawn.

Hypertrichosis. About 80% of patients taking minoxidil for 4 weeks or more develop hypertrichosis (excessive growth of hair). Hair growth begins on the face and later develops on the arms, legs, and back. Hypertrichosis appears to result from proliferation of epithelial cells at the base of the hair follicle; vaso-

dilation may also be involved. Hairiness is a cosmetic problem that can be controlled by shaving or using a depilatory. However, many patients, primarily women, find hypertrichosis both unmanageable and intolerable and refuse to continue treatment.

Pericardial Effusion. Rarely, minoxidil-induced fluid retention results in pericardial effusion (fluid accumulation beneath the pericardium). In most cases, pericardial effusion is asymptomatic. However, in some cases, fluid accumulation becomes so great as to cause cardiac tamponade (compression of the heart with a resultant decrease in cardiac performance). If tamponade occurs, it must be treated by pericardiocentesis or surgical drainage.

Other Adverse Effects. Minoxidil may cause *nausea, headache, fatigue, breast tenderness, glucose intolerance, thrombocytopenia, and skin reactions* (rashes, Stevens-Johnson syndrome). In addition, the drug has caused *hemorrhagic cardiac lesions* in experimental animals.

Preparations, Dosage, and Administration

Minoxidil is supplied in 2.5- and 10-mg tablets. The initial dosage is 5 mg once a day. The maximum dosage is 100 mg/day. The usual adult dosage is 10 to 40 mg/day administered in single or divided doses. When a rapid response is needed, a loading dose of 5 to 20 mg is given followed by doses of 2.5 to 10 mg every 4 hours.

A topical formulation [Rogaine, others] is available for treating baldness (see Chapter 105).

Sodium Nitroprusside

Sodium nitroprusside [Nitropress, Nipride[®]] is potent and efficacious, and acts faster than any other vasodilator available. Because of these qualities, nitroprusside is a drug of choice for hypertensive emergencies.

Cardiovascular Effects

In contrast to hydralazine and minoxidil, nitroprusside causes *venous* dilation in addition to *arteriolar* dilation. Curiously, although nitroprusside is an effective arteriolar dilator, reflex tachycardia is minimal. Administration is by IV infusion, and effects begin at once. By adjusting the infusion rate, blood pressure can be depressed to almost any level desired. When the infusion is stopped, blood pressure returns to pretreatment levels in minutes. Nitroprusside can trigger retention of sodium and water; furosemide can help counteract this effect.

Mechanism of Action

Once in the body, nitroprusside breaks down to release *nitric oxide* (Fig. 46-1), which then activates *guanylate cyclase*, an enzyme present in VSM. Guanylate cyclase catalyzes the production of *cyclic GMP*, which, through a series of reactions, causes vasodilation. This mechanism is similar to that of nitroglycerin.

Metabolism

As shown in Figure 46-1, nitroprusside contains five *cyanide* groups, which are split free in the first step of nitroprusside metabolism. *Nitric oxide*, the active component, is released next. Both reactions take place in smooth muscle. Once freed, the cyanide groups are converted to *thiocyanate* by the liver, using *thiosulfate* as a cofactor. Thiocyanate is eliminated by the kidneys over several days.

Therapeutic Uses

Hypertensive Emergencies. Nitroprusside is used to lower blood pressure rapidly in hypertensive emergencies. Oral antihypertensive medication should be initiated simulta-

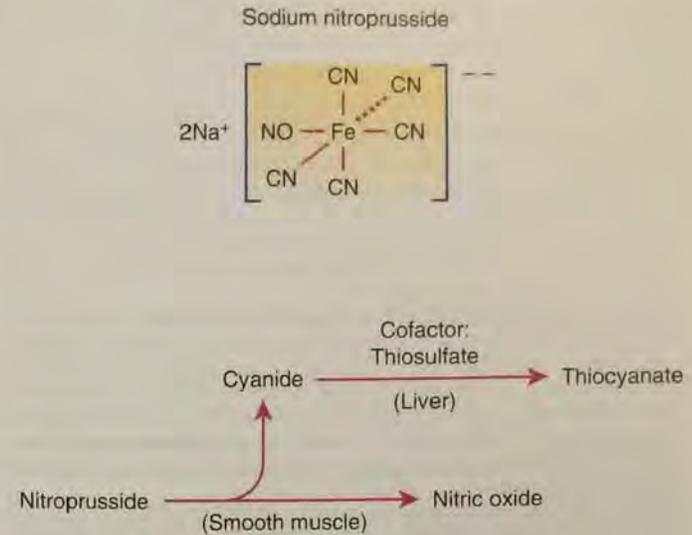


Figure 46-1 Structure and metabolism of sodium nitroprusside.

Note the five cyanide (CN) groups in nitroprusside and their liberation during metabolism. Note also the release of nitric oxide (NO), the active component of nitroprusside.

neously. During nitroprusside treatment, furosemide may be needed to prevent excessive retention of fluid.

Other Uses. Nitroprusside is approved for producing controlled hypotension during surgery (to reduce bleeding in the surgical field). In addition, the drug has been employed investigational to treat severe, refractory congestive heart failure and myocardial infarction.

Adverse Effects

Excessive Hypotension. If administered too rapidly, nitroprusside can cause a precipitous drop in blood pressure, resulting in headache, palpitations, nausea, vomiting, and sweating. Blood pressure should be monitored continuously.

Cyanide Poisoning. Rarely, lethal amounts of cyanide have accumulated. Cyanide buildup is most likely in patients with liver disease and in those with low stores of thiosulfate, the cofactor needed for cyanide detoxification. The chances of cyanide poisoning can be minimized by avoiding rapid infusion (faster than 5 mcg/kg/min) and by coadministering thiosulfate. If cyanide toxicity occurs, nitroprusside should be withdrawn.

Thiocyanate Toxicity. When nitroprusside is given for several days, thiocyanate may accumulate. Although much less hazardous than cyanide, thiocyanate can also cause adverse effects. These effects, which involve the central nervous system (CNS), include disorientation, psychotic behavior, and delirium. To minimize toxicity, patients receiving nitroprusside for more than 3 days should undergo monitoring of plasma thiocyanate, which must be kept below 0.1 mg/mL.

Preparations, Dosage, and Administration

Sodium nitroprusside [Nitropress] is available in powdered form (50 mg) to be dissolved and then diluted for IV infusion. Fresh solutions may have a faint brown color. Solutions that are deeply colored (blue, green, dark red) should be discarded. Nitroprusside in solution can be degraded by light, and hence should be protected with an opaque material.

Blood pressure can be adjusted to practically any level by increasing or decreasing the rate of infusion. The initial infusion rate is 0.3 mcg/kg/min. The maximal rate is 10 mcg/kg/min. If infusion at the maximal rate for 10 minutes fails to produce an adequate drop in blood pressure, administration should stop. During the infusion, blood pressure should be monitored con-

tinuously, with either an arterial line or an electronic monitoring device. No other drugs should be mixed with the nitroprusside solution.

Drugs Acting on the Renin-Angiotensin-Aldosterone System

As discussed in Chapter 44, the renin-angiotensin-aldosterone system (RAAS) plays an important role in the regulation of blood pressure, blood volume, and fluid and electrolyte balance. A key component of the system—angiotensin II—is a powerful vasoconstrictor that acts on arterioles and veins. Hence, by blocking either the formation or actions of angiotensin II, we can promote dilation of arterioles and veins.

Angiotensin-Converting Enzyme (ACE) Inhibitors. Inhibitors of ACE promote vasodilation by blocking the conversion of angiotensin I (a weak vasoconstrictor) into angiotensin II (a powerful vasoconstrictor). The result is dilation of arterioles and veins. The primary indications for ACE inhibitors are essential hypertension and heart failure. In addition, these drugs can help preserve renal function in people with diabetes. The basic pharmacology of the ACE inhibitors is presented in Chapter 44. Their use in hypertension and heart failure is discussed in Chapters 47 and 48, respectively.

Angiotensin II Receptor Blockers (ARBs). These drugs have effects much like those of the ACE inhibitors. However, instead of preventing formation of angiotensin II, these drugs block receptors for angiotensin II. Like the ACE inhibitors, ARBs dilate arterioles and veins. Currently, ARBs have three indications: hypertension, heart failure, and diabetic nephropathy. The basic pharmacology of the ARBs is discussed in Chapter 44.

Direct Renin Inhibitors (DRIs). Like ACE inhibitors, the DRIs prevent formation of angiotensin II. However, the mechanism is different: Rather than inhibiting ACE, the DRIs inhibit renin, the enzyme that forms angiotensin I; in the absence of angiotensin I, angiotensin II cannot be made. Like the ACE inhibitors and ARBs, the DRIs promote dilation of arterioles and veins. The only DRI currently available—aliskiren—is approved only for hypertension. The basic pharmacology of aliskiren is discussed in Chapter 44.

Organic Nitrates

The organic nitrates (eg, nitroglycerin, isosorbide dinitrate) produce selective dilation of veins; dilation of arterioles is minimal. The primary indication for these drugs is angina pectoris. In addition, nitroglycerin is given to treat heart failure and myocardial infarction, and to provide controlled hypotension during surgery. The pharmacology of the organic nitrates is discussed in Chapter 51.

Calcium Channel Blockers

The calcium channel blockers (eg, verapamil, nifedipine) produce vasodilation by preventing calcium entry into VSM. At therapeutic doses, these drugs produce selective dilation of arterioles. Primary indications are hypertension and angina pectoris. The calcium channel blockers are the subject of Chapter 45.

Sympatholytic Drugs

Sympatholytic drugs promote vasodilation by preventing the sympathetic nervous system from causing vasoconstriction. Some of these drugs act by direct blockade of vascular adrenergic receptors. Others act on sympathetic ganglia, adrenergic neurons, or the CNS.

Alpha-Adrenergic Blocking Agents. The alpha blockers (eg, phenolamine, prazosin) promote vasodilation by preventing activation of alpha-adrenergic receptors on veins and arterioles. In their capacity as vasodilators, these drugs have multiple therapeutic applications, including hypertension, peripheral vascular disease, and pheochromocytoma. The alpha blockers are discussed in Chapter 18.

Ganglionic Blocking Agents. Ganglionic blocking agents interrupt impulse transmission through all ganglia of the autonomic nervous system. By doing so, they prevent sympathetic stimulation of arterioles and veins, and thereby cause vasodilation. Unfortunately, ganglionic blockage also produces multiple side effects, including dry mouth, blurred vision, urinary retention, and paresis of the bowel. Because of these undesired effects, and because more desirable drugs are available, ganglionic blockers are no longer used. The last ganglionic blocker available—mecamylamine [Inversine]—was voluntarily withdrawn in 2009.

Adrenergic Neuron Blocking Agents. Adrenergic neuron blockers act within terminals of adrenergic neurons to reduce norepinephrine release. Vasodilation results from their effect on sympathetic nerves that innervate blood vessels. Reserpine, the only adrenergic neuron blocker now available, is discussed in Chapter 19.

Centrally Acting Agents. The centrally acting sympatholytics (eg, clonidine, methyldopa) act within the CNS to inhibit impulse outflow along sympathetic nerves. These agents are used primarily for hypertension. Their pharmacology is discussed in Chapter 19.

Nesiritide

Nesiritide [Natrecor] is a synthetic form of B-natriuretic peptide. The drug dilates arterioles and veins. Three mechanisms are involved: suppression of the RAAS, suppression of CNS sympathetic outflow, and a direct effect on VSM. Nesiritide is indicated only for short-term therapy of acutely decompensated heart failure (see Chapter 48).

Drugs for Pulmonary Arterial Hypertension

Four vasodilators—ambrisentan [Letairis], bosentan [Tracleer], epoprostenol [Flolan], and treprostinil [Remodulin]—are used to dilate pulmonary blood vessels in patients with pulmonary arterial hypertension. Ambrisentan and bosentan block vascular receptors for endothelin-1, a powerful vasoconstrictor. Epoprostenol and treprostinil stimulate production of cyclic AMP in vascular smooth muscle. All four drugs are discussed in Chapter 107.

KEY POINTS

- Some vasodilators are selective for arterioles, some are selective for veins, and some dilate both types of vessel.
- Drugs that dilate arterioles reduce cardiac afterload, and can thereby reduce cardiac work while increasing cardiac output and tissue perfusion.
- Drugs that dilate veins reduce cardiac preload, and can thereby reduce cardiac work, cardiac output, and tissue perfusion.
- Principal indications for vasodilators are essential hypertension, hypertensive crisis, angina pectoris, heart failure, and myocardial infarction.
- Drugs that dilate veins can cause orthostatic hypotension.
- Drugs that dilate arterioles or veins can cause reflex tachycardia, which increases cardiac work and elevates blood pressure. Reflex tachycardia can be blunted with a beta blocker.
- Drugs that dilate arterioles or veins can cause fluid retention, which can be blunted with a diuretic.
- Hydralazine causes selective dilation of arterioles.
- Hydralazine can cause a syndrome that resembles SLE.
- Minoxidil causes selective and profound dilation of arterioles.
- Minoxidil can cause hypertrichosis.
- Sodium nitroprusside dilates arterioles and veins.
- Prolonged infusion of nitroprusside can result in toxic accumulation of cyanide and thiocyanate.

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Box 47-2. And the Best Drug Is . . . the Cheap One!

Hypertension (elevated blood pressure [BP]) is a common, chronic disorder that affects about 2 million American children, 74 million American adults, and over 1 billion people worldwide. According to the World Health Organization, hypertension is the leading global risk for mortality, causing 12.8% of all human deaths. Left untreated, hypertension can lead to heart disease, kidney disease, and stroke. Conversely, a treatment program of lifestyle modifications and drug therapy can reduce BP and the risk of long-term complications. However, although we can reduce symptoms and long-term consequences, we can't cure hypertension. As a result, treatment must continue lifelong, making nonadherence a significant problem. Despite advances in management, hypertension remains undertreated: Among Americans with the disease, only 74% undergo treatment, and only 48% take sufficient medicine to bring their BP under control.

We can treat hypertension with 14 classes of drugs. Fortunately for you, all 14 were introduced in previous chapters. Hence, in this chapter, rather than struggling with a huge array of new drugs, all you have to do is learn the antihypertensive applications of drugs you already know about.

In 2003, the National Heart, Lung, and Blood Institute issued revised clinical guidelines on hypertension. This document—*The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*, known simply as *JNC 7*—was prepared by a special committee of the National High Blood Pressure Education Program. Recommendations in *JNC 7* update and simplify those of *JNC 6*, released in 1997. Important changes include a new BP classification scheme, increased emphasis on controlling systolic BP, and the recommendation to use thiazide diuretics as initial therapy for most patients. Throughout this chapter, clinical practice recommendations reflect those in *JNC 7*, except where noted otherwise.*

Note: An update of *JNC 7*—*JNC 8*—is long overdue. Publication was originally scheduled for 2010, but has been postponed. When *JNC 8* is finally released, I will revise the chapter and post the revision on the Evolve site. Elsevier sales reps will inform faculty as soon as the updated chapter is available.

BASIC CONSIDERATIONS IN HYPERTENSION

In this section, we consider three issues (1) classification of BP based on values for systolic and diastolic pressure, (2) types of hypertension, and (3) the damaging effects of chronic hypertension.

CLASSIFICATION OF BLOOD PRESSURE

JNC 7 defines four BP categories: normal, prehypertension, stage 1 hypertension, and stage 2 hypertension (Table 47-1). This scheme differs from that of *JNC 6* in three ways:

- The cutoff values for normal BP have been reduced.
- A new category—prehypertension—has been added.
- Two classes of hypertension—stages 2 and 3 from *JNC 6*—have been combined into one—stage 2 in *JNC 7*—because management of both is much the same.

Normal. In *JNC 7*, normal BP is defined as systolic BP below 120 mm Hg and diastolic BP below 80 mm Hg, com-

*Although *JNC 7* is the most influential guideline in the United States, it is not the only authoritative guideline available. Since the publication of *JNC 7*, updated treatment guidelines have been released by several organizations, including the American Society of Hypertension, the Canadian Hypertension Education Program, the European Society of Hypertension in conjunction with the European Society of Cardiology, and the World Health Organization in conjunction with the International Society of Hypertension. Recommendations in these guidelines generally parallel those in *JNC 7*. However, important differences do exist.

TABLE 47-1 ■ Classification of Blood Pressure for Adults Age 18 and Older

Classification*	Systolic (mm Hg)		Diastolic (mm Hg)
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥160	or	≥100

*Not taking any antihypertensive drugs and not acutely ill. When systolic and diastolic pressures fall into different categories, the higher category should be selected to classify BP status. For example, 160/92 mm Hg should be classified as stage 2 hypertension. Isolated systolic hypertension is defined as systolic BP of 140 mm Hg or higher and diastolic BP below 90 mm Hg and staged appropriately (eg, 170/82 is defined as stage 2 isolated systolic hypertension). Data from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 289:2560–2572, 2003.

pared with 130/85 in JNC 6. Why were the cutoff values reduced? Because the values from JNC 6 are not as safe as previously believed.

Prehypertension. Prehypertension is defined as systolic BP of 120 to 139 mm Hg or diastolic BP of 80 to 89 mm Hg. BP in this range carries an increased risk of cardiovascular disease, even though outright hypertension has not yet developed. Data from the Framingham Heart Study show that, relative to people with normal BP, those with BP in the prehypertension range have a two- to threefold increased risk of cardiovascular events. To reduce risk, these people should adopt certain health-promoting lifestyle changes (see below). Prehypertension affects about 30% of American adults (about 60 million people).

Hypertension. Hypertension is defined as systolic BP above 140 mm Hg or diastolic BP above 90 mm Hg. If systolic BP is above 140 mm Hg and diastolic BP is below 90 mm Hg, a diagnosis of *isolated systolic hypertension* (ISH) applies. When systolic BP and diastolic BP fall in different categories, BP classification is based on the higher category. For example, a reading of 160/92 mm Hg indicates stage 2 hypertension, and a reading of 170/82 indicates stage 2 ISH.

TYPES OF HYPERTENSION

There are two broad categories of hypertension: *primary hypertension* and *secondary hypertension*. As indicated in Table 47-2, primary hypertension is by far the most common form of hypertensive disease. Less than 10% of people with hypertension have a secondary form.

Primary (Essential) Hypertension

Primary hypertension is defined as hypertension that has no identifiable cause. A diagnosis of primary hypertension is made by ruling out probable specific causes of BP elevation. Primary hypertension is a chronic, progressive disorder. In the absence of treatment, patients will experience a continuous, gradual rise in BP over the rest of their lives.

TABLE 47-2 ■ Types of Hypertension and Their Frequency

Type of Hypertension	Frequency (%)
Primary (Essential) Hypertension	92
Secondary Hypertension	
Chronic renal disease	4
Renovascular disease	2
Oral contraceptive-induced	1
Coarctation of the aorta	0.3
Primary aldosteronism	0.2
Cushing's syndrome	0.1
Pheochromocytoma	0.1
Sleep apnea	?
Thyroid or parathyroid disease	?

In the United States, primary hypertension affects about 30% of adults. However, not all groups are at equal risk: Older people are at higher risk than younger people; African Americans and Hispanic Americans are at higher risk than white Americans; postmenopausal women are at higher risk than premenopausal women; and obese people are at higher risk than lean people.

Although the cause of primary hypertension is unknown, the condition *can* be successfully treated. Please understand, however, that treatment is not curative: Drugs can lower BP, but they can't eliminate the underlying pathology. Consequently, treatment must continue lifelong.

Primary hypertension is also referred to as *essential hypertension*. This alternative name preceded the term *primary hypertension* and reflects our ignorance about the cause of the problem. Historically, it had been noted that, as people grew older, their BP rose. Why older people had elevated BP was (and remains) unknown. One hypothesis noted that, as people aged, their vascular systems offered greater resistance to blood flow. In order to move blood against this increased resistance, a compensatory increase in BP was required. Therefore, the hypertension that occurred with age was seen as being "essential" for providing adequate tissue perfusion—hence, the term *essential hypertension*. Over time, the term came to be applied to all cases of hypertension for which an underlying cause could not be found.

Secondary Hypertension

Secondary hypertension is defined as an elevation of BP brought on by an identifiable primary cause. The most common are listed in Table 47-2.

Because secondary hypertension results from an identifiable cause, it may be possible to treat that cause directly, rather than relying on antihypertensive drugs for symptomatic relief. As a result, some individuals can actually be cured. For example, if hypertension occurs secondary to pheochromocytoma (a catecholamine-secreting tumor), surgical removal of the tumor may produce permanent cure. When cure is not possible, secondary hypertension can be managed with the same drugs used for primary hypertension.

BOX 47-1 ■ SPECIAL INTEREST TOPIC

ISOLATED SYSTOLIC HYPERTENSION:
THE REAL KILLER OF AGING AMERICANS

Over the past 20 years, several large randomized clinical trials involving older hypertensive patients have produced unequivocal evidence that, compared with elevated *diastolic* BP, elevated *systolic* BP is the stronger predictor of cardiovascular disease, kidney disease, stroke, and death. Additional studies have shown that, when elevated systolic BP is reduced, there is a corresponding reduction in the incidence of kidney failure, heart failure, MI, stroke, and death. Accordingly, in 2000, the Coordinating Committee of the National High Blood Pressure Education Program issued a clinical advisory recommending that systolic BP—rather than diastolic BP—be used as the major clinical endpoint for the detection, evaluation, and treatment of hypertension, especially in middle-aged and older Americans. The importance of elevated systolic pressure is reflected in the recommendations of JNC 7, released in 2003.

Some readers may be asking, “What’s new here? I mean, hasn’t elevated systolic BP always been a concern?” Well, no, it hasn’t. In fact, until recently, isolated systolic hypertension (ISH)—defined as systolic BP above 140 mm Hg and diastolic BP below 90 mm Hg—was considered a relatively benign condition that did not merit treatment. After all, most experts agreed that, in people with hypertension, elevated diastolic BP—not elevated systolic BP—was the principal cause of morbidity and mortality. Of course, this view has been proven dead wrong.

ISH is primarily a disease of the elderly. As we grow older, systolic BP gradually rises. The underlying cause is increased stiffness (reduced compliance) in large arteries—owing to progressive replacement of elastin with collagen in the arterial wall. Among older Americans, ISH is the most common form of hypertension: Of all hypertensive individuals over the age of 70, over 90% have ISH. Because of their ISH, older people are at increased risk, as demonstrated in the Multiple Risk Factor

Intervention Trial (MRFIT), which evaluated over 316,000 men and found a nearly linear relationship between increased systolic BP and increased risk of adverse cardiovascular events.

Does lowering elevated systolic BP reduce cardiovascular risk? Yes indeed! The benefits of treating ISH have been documented in several large, randomized controlled trials. Important among these are the Systolic Hypertension in the Elderly Program (SHEP) and the Systolic Hypertension in Europe (Syst-Eur) trial. An analysis of the results of these trials indicated that lowering systolic BP decreased overall mortality by 13%, cardiovascular mortality by 18%, cardiovascular complications by 26%, coronary events by 23%, and stroke by 30%.

Unfortunately, among people with ISH, control of BP is generally poor. For most hypertensive people, the target BP is 140/90 mm Hg. However, among elderly African Americans, only 25% achieve this goal. And among white Americans, the success rate is even worse: Only 18% achieve the goal. This low success rate is both sad and troubling, in that it means many people will experience unnecessary morbidity and mortality.

The low rate of BP control in the elderly, coupled with our heightened appreciation of the dangers of ISH, led the Coordinating Committee to issue its advisory. As noted, the Committee recommended that systolic BP, rather than diastolic BP, be the major consideration in the detection, evaluation, and treatment of hypertension—especially in older Americans. The Committee recommended using either a low-dose thiazide diuretic (with or without a beta blocker) or a long-acting dihydropyridine CCB for initial treatment. These recommendations were based in part on the successful use of these drugs in the SHEP and Syst-Eur trials. Although ACE inhibitors were not recommended by the Committee, recent evidence indicates that these drugs too can reduce the risk of stroke, MI, heart failure, and death in older hypertensive people.

CONSEQUENCES OF HYPERTENSION

Chronic hypertension is associated with increased morbidity and mortality. Left untreated, prolonged elevation of BP can lead to heart disease (myocardial infarction [MI], heart failure, angina pectoris), kidney disease, and stroke. The degree of injury is directly related to the degree of pressure elevation: The higher the pressure, the greater the risk. Among people 40 to 70 years old, the risk of cardiovascular disease is doubled for each 20 mm Hg increase in systolic BP or each 10 mm Hg increase in diastolic BP—beginning at 115/75 mm Hg and continuing through 185/155 mm Hg. For people over the age of 50, elevated *systolic* BP poses a greater risk than elevated *diastolic* BP (Box 47-1). For patients of all ages, hypertension-related deaths result largely from cerebral hemorrhage, renal failure, heart failure, and MI.

Unfortunately, despite its potential for serious harm, hypertension usually remains asymptomatic until long after injury has begun to develop. As a result, the disease can exist for years before overt pathology is evident. Because injury develops slowly and progressively, and because hypertension

rarely causes discomfort, many people who have the disease don’t know it. Furthermore, many who do know it forgo treatment anyway, largely because hypertension doesn’t make them feel bad—that is, until it’s too late.

MANAGEMENT OF CHRONIC HYPERTENSION

In this section we consider treatments for chronic hypertension. We begin by addressing patient evaluation and other basic issues, after which we discuss the two modes of management: lifestyle modifications and drug therapy.

BASIC CONSIDERATIONS

Diagnosis

According to JNC 7, diagnosis should be based on several BP readings, not just one. If an initial screen shows that BP is elevated (but does not represent an immediate danger), measurement should be repeated on two subsequent office visits.

TABLE 47-3 • Overview of Blood Pressure Management in Adults 18 Years and Older

BP Classification	Therapeutic Interventions	Blood Pressure Goal	
		Patients <i>Without</i> Diabetes or Chronic Kidney Disease	Patients <i>With</i> Diabetes or Chronic Kidney Disease
Normal	Encourage lifestyle changes	Prevent increase	Prevent increase
Prehypertension	Initiate lifestyle changes	Prevent increase/promote decrease	Prevent increase/promote decrease
Stage 1 Hypertension	Initiate or continue lifestyle changes and begin antihypertensive drug therapy	<140/<90 mm Hg	<130/<80 mm Hg
Stage 2 Hypertension	Initiate or continue lifestyle changes and begin or intensify antihypertensive drug therapy	<140/<90 mm Hg	<130/<80 mm Hg

Recommendations from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 289:2560–2572, 2003.

At each visit, two measurements should be made, at least 5 minutes apart. The patient should be seated in a chair—not on an examination table—with his or her feet on the floor. High readings should be confirmed in the contralateral arm. If the mean of all readings shows that systolic BP is indeed greater than 140 mm Hg or that diastolic BP is greater than 90 mm Hg, a diagnosis of hypertension can be made.

Ideally, diagnosis would be based on *ambulatory blood pressure monitoring* (ABPM). Why? Because office-based measurements are often abnormally high, causing individuals to be diagnosed with hypertension when they don't really have it. By contrast, when BP is measured with ABPM, false-positive diagnoses can be avoided. Accordingly, some experts recommend that office-based measurements be used only for *screening*, and that treatment be postponed until the diagnosis is confirmed using ABPM. In this way, the risks and expense of unnecessary treatment will be avoided.

Benefits of Lowering Blood Pressure

Multiple clinical trials have demonstrated unequivocally that, when the BP of hypertensive individuals is lowered, morbidity is decreased and life is prolonged. Treatment reduces the incidence of stroke by 35% to 40%, MI by 20% to 25%, and heart failure by more than 50%. Although reductions in morbidity are not as dramatic, they are nonetheless significant: Among patients with stage 1 hypertension plus additional cardiovascular risk factors, one death would be prevented for every 11 patients who reduced systolic pressure by 12 mm Hg for a period of 10 years—and among those with hypertension plus cardiovascular disease or target-organ damage, one death would be prevented for every 9 patients who achieved a sustained 12 mm Hg reduction in pressure.

Patient Evaluation

Evaluation of patients with hypertension has two major objectives. Specifically, we must assess for (1) identifiable causes of hypertension, and (2) factors that increase cardiovascular risk. To aid evaluation, diagnostic tests are required.

Hypertension with a Treatable Cause. As discussed above, some forms of hypertension result from a treatable

cause, such as Cushing's syndrome, pheochromocytoma, and use of oral contraceptives (see Table 47-2). Patients should be evaluated for these causes and managed appropriately. In many cases, direct treatment of the underlying cause can control BP, thereby eliminating the need for further antihypertensive therapy.

Factors That Increase Cardiovascular Risk. Two types of factors—existing target-organ damage and major cardiovascular risk factors—increase the risk of cardiovascular events in people with hypertension. When these factors are present, aggressive therapy is indicated. Accordingly, in order to select appropriate interventions, we must identify patients with the following types of *target-organ damage*:

- Heart disease
 - Left ventricular hypertrophy
 - Angina pectoris
 - Prior MI
 - Prior coronary revascularization
 - Heart failure
- Stroke or transient ischemic attack
- Chronic kidney disease
- Peripheral arterial disease
- Retinopathy

as well as patients with the following *major cardiovascular risk factors* (other than hypertension):

- Cigarette smoking
- Obesity
- Inadequate exercise
- Dyslipidemia
- Diabetes
- Microalbuminuria
- Advancing age (above 55 years for men, above 65 years for women)
- Family history of premature cardiovascular disease

Diagnostic Tests. The following tests should be done in all patients: electrocardiogram; complete urinalysis; hemoglobin and hematocrit; and blood levels of sodium, potassium,

calcium, creatinine, glucose, uric acid, triglycerides, and cholesterol (total, LDL, and HDL cholesterol).

Treatment Goals

The ultimate goal in treating hypertension is to reduce cardiovascular and renal morbidity and mortality. Hopefully, this can be accomplished without decreasing quality of life with the drugs employed. For most patients with stage 1 or stage 2 hypertension, the goal is to maintain systolic BP below 140 mm Hg and diastolic BP below 90 mm Hg. For patients with diabetes or chronic kidney disease, the target BP is lower: 130/80 mm Hg. As discussed later in the chapter, treatment of elderly patients focuses on *systolic* pressure. The treatment goal is a pressure below 140 mm Hg (for patients ages 65 to 79) or below 145 mm Hg (for patients age 80 and older).

Therapeutic Interventions

We can reduce BP in two ways: We can implement healthy lifestyle changes and we can treat with antihypertensive drugs. As shown in Table 47-3, for people with *prehypertension*, lifestyle changes are all that is needed. In contrast, for those with *hypertension*—either stage 1 or stage 2—a *combination* of lifestyle changes and drugs is indicated. Lifestyle changes and drug therapy are discussed in detail below.

LIFESTYLE MODIFICATIONS

Lifestyle changes offer multiple cardiovascular benefits—and they do so with little cost and minimal risk. When implemented before hypertension develops, they may actually prevent hypertension. When implemented after hypertension has developed, they can lower BP, thereby decreasing or eliminating the need for drugs. Lastly, lifestyle modifications can decrease other cardiovascular risk factors. Accordingly, all patients should be strongly encouraged to adopt a healthy lifestyle. Key components are discussed below.

Weight Loss. There is a direct relationship between obesity and elevation of BP. Fortunately, weight loss can reduce BP in 60% to 80% of overweight hypertensive individuals. In addition, weight loss can enhance responses to antihypertensive drugs. Consequently, a program of calorie restriction and exercise is recommended for all patients who are overweight. The goal is to achieve a body mass index in the normal range (18.5 to 24.9).*

Sodium Restriction. Reducing sodium chloride (salt) intake can lower BP in people with hypertension, and can help prevent overt hypertension in those with prehypertension. In addition, salt restriction can enhance the hypotensive effects of drugs. However, the benefits of sodium restriction are both small and short lasting: Over time, BP returns to its original level, despite continued salt restriction. Nonetheless, JNC 7 recommends that all people with hypertension consume no more than 6 gm of sodium chloride (2.4 gm of sodium) a day. The Institute of Medicine recommends even lower salt consumption: 3.8 gm/day for adults age 50 and younger, 3.2 gm/day for adults ages 51 to 70, and 2.9 gm/day for adults age 71 and older. To facilitate salt restriction, patients should be given information on the salt content of foods.

*The definition and calculation of body mass index are presented in Chapter 82.

Experts disagree about the relationship between salt intake and BP in *normotensive* patients. In particular, they disagree as to whether a high-salt diet *causes* hypertension. Hence, for people with normal BP, a low-salt diet may be considered healthy or unnecessary, depending on the expert you consult.

The DASH Eating Plan. Two studies have shown that we can reduce BP by adopting a healthy diet, known as the Dietary Approaches to Stop Hypertension (DASH) eating plan. This diet is rich in fruits, vegetables, and low-fat dairy products, and low in total fat, saturated fats, and cholesterol. In addition, the plan encourages intake of whole-grain products, fish, poultry, and nuts, and recommends minimal intake of red meat and sweets. Details are available online at www.nhlbi.nih.gov/health/public/heart/hbp/dash.

Alcohol Restriction. Excessive alcohol consumption can raise BP and create resistance to antihypertensive drugs. Accordingly, patients should limit alcohol intake: Most men should consume no more than 1 ounce/day; women and lighter weight men should consume no more than 0.5 ounce/day. (One ounce of ethanol is equivalent to about two mixed drinks, two glasses of wine, or two cans of beer.)

Aerobic Exercise. Regular aerobic exercise (eg, jogging, walking, swimming, bicycling) can reduce BP by about 10 mm Hg. In addition, exercise facilitates weight loss, reduces the risk of cardiovascular disease, and reduces all-cause mortality. In normotensive people, exercise decreases the risk of developing hypertension. Accordingly, all people with a sedentary lifestyle should be encouraged to develop an exercise program. An activity as simple as brisk walking 30 to 45 minutes most days of the week is beneficial.

Smoking Cessation. Smoking is a major risk factor for cardiovascular disease. Each time a cigarette is smoked, BP rises. In patients with hypertension, smoking can reduce the effects of antihypertensive drugs. Clearly, all patients who smoke should be strongly encouraged to quit. (Pharmacologic aids to smoking cessation are discussed in Chapter 39.) As a rule, use of nicotine replacement products (eg, nicotine gum, nicotine patch) does not elevate BP. The cardiovascular benefits of quitting become evident within 1 year.

Maintenance of Potassium and Calcium Intake. Potassium has a beneficial effect on BP. In patients with hypertension, potassium can lower BP. In normotensive people, high potassium intake helps protect against hypertension, whereas low intake elevates BP. For optimal cardiovascular effects, all people should take in 50 to 90 mmol of potassium a day. Preferred sources are fresh fruits and vegetables. If hypokalemia develops secondary to diuretic therapy, dietary intake may be insufficient to correct the problem. In this case, the patient may need to use a potassium supplement, a potassium-sparing diuretic, or a potassium-containing salt substitute.

Although adequate calcium is needed for overall good health, the impact of calcium on BP is only modest. In epidemiologic studies, high calcium intake is associated with a reduced incidence of hypertension. Among patients with hypertension, a few may be helped by increasing calcium intake. To maintain good health, calcium intake should be 1000 mg/day (for males ages 19 to 70, and females ages 19 to 50), and 1200 mg/day (for males over age 70, and females over age 50).

DRUG THERAPY

Drug therapy, together with lifestyle modifications, can control BP in all patients with chronic hypertension. The decision to use drugs should be the result of collaboration between prescriber and patient. We have a wide assortment of antihypertensive drugs. Consequently, for the majority of patients, it should be possible to establish a program that is effective and yet devoid of objectionable side effects.

Review of Blood Pressure Control

Before discussing the antihypertensive drugs, we need to review the major mechanisms by which BP is controlled. This information will help you understand the mechanisms by which drugs lower BP.

Principal Determinants of Blood Pressure

The principal determinants of BP are summarized in Figure 47-1. As indicated, arterial pressure is the product of cardiac output and peripheral resistance. An increase in either will increase BP.

Cardiac Output. Cardiac output is influenced by four factors: (1) heart rate, (2) myocardial contractility (force of contraction), (3) blood volume, and (4) venous return of blood to the heart. An increase in any of these will increase cardiac output, thereby causing BP to rise. Conversely, a decrease in these factors will make BP fall. Hence, to reduce BP, we might give a beta blocker to reduce cardiac output, or a diuretic to reduce blood volume, or a venodilator to reduce venous return.

Peripheral Vascular Resistance. Vascular resistance is increased by arteriolar constriction. Accordingly, we can reduce BP with drugs that promote arteriolar dilation.

Systems That Help Regulate Blood Pressure

Having established that BP is determined by heart rate, myocardial contractility, blood volume, venous return, and arteriolar constriction, we can now examine how these factors are regulated. Three regulatory systems are of particular significance: (1) the sympathetic nervous system, (2) the renin-angiotensin-aldosterone system (RAAS), and (3) the kidney.

Sympathetic Baroreceptor Reflex. The sympathetic nervous system employs a reflex circuit—the baroreceptor reflex—to keep BP at a preset level. This circuit operates as follows: (1) Baroreceptors in the aortic arch and carotid sinus sense BP and relay this information to the brainstem. (2) When BP is perceived as too low, the brainstem sends impulses along sympathetic nerves to stimulate the heart and blood vessels. (3) BP is then elevated by (a) activation of beta₁ receptors in the heart, resulting in increased cardiac output; and (b) activation of vascular alpha₁ receptors, resulting in vasoconstriction. (4) When BP has been restored to an acceptable level, sympathetic stimulation of the heart and vascular smooth muscle subsides.

The baroreceptor reflex frequently opposes our attempts to reduce BP with drugs. Opposition occurs because the “set point” of the baroreceptors is high in people with hypertension. That is, the baroreceptors are set to perceive excessively high BP as “normal” (ie, appropriate). As a result, the system operates to maintain BP at pathologic levels. Consequently, when we attempt to lower BP using drugs, the reduced

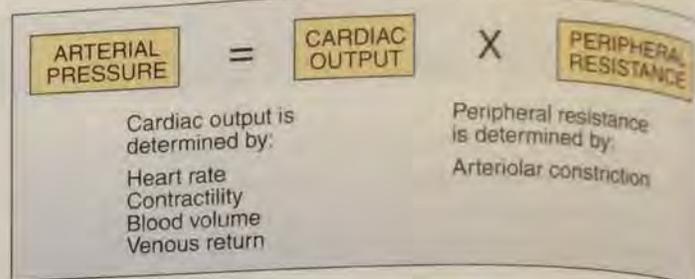


Figure 47-1 • Primary determinants of arterial blood pressure.

(healthier) pressure is interpreted by the baroreceptors as below what it should be, and, in response, signals are sent along sympathetic nerves to “correct” the reduction. These signals produce reflex tachycardia and vasoconstriction—responses that can counteract the hypotensive effects of drugs. Clearly, if treatment is to succeed, the regimen must compensate for the resistance offered by this reflex. Taking a *beta blocker*, which will block reflex tachycardia, can be an effective method of compensation. Fortunately, when BP has been suppressed with drugs for an extended time, the baroreceptors become reset at a lower level. Consequently, as therapy proceeds, sympathetic reflexes offer progressively less resistance to the hypotensive effects of medication.

Renin-Angiotensin-Aldosterone System. The RAAS can elevate BP, thereby negating the hypotensive effects of drugs. The RAAS is discussed at length in Chapter 44 and reviewed briefly here.

How does the RAAS elevate BP? The process begins with the release of renin from juxtaglomerular cells of the kidney. These cells release renin in response to reduced renal blood flow, reduced blood volume, reduced BP, and activation of beta₁-adrenergic receptors on the cell surface. Following its release, *renin* catalyzes the conversion of angiotensinogen into angiotensin I, a weak vasoconstrictor. After this, *angiotensin-converting enzyme* (ACE) acts on angiotensin I to form *angiotensin II*, a compound that constricts systemic and renal blood vessels. Constriction of systemic blood vessels elevates BP by increasing peripheral resistance. Constriction of renal blood vessels elevates BP by reducing glomerular filtration, which causes retention of salt and water, which in turn increases blood volume and BP. In addition to causing vasoconstriction, angiotensin II causes release of *aldosterone* from the adrenal cortex. Aldosterone acts on the kidney to further increase retention of sodium and water.

Since drug-induced reductions in BP can activate the RAAS, this system can counteract the effect we are trying to achieve. We have five ways to cope with this problem. First, we can suppress renin release with *beta blockers*. Second, we can prevent conversion of angiotensinogen to angiotensin I with a *direct renin inhibitor*. Third, we can prevent the conversion of angiotensin I into angiotensin II with an *ACE inhibitor*. Fourth, we can block receptors for angiotensin II with an *angiotensin II receptor blocker*. And fifth, we can block receptors for aldosterone with an *aldosterone antagonist*.

Renal Regulation of Blood Pressure. As discussed in Chapter 43, the kidney plays a central role in long-term regulation of BP. When BP falls, glomerular filtration rate (GFR) falls too, thereby promoting retention of sodium chloride.

and water. The resultant increase in blood volume increases venous return to the heart, causing an increase in cardiac output, which in turn increases arterial pressure. We can neutralize renal effects on BP with *diuretics*.

Antihypertensive Mechanisms: Sites of Drug Action and Effects Produced

As discussed above, drugs can lower BP by reducing heart rate, myocardial contractility, blood volume, venous return, and the tone of arteriolar smooth muscle. In this section we

survey the principal mechanisms by which drugs produce these effects.

The major mechanisms for lowering BP are summarized in Figure 47-2 and Table 47-4. The figure depicts the principal sites at which antihypertensive drugs act. The table summarizes the effects elicited when drugs act at these sites. The numbering system used below corresponds with the system used in Figure 47-2 and Table 47-4.

1—Brainstem. Antihypertensive drugs acting in the brainstem suppress sympathetic outflow to the heart and blood vessels, resulting in decreased heart rate, decreased

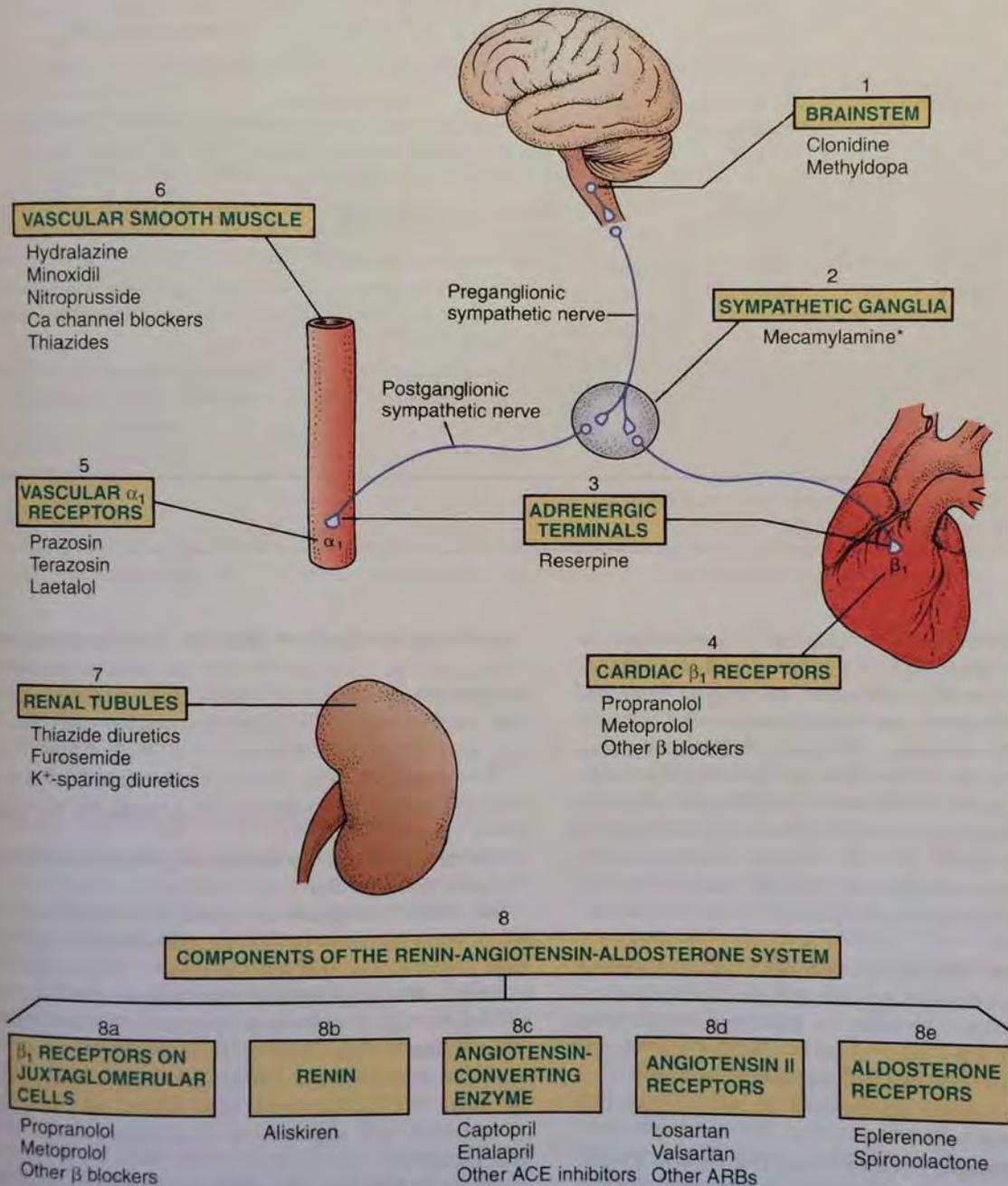


Figure 47-2 • Sites of action of antihypertensive drugs.

Note that some antihypertensive agents act at more than one site: beta blockers act at sites 4 and 8a, and thiazides act at sites 6 and 7. The hemodynamic consequences of drug actions at the sites depicted are summarized in Table 47-4. (ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker.)

*No longer available in the United States.

TABLE 47-4 ■ Summary of Antihypertensive Effects Elicited by Drug Actions at Specific Sites

Site of Drug Action*	Representative Drug	Drug Effects
1. Brainstem	Clonidine	Suppression of sympathetic outflow decreases sympathetic stimulation of the heart and blood vessels.
2. Sympathetic ganglia	Mecamylamine [†]	Ganglionic blockade reduces sympathetic stimulation of the heart and blood vessels.
3. Adrenergic nerve terminals	Reserpine	Reduced norepinephrine release decreases sympathetic stimulation of the heart and blood vessels.
4. Cardiac beta ₁ receptors	Propranolol	Beta ₁ blockade decreases heart rate and myocardial contractility.
5. Vascular alpha ₁ receptors	Prazosin	Alpha ₁ blockade causes vasodilation.
6. Vascular smooth muscle	Hydralazine	Relaxation of vascular smooth muscle causes vasodilation.
7. Renal tubules	Hydrochlorothiazide	Promotion of diuresis decreases blood volume.
<i>Components of the renin-angiotensin-aldosterone system (8a to 8e)</i>		
8a. Beta ₁ receptors on juxtaglomerular cells	Propranolol	Beta ₁ blockade suppresses renin release, resulting in (1) vasodilation secondary to reduced production of angiotensin II, and (2) prevention of aldosterone-mediated volume expansion.
8b. Renin	Aliskiren	Inhibition of renin suppresses formation of angiotensin I, which in turn decreases formation of angiotensin II, and thereby reduces (1) vasoconstriction and (2) aldosterone-mediated volume expansion.
8c. Angiotensin-converting enzyme (ACE)	Captopril	Inhibition of ACE decreases formation of angiotensin II and thereby prevents (1) vasoconstriction, and (2) aldosterone-mediated volume expansion.
8d. Angiotensin II receptors	Losartan	Blockade of angiotensin II receptors prevents angiotensin-mediated vasoconstriction and aldosterone-mediated volume expansion.
8e. Aldosterone receptors	Eplerenone	Blockade of aldosterone receptors in the kidney promotes excretion of sodium and water, and thereby reduces blood volume.

*Site numbers in this table correspond with site numbers in Figure 47-2.

[†]No longer available in the United States.

myocardial contractility, and vasodilation. Vasodilation contributes the most to reducing BP. Dilation of arterioles reduces BP by decreasing vascular resistance. Dilation of veins reduces BP by decreasing venous return to the heart.

2—Sympathetic Ganglia. Ganglionic blockade reduces sympathetic stimulation of the heart and blood vessels. Antihypertensive effects result primarily from dilation of arterioles and veins. Ganglionic blocking agents produce such a profound reduction in BP that they are used rarely, and then only for hypertensive emergencies. Because use is so limited, the last one available—mecamylamine—was voluntarily withdrawn in 2009.

3—Terminals of Adrenergic Nerves. Antihypertensive agents that act at adrenergic nerve terminals decrease the release of norepinephrine, resulting in decreased sympathetic stimulation of the heart and blood vessels. These drugs, known as adrenergic neuron blocking agents, are used only rarely. In the United States, reserpine is the only drug in this class still on the market.

4—Beta₁-Adrenergic Receptors on the Heart. Blockade of cardiac beta₁ receptors prevents sympathetic stimulation of the heart. As a result, heart rate and myocardial contractility decline.

5—Alpha₁-Adrenergic Receptors on Blood Vessels. Blockade of vascular alpha₁ receptors promotes dilation of arterioles and veins. Arteriolar dilation reduces peripheral resistance. Venous dilation reduces venous return to the heart.

6—Vascular Smooth Muscle. Several antihypertensive drugs (see Fig. 47-2) act directly on vascular smooth muscle to cause relaxation. One of these agents—sodium nitropruside—is used only for hypertensive emergencies. The rest are used for chronic hypertension.

7—Renal Tubules. Diuretics act on renal tubules to promote salt and water excretion. As a result, blood volume declines, causing BP to fall.

Components of the Renin-Angiotensin-Aldosterone System (8a to 8e)

8a—Beta₁ Receptors on Juxtaglomerular Cells. Blockade of beta₁ receptors on juxtaglomerular cells suppresses release of renin. The resultant decrease in angiotensin II levels has three effects: peripheral vasodilation, renal vasodilation, and suppression of aldosterone-mediated volume expansion.

8b—Renin. Inhibition of renin decreases conversion of angiotensinogen into angiotensin I, and thereby suppresses the entire RAAS. The result is peripheral vasodilation, renal vasodilation, and suppression of aldosterone-mediated volume expansion.

8c—Angiotensin-Converting Enzyme. Inhibitors of ACE suppress formation of angiotensin II. The result is peripheral vasodilation, renal vasodilation, and suppression of aldosterone-mediated volume expansion.

8d—Angiotensin II Receptors. Blockade of angiotensin II receptors prevents the actions of angiotensin II. Hence blockade results in peripheral vasodilation, renal vasodila-

TABLE 47-5 ■ Drugs for Chronic Hypertension

Diuretics	Sympatholytics	RAAS Suppressants	Others
Thiazides and Related Diuretics	Beta Blockers	ACE Inhibitors	Direct-Acting Vasodilators
Bendroflumethiazide	Acebutolol (has ISA)	Benazepril	Hydralazine
Benzthiazide	Atenolol	Captopril	Minoxidil
Chlorothiazide	Betaxolol	Enalapril	Calcium Channel Blockers
Chlorthalidone	Bisoprolol	Fosinopril	Amlodipine
Cyclothiazide	Carteolol (has ISA)	Lisinopril	Diltiazem (non-DHP)
Hydrochlorothiazide	Metoprolol	Moexipril	Felodipine
Hydroflumethiazide	Nadolol	Quinapril	Isradipine
Indapamide	Nebivolol	Ramipril	Nicardipine
Methyclothiazide	Penbutolol (has ISA)	Trandolapril	Nifedipine
Metolazone	Pindolol (has ISA)	Angiotensin II Receptor Blockers	Nimodipine
Polythiazide	Propranolol	Candesartan	Nisoldipine
Quinethazone	Timolol	Eprosartan	Verapamil (non-DHP)
Trichlormethiazide	Alpha₁ Blockers	Irbesartan	
Loop Diuretics	Doxazosin	Losartan	
Bumetanide	Prazosin	Olmesartan	
Ethacrynic acid	Terazosin	Telmisartan	
Furosemide	Alpha/Beta Blockers	Valsartan	
Torsemide	Carvedilol	Direct Renin Inhibitor	
Potassium-Sparing Diuretics	Labetalol	Aliskiren	
Amiloride	Centrally Acting Alpha₂ Agonists	Aldosterone Antagonists	
Spironolactone	Clonidine	Eplerenone	
Triamterene	Guanabenz	Spironolactone	
	Guanfacine		
	Methyldopa		
	Adrenergic Neuron Blockers		
	Reserpine		

DHP = dihydropyridine, ISA = intrinsic sympathomimetic activity, RAAS = renin-angiotensin-aldosterone system.

tion, and suppression of aldosterone-mediated volume expansion.

8e—Aldosterone Receptors. Blockade of aldosterone receptors in the kidney promotes excretion of sodium and water, and thereby reduces blood volume.

Classes of Antihypertensive Drugs

In this section we consider the principal drugs employed to treat chronic hypertension. Drugs for hypertensive emergencies and hypertensive disorders of pregnancy are considered separately.

Individual antihypertensive drugs and their classes are summarized in Table 47-5. Combination products are summarized in Table 47-6. All of these drugs have been discussed in previous chapters. Accordingly, discussion here is limited to their use in hypertension. Of primary interest are mechanisms of antihypertensive action and major adverse effects.

Diuretics

Diuretics are a mainstay of antihypertensive therapy. These drugs reduce BP when used alone, and they can enhance the effects of other hypotensive drugs. The basic pharmacology of the diuretics is discussed in Chapter 41.

Thiazide Diuretics. Thiazide diuretics (eg, hydrochlorothiazide, chlorthalidone) are first-line drugs for hypertension. They reduce BP by two mechanisms: reduction of blood volume and reduction of arterial resistance. Reduced blood vol-

ume is responsible for initial antihypertensive effects. Reduced vascular resistance develops over time and is responsible for long-term antihypertensive effects. The mechanism by which thiazides reduce vascular resistance has not been determined.

Of the thiazides available, hydrochlorothiazide is used most widely. In fact, hydrochlorothiazide is used more widely than any other antihypertensive drug. Nonetheless, other thiazides, especially chlorthalidone, may be more effective.

The principal adverse effect of thiazides is *hypokalemia*. This can be minimized by consuming potassium-rich foods (eg, bananas, citrus fruits) and using potassium supplements or a potassium-sparing diuretic. Other side effects include *dehydration*, *hyperglycemia*, and *hyperuricemia*.

As discussed in Box 47-2, thiazides are superior to calcium channel blockers and ACE inhibitors as monotherapy, and hence are preferred to these more expensive drugs.

High-Ceiling (Loop) Diuretics. High-ceiling diuretics (eg, furosemide) produce much greater diuresis than the thiazides. For most individuals with chronic hypertension, the amount of fluid loss that loop diuretics can produce is greater than needed or desirable. Consequently, loop diuretics are not used routinely. Rather, they are reserved for (1) patients who need greater diuresis than can be achieved with thiazides and (2) patients with a low GFR (because thiazides won't work when GFR is low). Like the thiazides, the loop diuretics lower BP by reducing blood volume and promoting vasodilation.

TABLE 47-6 ■ Combination Products for Chronic Hypertension

Generic Name	Trade Name
TWO-DRUG COMBINATIONS	
Thiazide Plus a Beta Blocker	
Hydrochlorothiazide + atenolol	generic only
Hydrochlorothiazide + metoprolol	Lopressor HCT
Hydrochlorothiazide + bisoprolol	Ziac
Hydrochlorothiazide + pindolol	Viskazine ♦
Bendroflumethiazide + nadolol	Corzide
Chlorthalidone + atenolol	Tenoretic
Thiazide Plus an ACE Inhibitor	
Hydrochlorothiazide + captopril	Capozide
Hydrochlorothiazide + benazepril	Lotensin HCT
Hydrochlorothiazide + enalapril	Vaseretic
Hydrochlorothiazide + fosinopril	Monopril HCT
Hydrochlorothiazide + lisinopril	Prinzide, Zestoretic
Hydrochlorothiazide + moexipril	Uniretic
Hydrochlorothiazide + quinapril	Accuretic, Quinaretic
Indapamide + perindopril	Coversyl Plus ♦
Thiazide Plus an ARB	
Hydrochlorothiazide + losartan	Hyzaar
Hydrochlorothiazide + valsartan	Diovan HCT
Hydrochlorothiazide + candesartan	Atacand HCT
Hydrochlorothiazide + eprosartan	Teveten HCT
Hydrochlorothiazide + irbesartan	Avalide
Hydrochlorothiazide + telmisartan	Micardis HCT
Hydrochlorothiazide + olmesartan	Benicar HCT, Olmetec Plus ♦
Thiazide Plus a Potassium-Sparing Diuretic	
Hydrochlorothiazide + spironolactone	Aldactazide
Hydrochlorothiazide + triamterene	Dyazide, Maxzide
Hydrochlorothiazide + amiloride	Moduretic
Thiazide Plus an Alpha₂ Agonist	
Chlorthalidone + clonidine	Clorpres
Hydrochlorothiazide + methyldopa	generic only
Thiazide Plus a Direct-Acting Vasodilator	
Hydrochlorothiazide + hydralazine	generic only
CCB Plus an ACE Inhibitor	
Amlodipine + benazepril	Lotrel
Felodipine + enalapril	Lexxel
Verapamil + trandolapril	Tarka
CCB Plus an ARB	
Amlodipine + olmesartan	Azor
Amlodipine + valsartan	Exforge
Amlodipine + telmisartan	Twynsta
Aliskiren (a DRI) Plus Another Drug	
Aliskiren + amlodipine	Tekamlo
Aliskiren + hydrochlorothiazide	Tekturna HCT, Rasilez HCT ♦
Aliskiren + valsartan	Valturna
THREE-DRUG COMBINATIONS	
Hydrochlorothiazide + amlodipine + valsartan	Exforge HCT
Hydrochlorothiazide + amlodipine + olmesartan	Tribenzor
Hydrochlorothiazide + amlodipine + aliskiren	Amturnide

ACE = angiotensin converting enzyme, ARB = angiotensin II receptor blocker, CCB = calcium channel blocker, DRI = direct renin inhibitor.

BOX 47-2 ■ SPECIAL INTEREST TOPIC

AND THE BEST DRUG IS . . . THE CHEAP ONE!

Results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),¹ published in 2002, show unequivocally that the least expensive drugs for hypertension, the thiazide diuretics, are also the most effective—a welcome revelation in these cost-conscious times. ALLHAT is an important trial that has had a profound impact on clinical practice.

ALLHAT was a large, double-blind trial that compared the impact of four antihypertensive drugs—chlorthalidone (a thiazide diuretic), amlodipine (a CCB), lisinopril (an ACE inhibitor), and doxazosin (an alpha blocker)—on the incidence of adverse cardiovascular (CV) events. The study enrolled 33,357 patients, including more women (47%), blacks (32%), and Hispanics (19%) than most earlier trials. All participants had stage 1 or stage 2 hypertension plus at least one additional risk factor for coronary heart disease (CHD). The mean follow-up time was 4.9 years.

The results? With one drug—doxazosin—the incidence of adverse CV events was substantially higher than with the others, and hence this arm of the study was terminated early. Effects of the remaining three drugs—chlorthalidone, amlodipine, and lisinopril—were similar in some respects but significantly different in others. With all three, rates of (1) fatal CHD or nonfatal heart attacks and (2) all-cause mortality were identical. However, in other ways, chlorthalidone was clearly superior. Specifically, chlorthalidone was slightly better at reducing systolic BP. More importantly, chlorthalidone was associated with fewer adverse CV events: Compared with patients taking chlorthalidone, those taking amlodipine experienced a higher 6-year rate of heart failure (10.2% vs. 7.7%), and those taking lisinopril experienced higher 6-year rates of stroke (6.3% vs. 5.6%), heart failure (8.7% vs. 7.7%), and combined CV disease (33.3% vs. 30.9%).

You might ask “Can the results seen with chlorthalidone, lisinopril, and amlodipine be extended to other members of the drug families they represent?” The answer is a qualified “Yes.” All thiazide diuretics are very similar, and hence the results seen with chlorthalidone are likely to be seen with other thiazides. Similarly, all ACE inhibitors are much the same, and hence the results seen with lisinopril are probably representative. The story with amlodipine is different. Amlodipine belongs to a subclass of CCBs known as dihydropyridines (DHPs), which differ significantly from CCBs in other subclasses. Accordingly, extrapolation of the results seen with amlodipine should probably be limited to CCBs in the DHP subclass.

How do thiazides compare with beta blockers? Unfortunately, beta blockers were not included in ALLHAT. However, data from other large studies indicate that beta blockers are certainly no more effective than thiazides, and may well be less effective.

The message from ALLHAT is both clear and compelling: Thiazide diuretics should be the initial drugs of choice for most patients with hypertension. These drugs are at least as effective as the alternatives, and they cost *much* less. Hydrochlorothiazide, for example, costs about 10 cents a day, compared with about \$1 a day for amlodipine. Clearly, if most patients were to switch from amlodipine (and other expensive drugs) to the thiazides, the savings for our health system would be huge—and would quickly offset the \$120 million that taxpayers invested on ALLHAT. Wouldn't it be great if more clinical studies led to the same good news: The best drug for what ails you is also the cheapest.

Postscript

Do the results of the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA)² refute the results of ALLHAT? Not really. Although ASCOT-BPLA is an important clinical trial that may well lead to changes in hypertension treatment, the trial does not directly challenge the superiority of thiazides—at least when thiazides are used alone. ASCOT-BPLA enrolled 19,257 patients, most of whom were treated with either (1) a *combination* of amlodipine plus perindopril (nearly identical to the CCB/ACE inhibitor combination used in ALLHAT) or (2) a *combination* of atenolol (a beta blocker) plus bendroflumethiazide (a thiazide diuretic). The result? After a median follow-up of 5.5 years, patients taking the CCB/ACE inhibitor combination experienced significantly fewer adverse CV events than did patients taking the beta blocker/thiazide combination, indicating that one *combination* is better than the other. The results do not say, however, that the CCB *alone* or the ACE inhibitor *alone* is superior to the thiazide *alone*. Hence we cannot compare these results directly with those of ALLHAT (which showed that, when used alone, a thiazide is better than a CCB or an ACE inhibitor). What ASCOT-BPLA *does* suggest is that a CCB/ACE inhibitor combination would be better as first-line therapy of hypertension than the currently recommended beta blocker/thiazide combination. Whether a thiazide/CCB combination or a thiazide/ACE inhibitor combination would be better still has yet to be determined.

¹The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker versus diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288:2981–2997, 2002.

²Dinlof B, Sever PS, Poulter NR, for the ASCOT Investigators: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA): A multicenter randomized controlled trial. *Lancet* 366:895–906, 2005.

Most adverse effects are like those of the thiazides: *hypokalemia*, *dehydration*, *hyperglycemia*, and *hyperuricemia*. In addition, high-ceiling agents can cause *hearing loss*.

Potassium-Sparing Diuretics. The degree of diuresis induced by the potassium-sparing agents (eg, spironolactone) is small. Consequently, these drugs have only modest hypotensive effects. However, because of their ability to conserve potassium, these drugs can play an important role in an antihypertensive regimen. Specifically, they can balance potassium loss caused by thiazides or loop diuretics. The most significant adverse effect of the potassium-sparing agents is *hyperkalemia*. Because of the risk of hyperkalemia, potassium-sparing diuretics must not be used in combination with one another or with potassium supplements. Also, they should not be used routinely with ACE inhibitors, angiotensin II receptor blockers, or aldosterone antagonists, all of which promote significant hyperkalemia.

Sympatholytics (Antiadrenergic Drugs)

Sympatholytic drugs suppress the influence of the sympathetic nervous system on the heart, blood vessels, and other structures. These drugs are used widely for hypertension.

As indicated in Table 47-5, there are five subcategories of sympatholytic drugs: (1) beta blockers, (2) alpha₁ blockers, (3) alpha/beta blockers, (4) centrally acting alpha₂ agonists, and (5) adrenergic neuron blockers.

Beta-Adrenergic Blockers. Like the thiazides, beta blockers (eg, propranolol, metoprolol) are widely used antihypertensive drugs. However, despite their efficacy and frequent use, the exact mechanism by which they reduce BP is somewhat uncertain. Beta blockers are less effective in African Americans than in whites.

The beta blockers have at least four useful actions in hypertension. First, blockade of cardiac beta₁ receptors decreases heart rate and contractility, thereby causing cardiac output to decline. Second, beta blockers can suppress reflex tachycardia caused by vasodilators. Third, blockade of beta₁ receptors on juxtaglomerular cells of the kidney reduces release of renin, and thereby reduces angiotensin II-mediated vasoconstriction and aldosterone-mediated volume expansion. Fourth, long-term use of beta blockers reduces peripheral vascular resistance—by a mechanism that is unknown. This action could readily account for most of their antihypertensive effects.

Four beta blockers have *intrinsic sympathomimetic activity* (see Table 47-5). That is, they can produce mild activation of beta receptors while blocking receptor activation by strong agonists (eg, norepinephrine). As a result, heart rate at rest is slowed less than with other beta blockers. Accordingly, if a patient develops symptomatic bradycardia with another beta blocker, switching to one of these may help.

Beta blockers can produce several adverse effects. Blockade of cardiac beta₁ receptors can produce *bradycardia*, *decreased atrioventricular (AV) conduction*, and *reduced contractility*. Consequently, beta blockers should not be used by patients with sick sinus syndrome or second- or third-degree AV block—and must be used with care in patients with heart failure. Blockade of beta₂ receptors in the lung can promote *bronchoconstriction*. Accordingly, beta blockers should be avoided by patients with asthma. If an asthmatic individual absolutely must use a beta blocker, a beta₁-selective agent (eg, metoprolol) should be employed. Beta blockers can mask signs of hypoglycemia, and therefore must be used with cau-

tion in patients with diabetes. Although conventional wisdom has it that beta blockers can cause depression, insomnia, bizarre dreams, and sexual dysfunction, a review of older clinical trials has shown that the risk is small or nonexistent.

The basic pharmacology of the beta blockers is discussed in Chapter 18.

Alpha₁ Blockers. The alpha₁ blockers (eg, doxazosin, terazosin) prevent stimulation of alpha₁ receptors on arterioles and veins, thereby preventing sympathetically mediated vasoconstriction. The resultant vasodilation reduces both peripheral resistance and venous return to the heart.

The most disturbing side effect of alpha blockers is *orthostatic hypotension*. Hypotension can be especially severe with the initial dose. Significant hypotension continues with subsequent doses but is less profound.

The American College of Cardiology recommends that alpha blockers *not* be used as first-line therapy for hypertension. Why? Because in a huge clinical trial known as ALLHAT, in which doxazosin was compared with chlorthalidone (a thiazide diuretic), patients taking doxazosin experienced 25% more cardiovascular events and were twice as likely to be hospitalized for heart failure. It is not clear whether doxazosin *increased* cardiovascular risk or chlorthalidone *decreased* risk. Either way, the diuretic is clearly preferred to the alpha blocker.

The basic pharmacology of the alpha blockers is discussed in Chapter 18.

Alpha/Beta Blockers: Carvedilol and Labetalol. Carvedilol and labetalol are unusual in that they can block alpha₁ receptors as well as beta receptors. Blood pressure reduction results from a combination of actions: (1) alpha₁ blockade promotes dilation of arterioles and veins, (2) blockade of cardiac beta₁ receptors reduces heart rate and contractility, and (3) blockade of beta₁ receptors on juxtaglomerular cells suppresses release of renin. Presumably, these drugs also share the ability of other beta blockers to reduce peripheral vascular resistance. Like other nonselective beta blockers, labetalol and carvedilol can exacerbate bradycardia, AV heart block, and asthma. Blockade of venous alpha₁ receptors can produce postural hypotension.

Centrally Acting Alpha₂ Agonists. As discussed in Chapter 19, these drugs (eg, clonidine, methyldopa) act within the brainstem to suppress sympathetic outflow to the heart and blood vessels. The result is vasodilation and reduced cardiac output, both of which help lower BP. All central alpha₂ agonists can cause *dry mouth* and *sedation*. In addition, clonidine can cause severe *rebound hypertension* if treatment is abruptly discontinued. Additional adverse effects of methyldopa are *hemolytic anemia* (accompanied by a positive direct Coombs' test) and *liver disorders*.

Adrenergic Neuron Blockers. Reserpine—the only adrenergic neuron blocker still available—depletes norepinephrine from postganglionic sympathetic nerve terminals, and thereby reduces sympathetic stimulation of the heart and blood vessels. The result is a drop in cardiac output and blood pressure. In addition to its peripheral effects, reserpine depletes serotonin and catecholamines from neurons in the central nervous system, causing deep emotional depression. Accordingly, reserpine is absolutely contraindicated for patients with a history of depressive illness. Because reserpine can cause depression, and because more desirable antihypertensive drugs are available, reserpine is not a preferred agent.

for treating hypertension. The basic pharmacology of reserpine is discussed in Chapter 19.

Direct-Acting Vasodilators: Hydralazine and Minoxidil

Hydralazine and minoxidil reduce BP by promoting dilation of arterioles. Neither drug causes significant dilation of veins. Because venous dilation is minimal, the risk of orthostatic hypotension is low. With both drugs, lowering of BP may be followed by reflex tachycardia, renin release, and fluid retention. Reflex tachycardia and release of renin can be prevented with a beta blocker. Fluid retention can be prevented with a diuretic.

The most disturbing adverse effect of *hydralazine* is a syndrome resembling *systemic lupus erythematosus* (SLE). Fortunately, this reaction is rare at recommended doses. If an SLE-like reaction occurs, hydralazine should be withdrawn. Hydralazine is considered a third-line drug for chronic hypertension.

Minoxidil is substantially more dangerous than hydralazine. By causing fluid retention, minoxidil can promote *pericardial effusion* (accumulation of fluid beneath the myocardium) that in some cases progresses to *cardiac tamponade* (compression of the heart). A less serious effect is *hypertrichosis* (excessive hair growth). Because of its capacity for significant harm, minoxidil is not used routinely for chronic hypertension. Instead, the drug is reserved for patients with severe hypertension that has not responded to safer drugs.

The basic pharmacology of hydralazine and minoxidil is discussed in Chapter 46.

Calcium Channel Blockers

The calcium channel blockers (CCBs) fall into two groups: dihydropyridines (eg, nifedipine) and nondihydropyridines (verapamil and diltiazem). Drugs in both groups promote dilation of arterioles. In addition, verapamil and diltiazem have direct suppressant effects on the heart.

Like other vasodilators, CCBs can cause *reflex tachycardia*. This reaction is greatest with the dihydropyridines and minimal with verapamil and diltiazem. Reflex tachycardia is low with verapamil and diltiazem because of cardiosuppression. Since dihydropyridines do not block cardiac calcium channels, reflex tachycardia with these drugs can be substantial.

Because of their ability to compromise cardiac performance, verapamil and diltiazem must be used cautiously in patients with bradycardia, heart failure, or AV heart block. These precautions do not apply to dihydropyridines.

The *rapid-acting* formulation of *nifedipine* has been associated with increased mortality in patients with MI and unstable angina. As a result, the National Heart, Lung, and Blood Institute has recommended that rapid-acting nifedipine be used with great caution, if at all.

The basic pharmacology of the CCBs is discussed in Chapter 45.

Drugs That Suppress the RAAS

Because the RAAS plays an important role in controlling BP, drugs that suppress the system—especially the ACE inhibitors—have a significant role in controlling hypertension. The basic pharmacology of these drugs is discussed in Chapter 44.

ACE Inhibitors. The ACE inhibitors (eg, captopril, enalapril) lower BP by preventing formation of angiotensin II, and

thereby prevent angiotensin II-mediated vasoconstriction and aldosterone-mediated volume expansion. In hypertensive diabetic patients with renal damage, these actions slow progression of kidney injury. Like the beta blockers, ACE inhibitors are less effective in African Americans than in whites. Principal adverse effects are *persistent cough*, *first-dose hypotension*, *angioedema*, and *hyperkalemia* (secondary to suppression of aldosterone release). Because of the risk of hyperkalemia, combined use with potassium supplements or potassium-sparing diuretics is generally avoided. ACE inhibitors can cause serious *fetal harm*, especially during the second and third trimesters of pregnancy, and hence must not be given to pregnant women. ACE inhibitors—along with angiotensin receptor blockers (ARBs) and direct renin inhibitors (DRIs)—are the only antihypertensive drugs specifically contraindicated during pregnancy.

Angiotensin II Receptor Blockers. ARBs lower BP in much the same way as do ACE inhibitors. Like the ACE inhibitors, ARBs prevent angiotensin II-mediated vasoconstriction and release of aldosterone. The only difference is that ARBs do so by blocking the *actions* of angiotensin II, whereas ACE inhibitors block the *formation* of angiotensin II. Both groups lower BP to the same extent. Like the ACE inhibitors, ARBs can cause *fetal harm* and must not be used during pregnancy. In contrast to ACE inhibitors, ARBs do not induce cough or significant hyperkalemia, but they do cause angioedema.

Direct Renin Inhibitors. DRIs act directly on renin to inhibit conversion of angiotensinogen into angiotensin II. As a result, DRIs can suppress the entire RAAS. At this time, only one DRI—*aliskiren* [Tekturna, Rasilez♦]—is available. Antihypertensive effects equal those of ACE inhibitors, ARBs, and CCBs. Compared with ACE inhibitors, aliskiren causes less hyperkalemia, cough, or angioedema—but poses a similar risk of *fetal harm*. In addition, aliskiren causes *diarrhea* in 2.3% of patients. Although we know that aliskiren can lower BP, we don't yet know if it reduces adverse outcomes (eg, stroke, kidney failure, MI). Accordingly, until experience with the drug is more extensive, other antihypertensives should be considered first.

Aldosterone Antagonists. Aldosterone antagonists lower BP by promoting renal excretion of sodium and water. Only two agents are available: *eprenone* and *spironolactone*. (In case you're confused about spironolactone, yes, it's the same drug we discussed above under *potassium-sparing diuretics*. We're discussing it here because it produces diuresis through aldosterone receptor blockade.) Both spironolactone and eplerenone promote renal retention of potassium, and hence pose a risk of *hyperkalemia*. Accordingly, they should not be given to patients with existing hyperkalemia, and should not be combined with potassium-sparing diuretics or potassium supplements. Combined use with ACE inhibitors, ARBs, and DRIs is permissible, but must be done with caution. Spironolactone is discussed in Chapter 41, eplerenone is discussed in Chapter 44, and both are discussed again in Chapter 48.

Fundamentals of Hypertension Drug Therapy

Treatment Algorithm

The basic approach to treating hypertension is outlined in Figure 47-3. As shown, lifestyle changes should be instituted first. If these fail to lower BP enough, drug therapy should be

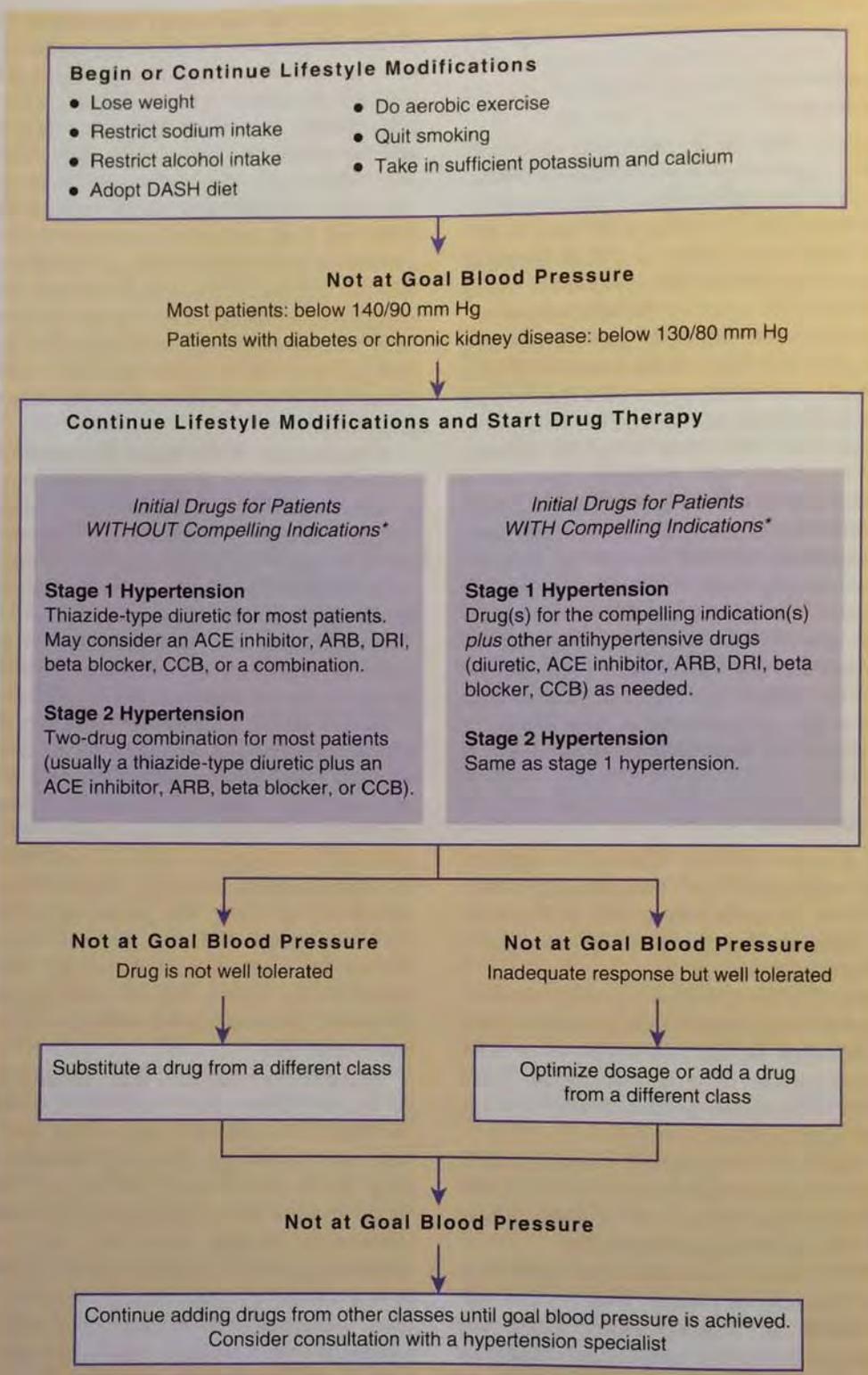


Figure 47-3 • Algorithm for treating hypertension.

(ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, CCB = calcium channel blocker, DASH = Dietary Approaches to Stop Hypertension, DRI = direct renin inhibitor.)

*A "compelling indication" is a comorbid condition (eg, heart failure, diabetes) for which a specific class of antihypertensive drugs has been shown to improve outcomes. See text for details. (Modified from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 289:2560–2572, 2003.)

TABLE 47-7 ■ Classes of Antihypertensive Drugs Recommended for Initial Therapy of Hypertension in Patients with Certain High-Risk Comorbid Conditions

High-Risk Comorbid Conditions That Constitute Compelling Indications for the Drugs Checked	Drug Classes Recommended for Initial Therapy of Hypertension*					
	Diuretic	Beta Blocker	ACE Inhibitor	ARB	CCB	Aldosterone Antagonist
Heart failure	✓	✓	✓	✓		✓
Post-myocardial infarction		✓	✓			✓
High coronary disease risk	✓	✓	✓		✓	
Diabetes	✓	✓	✓	✓	✓	
Chronic kidney disease			✓	✓		
Recurrent stroke prevention	✓		✓			

*ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, CCB = calcium channel blocker.

Adapted from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 289:2560-2572, 2003.

started—and the lifestyle changes should continue. Treatment often begins with a single drug. If needed, another drug may be *added* (if the initial drug was well tolerated but inadequate) or *substituted* (if the initial drug was poorly tolerated). However, before another drug is considered, possible reasons for failure of the initial drug should be assessed. Among these are insufficient dosage, poor adherence, excessive salt intake, and the presence of secondary hypertension. If treatment with two drugs is unsuccessful, a third and even fourth may be added.

Initial Drug Selection

Initial drug selection is determined by the presence or absence of a *compelling indication*, defined as a comorbid condition for which a specific class of antihypertensive drugs has been shown to improve outcomes. Initial drugs for patients with and without compelling indications are discussed below.

Patients WITHOUT Compelling Indications. For initial therapy in the absence of a compelling indication, a *thiazide diuretic* is currently recommended for most patients. This preference is based on long-term controlled trials showing conclusively that thiazides can reduce morbidity and mortality in hypertensive patients, and are well tolerated and inexpensive too (see Box 47-2). Other options for initial therapy—*ACE inhibitors, ARBs, DRIs, CCBs, and alpha/beta blockers*—equal diuretics in their ability to lower BP. However, they may not be as effective at reducing morbidity and mortality. Accordingly, these drugs should be reserved for special indications and for patients who have not responded to thiazides. Certain other alternatives—*centrally acting sympatholytics, adrenergic neuron blockers, and direct-acting vasodilators*—are associated with a high incidence of undesirable effects, and hence are not well suited for initial monotherapy. One last alternative—*alpha₁ blockers*—is no longer recommended as first-line therapy. As noted, when the alpha blocker doxazosin was compared with the diuretic chlorthalidone, doxazosin was associated with a much higher incidence of adverse cardiovascular events.

Beta blockers require special comment. In JNC 7, these drugs are recommended as first-line alternatives to thiazides for initial therapy of uncomplicated hypertension. However, several studies have shown that newer drugs—*ACE inhibitors, ARBs, and CCBs*—are superior to beta blockers at pre-

venting stroke and cardiac events in this population. Accordingly, the American Heart Association now recommends against using beta blockers as first-line therapy in patients without a compelling indication. On the other hand, if a patient already *has* heart disease (eg, angina pectoris, systolic heart failure, tachydysrhythmias, prior MI), beta blockers clearly improve outcomes, and hence remain first-choice drugs for these patients.

How many drugs should be used for initial therapy? The answer depends on the hypertension stage. For patients with stage 1 hypertension, treatment with just one drug—usually a thiazide diuretic—is recommended. For patients with stage 2 hypertension, initial therapy should consist of two drugs—typically a thiazide combined with either an ACE inhibitor, ARB, or CCB.

Patients WITH Compelling Indications. For patients with hypertension plus certain comorbid conditions (eg, heart failure, diabetes), there is strong evidence that specific antihypertensive drugs can reduce morbidity and mortality. Drugs shown to improve outcomes for six comorbid conditions are indicated in Table 47-7. Clearly, these drugs should be used for initial therapy. If needed, other antihypertensive agents can be added to the regimen. Management of hypertension in patients with diabetes and renal disease—two specific comorbid conditions—is discussed further under *Individualizing Therapy*.

Adding Drugs to the Regimen

Rationale for Drug Selection. When using two or more drugs to treat hypertension, each drug should come from a different class. That is, each drug should have a different mechanism of action. In accord with this guideline, it would be appropriate to combine a beta blocker, a diuretic, and a vasodilator, since each lowers BP by a different mechanism. In contrast, it would be inappropriate to combine two thiazide diuretics or two beta blockers or two vasodilators.

Benefits of Multidrug Therapy. Treatment with multiple drugs offers significant benefits. First, by employing drugs that have different mechanisms, we can increase the chance of success: Attacking BP control at several sites is likely to be more effective than attacking at one site. Second, when drugs are used in combination, each can be administered in a lower dosage than would be possible if it were used alone. As a re-

sult, both the frequency and the intensity of side effects are reduced. Third, when proper combinations are selected, one agent can offset the adverse effects of another. For example, if a vasodilator is used alone, reflex tachycardia is likely. However, if a vasodilator is combined with a beta blocker, reflex tachycardia will be minimal.

Dosing

For each drug in the regimen, *dosage should be low initially and then gradually increased*. Why? First, for most people with chronic hypertension, the disease poses no immediate threat. Hence, there is no need to lower BP rapidly using large doses. Second, when BP is reduced slowly, baroreceptors gradually reset to the new, lower pressure. As a result, sympathetic reflexes offer less resistance to the hypotensive effects of therapy. And third, since there is no need to drop BP rapidly, and since higher doses carry a higher risk of adverse effects, use of high initial doses would needlessly increase the risk of unpleasant responses.

Step-Down Therapy

After BP has been controlled for at least 1 year, an attempt should be made to reduce dosages and the number of drugs in the regimen. Of course, lifestyle modifications should continue. When reductions are made slowly and progressively, many patients are able to maintain BP control with less medication—and some can be maintained with no medication at all. If drugs are discontinued, regular follow-up is essential, because BP usually returns to hypertensive levels—although it may take years to do so.

Individualizing Therapy

Patients with Comorbid Conditions

Comorbid conditions complicate treatment. Two conditions that are especially problematic—renal disease and diabetes—are discussed below. Preferred drugs for patients with these and other comorbid conditions are summarized in Table 47-7. Drugs to avoid in patients with specific comorbid conditions are summarized in Table 47-8.

Renal Disease. Nephrosclerosis (hardening of the kidney) secondary to hypertension is among the most common causes of progressive renal disease. Pathophysiologic changes include degeneration of renal tubules and fibrotic thickening of the glomeruli, both of which contribute to renal insufficiency. Nephrosclerosis sets the stage for a downward spiral: Renal insufficiency causes water retention, which in turn causes BP to rise higher, which in turn promotes even more renal injury, and so forth. Accordingly, early detection and treatment are essential. To retard progression of renal damage, the most important action is to lower BP. The target BP is 130/80 mm Hg or lower. Achieving this goal often requires three or more drugs. Although all classes of antihypertensive agents are effective in nephrosclerosis, ACE inhibitors and ARBs work best. Hence, in the absence of contraindications, all patients should get one of these drugs. In most cases, a diuretic is used too. In patients with advanced renal insufficiency, thiazide diuretics are ineffective, hence a loop diuretic should be employed. Potassium-sparing diuretics should be avoided.

Diabetes. In patients with diabetes, the target BP is 130/80 mm Hg or less. Preferred antihypertensive drugs are

ACE inhibitors, ARBs, CCBs, and diuretics (in low doses). In patients with diabetic nephropathy, ACE inhibitors and ARBs can slow progression of renal damage and reduce albuminuria. In diabetic patients, as in nondiabetics, beta blockers and diuretics can decrease morbidity and mortality. Keep in mind, however, that beta blockers can suppress glycogenolysis and mask early signs of hypoglycemia, and therefore must be used with caution. Thiazides and high-ceiling diuretics promote hyperglycemia, and hence should be used with care.

How do ACE inhibitors compare with CCBs in patients with hypertension and diabetes? In one large study, patients taking nisoldipine (a CCB) had a higher incidence of MI than did patients taking enalapril (an ACE inhibitor). Because the study was not placebo controlled, it was impossible to distinguish between two possible interpretations: (1) the CCB increased the risk of MI or (2) the ACE inhibitor protected against MI. Either way, it seems clear that ACE inhibitors are better than CCBs for patients with hypertension and diabetes.

Patients in Special Populations

African Americans. Hypertension is a major health problem for African American adults. Hypertension develops earlier in blacks than in whites, has a much higher incidence, and is likely to be more severe. As a result, African Americans face a greater risk of heart disease, end-stage renal disease, and stroke. Compared with the general population, African Americans experience a 50% higher rate of death from heart disease, an 80% higher rate of death from stroke, and a 320% higher rate of hypertension-related end-stage renal disease.

With timely treatment, the disparity between blacks and nonblacks can be greatly reduced, if not eliminated. We know that blacks and whites respond equally to treatment (although not always to the same drugs). The primary problem is that, among blacks, hypertension often goes untreated until after significant organ damage has developed. If hypertension were diagnosed and treated earlier, the prognosis would be greatly improved. Accordingly, it is important that African Americans undergo routine monitoring of BP. If hypertension is diagnosed, treatment should begin at once. Because African Americans have a high incidence of salt sensitivity, obesity, and cigarette use, lifestyle modifications are an important component of treatment.

African Americans respond better to some antihypertensive drugs than to others. Controlled trials have shown that *diuretics* can decrease morbidity and mortality in blacks. Accordingly, diuretics are drugs of first choice. *CCBs* and *alpha/beta blockers* are also effective. In contrast, monotherapy with *beta blockers* or *ACE inhibitors* is less effective in blacks than in whites. Nonetheless, beta blockers and ACE inhibitors should be used if they are strongly indicated for a comorbid condition. For example, ACE inhibitors should be used in black patients who have type 1 diabetes with proteinuria. Also, ACE inhibitors should be used in patients with hypertensive nephrosclerosis, a condition for which ACE inhibitors are superior to CCBs. When BP cannot be adequately controlled with a single drug, several two-drug combinations are recommended: an ACE inhibitor plus a thiazide diuretic, an ACE inhibitor plus a CCB, and a beta blocker plus a thiazide.

In 2010, the International Society on Hypertension in Blacks (ISHIB) issued updated guidelines on managing hypertension in African Americans. Because hypertension takes a high toll on the black community, these guidelines call for

TABLE 47-8 ■ Comorbid Conditions That Require Cautious Use or Complete Avoidance of Certain Antihypertensive Drugs

Comorbid Condition	Drugs to Be Avoided or Used with Caution	Reason for Concern
Cardiovascular Disorders		
Heart failure	Verapamil Diltiazem	These drugs act on the heart to decrease myocardial contractility and can thereby further reduce cardiac output.
AV heart block	Beta blockers Labetalol Verapamil Diltiazem	These drugs act on the heart to suppress AV conduction and can thereby intensify AV block.
Coronary artery disease	Hydralazine	Reflex tachycardia induced by these drugs can precipitate an anginal attack.
Post-myocardial infarction	Hydralazine	Reflex tachycardia induced by these drugs can increase cardiac work and oxygen demand.
Other Disorders		
Dyslipidemia	Beta blockers Diuretics	These drugs may exacerbate dyslipidemia.
Renal insufficiency	K ⁺ -sparing diuretics K ⁺ supplements	Use of these agents can lead to dangerous accumulations of potassium.
Asthma	Beta blockers Labetalol	Beta ₂ blockade promotes bronchoconstriction.
Depression	Reserpine	Reserpine can cause depression.
Diabetes mellitus	Thiazides Furosemide Beta blockers	Thiazides and furosemide promote hyperglycemia, and beta blockers suppress glycogenolysis and can mask signs of hypoglycemia.
Gout	Thiazides Furosemide	These diuretics promote hyperuricemia.
Hyperkalemia	K ⁺ -sparing diuretics ACE inhibitors Direct renin inhibitors Aldosterone antagonists	These drugs cause potassium accumulation.
Hypokalemia	Thiazides Furosemide	These drugs cause potassium loss.
Collagen diseases	Hydralazine	Hydralazine can precipitate a lupus erythematosus–like syndrome.
Liver disease	Methyldopa	Methyldopa is hepatotoxic.
Preeclampsia	ACE inhibitors ARBs Direct renin inhibitors	These drugs can injure the fetus.

ACE = angiotensin-converting enzyme, ARBs = angiotensin II receptor blockers, AV = atrioventricular.

strict new BP goals: under 135/85 mm Hg for most patients, and under 130/80 mm Hg for those at high risk of a cardiovascular event. Some experts, however, have criticized these goals, arguing there is insufficient evidence to support them.

Children and Adolescents. The incidence of secondary hypertension in children is much higher than in adults. Accordingly, efforts to diagnose and treat an underlying cause should be especially diligent. For children with primary hypertension, treatment is the same as for adults—although doses are lower and should be adjusted with care. Because ACE inhibitors and ARBs can cause fetal harm, they should be avoided in girls who are sexually active or pregnant.

The Elderly. By age 65, most Americans have hypertension. Furthermore, as noted in Box 47-1, high blood pressure in this group almost always presents as *isolated systolic hypertension*; diastolic pressure is usually normal or low. The good news, as shown in the Hypertension in the Very Elderly

Trial (HYVET), is that treatment can reduce the incidence of heart failure, fatal stroke, and all-cause mortality. The bad news is that most older people are not treated.

In 2011, the American College of Cardiology and the American Heart Association issued the first-ever guidelines on the prevention and treatment of hypertension in people age 65 and older. According to the guidelines, the target *systolic* pressure is below 140 mm Hg (for patients ages 65 to 79) and below 145 mm Hg (for patients 80 and older). Treatment should start with a single drug, followed by the addition of a second drug, if needed. For initial therapy, the guidelines recommend a low-dose thiazide: hydrochlorothiazide, chlorthalidone, or bendroflumethiazide. Recommended add-on drugs include beta blockers, ACE inhibitors, ARBs, and long-acting dihydropyridine CCBs.

Because cardiovascular reflexes are blunted in the elderly, treatment carries a significant risk of orthostatic hypotension.

Accordingly, initial doses should be low—about one-half those used for younger adults—and dosage escalation should be done slowly. Drugs that are especially likely to cause orthostatic hypotension (eg, reserpine, α_1 blockers, α/β blockers) should be used with caution.

Minimizing Adverse Effects

Antihypertensive drugs can produce many unwanted effects, including hypotension, sedation, and sexual dysfunction. (Although not stressed previously, practically all antihypertensive drugs can interfere with sexual feelings or performance.)

The fundamental strategy for decreasing side effects is to tailor the regimen to the sensitivities of the patient. Simply put, if one drug causes effects that are objectionable, a more acceptable drug should be substituted. The best way to identify unacceptable responses is to encourage patients to report them.

Adverse effects caused by exacerbation of comorbid diseases are both predictable and avoidable. We know, for example, that β blockers can intensify asthma and AV block, and hence should not be taken by people with these disorders. Other conditions that can be aggravated by antihypertensive drugs are listed in Table 47-8. To help avoid drug-disease mismatches, the medical history should identify all comorbid conditions. With this information, the prescriber can choose drugs that are least likely to make the comorbid condition worse.

High initial doses and rapid dosage escalation can increase the incidence and severity of adverse effects. Accordingly, doses should be low at first and then gradually increased. Remember, there is usually no need to reduce BP rapidly. Hence, it makes no sense to give large initial doses that can produce a rapid fall in BP but that also produce intense undesired responses.

Promoting Adherence

The major cause of treatment failure in patients with chronic hypertension is lack of adherence to the prescribed regimen. In this section we consider the causes of nonadherence and discuss some solutions.

Why Adherence Is Often Hard to Achieve

Much of the difficulty in promoting adherence stems from the nature of hypertension itself. Hypertension is a chronic, slowly progressing disease that, through much of its course, is devoid of overt symptoms. Because symptoms are absent, it can be difficult to convince patients that they are ill and need treatment. In addition, since there are no symptoms to relieve, drugs cannot produce an obvious therapeutic response. In the absence of such a response, it can be difficult for patients to believe that their medication is doing anything useful.

Because hypertension progresses very slowly, the disease tends to encourage procrastination. For most people, the adverse effects of hypertension will not become manifest for many years. Realizing this, patients may reason (incorrectly) that they can postpone therapy without significantly increasing risk.

The negative aspects of treatment also contribute to nonadherence. Antihypertensive regimens can be complex and expensive. In addition, treatment must continue lifelong. Lastly, antihypertensive drugs can cause a number of adverse effects, ranging from sedation to hypotension to impaired sexual

function. It is difficult to convince people who are feeling good to take drugs that may make them feel worse. Some people may decide that exposing themselves to the negative effects of therapy today is paying too high a price to avoid the adverse consequences of hypertension at some indefinite time in the future.

Ways to Promote Adherence

Patient Education. Adherence requires motivation, and patient education can help provide it. Patients should be taught about the consequences of hypertension and the benefits of treatment. Because hypertension does not cause discomfort, it may not be clear to patients that their condition is indeed serious. Patients must be helped to understand that, left untreated, hypertension can cause heart disease, kidney disease, and stroke. In addition, patients should appreciate that, with proper therapy, the risks of these long-term complications can be minimized, resulting in a longer and healthier life. Lastly, patients must understand that drugs do not cure hypertension—they only control symptoms. Hence, for treatment to be effective, medication must be taken lifelong.

Teach Self-Monitoring. Patients should be taught the goal of treatment (usually maintenance of BP below 140/90 mm Hg), and they should be taught to monitor and record their BP daily. This increases patient involvement and provides positive feedback that can help promote adherence.

Minimize Side Effects. Common sense dictates that, if we expect patients to comply with long-term treatment, we must keep undesired effects to a minimum. As discussed above, adverse effects can be minimized by (1) encouraging patients to report side effects, (2) discontinuing objectionable drugs and substituting more acceptable ones, (3) avoiding drugs that can exacerbate comorbid conditions, and (4) using doses that are low initially and then gradually increased.

Establish a Collaborative Relationship. The patient who feels like a collaborative partner in the treatment program is more likely to comply than is the patient who feels that treatment is being imposed. Collaboration allows the patient to help set treatment goals, create the treatment program, and evaluate progress. In addition, a collaborative relationship facilitates communication about side effects. This is especially important with respect to drug-induced sexual dysfunction, which patients may be reluctant to disclose.

Simplify the Regimen. Antihypertensive regimens may consist of several drugs taken multiple times a day. Such complex regimens deter adherence. Therefore, in order to promote adherence, the dosing schedule should be as simple as possible. Once an effective regimen has been established, dosing just once or twice daily should be tried. If an appropriate combination product is available (eg, a fixed-dose combination of a thiazide diuretic plus an ACE inhibitor), the combination product may be substituted for its components.

Other Measures. Adherence can be promoted by giving positive reinforcement when therapeutic goals are achieved. Involvement of family members can be helpful. Also, adherence can be promoted by scheduling office visits at convenient times and by following up when appointments are missed. For many patients, antihypertensive therapy represents a significant economic burden; devising a regimen that is effective but inexpensive will help.

DRUGS FOR HYPERTENSIVE EMERGENCIES

A hypertensive emergency exists when *diastolic* BP exceeds 120 mm Hg. The severity of the emergency is determined by the likelihood of organ damage. When excessive BP is associated with papilledema (edema of the retina), intracranial hemorrhage, MI, or acute congestive heart failure, a severe emergency exists—and BP must be lowered rapidly (within 1 hour). If severe hypertension is present but does not yet pose an immediate threat of organ damage, reducing BP more slowly (over 24 to 48 hours) is preferable. Why? Because rapid reductions can cause cerebral ischemia, MI, and renal failure. Hence, pressure should be reduced gradually whenever possible.

The major drugs used for hypertensive emergencies are discussed below. All reduce BP by causing vasodilation, and all are given IV.

Sodium Nitroprusside. When acute, severe hypertension demands a rapid but controlled reduction in BP, IV nitroprusside [Nitropress] is usually the drug of first choice. Nitroprusside is a direct-acting vasodilator that relaxes smooth muscle of arterioles and veins. Effects begin in seconds and then fade rapidly when administration ceases. Nitroprusside is administered by continuous IV infusion using a pump to control the rate. The usual rate is 0.5 to 8 mcg/kg/min. To avoid overshoot, continuous BP monitoring is required. Because nitroprusside has an extremely short duration, overshoot can be corrected quickly by reducing the rate of infusion. Prolonged infusion (longer than 72 hours) can produce toxic accumulation of thiocyanate and should be avoided. The basic pharmacology of nitroprusside is discussed in Chapter 46.

Fenoldopam. Fenoldopam [Corlopan] is an IV drug indicated for short-term management of hypertensive emergencies. Benefits equal those of nitroprusside. Fenoldopam lowers BP by activating dopamine₁ receptors on arterioles, to cause vasodilation. In animal models, the drug dilates renal, coronary, mesenteric, and peripheral vessels.

Fenoldopam differs from other antihypertensives in that it helps maintain (or even improve) renal function. Two mechanisms are involved. First, the drug dilates renal blood vessels, and thereby increases renal blood flow (despite reducing arterial pressure). Second, fenoldopam promotes sodium and water excretion through direct effects on renal tubules.

Fenoldopam has a rapid onset and short duration. Effects begin in less than 5 minutes. The drug undergoes rapid hepatic metabolism followed by renal excretion. Its plasma half-life is only 5 minutes.

Fenoldopam is generally well tolerated. The most common side effects are hypotension, headache, flushing, dizziness, and reflex tachycardia—all of which occur secondary to vasodilation. Tachycardia may cause ischemia in patients with angina. Combined use with a beta blocker can minimize tachycardia, but may also result in excessive lowering of BP. Fenoldopam can elevate intraocular pressure, and hence should be used with caution in patients with glaucoma.

Fenoldopam is administered by continuous IV infusion. To minimize tachycardia, the initial dosage should be low. The typical infusion rate is 0.1 to 0.3 mcg/kg/min. With continuous 24-hour infusion, no tolerance develops to antihypertensive effects, and there is no rebound increase in BP when the infusion is stopped. With a 48-hour infusion, some tolerance may develop. Oral antihypertensive therapy can be added as soon as BP has stabilized.

Labetalol. Labetalol [Trandate] blocks alpha- and beta-adrenergic receptors. BP is reduced by arteriolar dilation secondary to alpha blockade. Beta blockade prevents reflex tachycardia in response to reduced arterial pressure, and hence the drug is probably safe for patients with angina or MI. Beta blockade can aggravate bronchial asthma, heart failure, AV block, cardiogenic shock, and bradycardia. Accordingly, labetalol should not be given to patients with these disorders. Administration is by slow IV injection.

Clevidipine. Clevidipine [Cleviprex], approved in 2008, is a dihydropyridine CCB with an ultrashort half-life (about 1 minute). Administration is by IV infusion. As with nitroprusside, effects begin rapidly and then fade rapidly when the infusion is slowed or stopped. As a result, BP can be easily

titrated. For patients with severe hypertension, the infusion rate is 1 to 2 mg/hr initially, and can be doubled every 3 minutes up to a maximum of 32 mg/hr. In clinical trials, the average time to reach the target BP was 10.9 minutes. The most common side effects are headache, nausea, and vomiting. The basic pharmacology of clevidipine is discussed in Chapter 45.

DRUGS FOR HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertension is the most common complication of pregnancy, with an incidence of about 10%. When hypertension develops, it is essential to distinguish between chronic hypertension and preeclampsia. Why? Because chronic hypertension is relatively benign, whereas preeclampsia can lead to life-threatening complications for the mother and fetus.

CHRONIC HYPERTENSION

Chronic hypertension, seen in 5% of pregnancies, is defined as hypertension that was present before pregnancy or that developed prior to the 20th week of gestation. Persistent *severe* hypertension carries a risk to both the mother and fetus. Potential adverse outcomes include placental abruption, maternal cardiac decompensation, premature birth, fetal growth retardation, central nervous system hemorrhage, and renal failure. The goal of treatment is to minimize the risk of hypertension to the mother and fetus while avoiding drug-induced harm to the fetus. With the exception of ACE inhibitors, ARBs, and DRIs, antihypertensive drugs that were being taken before pregnancy can be continued. *ACE inhibitors, ARBs, and DRIs are contraindicated owing to their potential for harm* (fetal growth retardation, congenital malformations, neonatal renal failure, neonatal death). When drug therapy is initiated *during* pregnancy, *methyldopa* is the traditional agent of choice. The drug has limited effects on uteroplacental and fetal hemodynamics, and does not adversely affect the fetus or neonate. Regardless of the drug selected, treatment should not be too aggressive. Why? Because an excessive drop in BP could compromise uteroplacental blood flow.

How high can BP rise before drug therapy is indicated? According to guidelines issued in 2001 by the American College of Obstetricians and Gynecologists (ACOG), “severe” hypertension requires treatment, whereas “mild” hypertension generally does not. (The ACOG defines severe hypertension as systolic BP above 180 mm Hg or diastolic BP above 110 mm Hg, and mild hypertension as systolic BP 140 to 179 mm Hg or diastolic BP 90 to 109 mm Hg.) There is good evidence that treating severe hypertension reduces risk. In contrast, there is little evidence that treating mild hypertension offers significant benefit.

Women who have chronic hypertension during pregnancy are at increased risk of developing preeclampsia (see below). Unfortunately, reducing BP does *not* lower this risk.

PREECLAMPSIA AND ECLAMPSIA

Preeclampsia is a multisystem disorder characterized by the combination of elevated BP (above 140/90 mm Hg) and proteinuria (300 mg or more in 24 hours) that develop after the 20th week of gestation. The disorder occurs in about 5% of

pregnancies. Rarely, women with preeclampsia develop seizures. If seizures do develop, the condition is then termed *eclampsia*. Risk factors for preeclampsia include obesity, black race, chronic hypertension, diabetes, collagen vascular disorders, and previous preeclampsia. The etiology of preeclampsia is complex and incompletely understood.

Preeclampsia poses serious risks for the fetus and mother. Risks for the fetus include intrauterine growth restriction, premature birth, and even death. The mother is at risk for seizures (eclampsia), renal failure, pulmonary edema, stroke, and death.

Management of preeclampsia is based on the severity of the disease, the status of mother and fetus, and the length of gestation. The objective is to preserve the health of the mother and deliver an infant who will not require intensive and prolonged neonatal care. Success requires close maternal and fetal monitoring. Although drugs can help reduce BP, delivery is the only cure.

Management of *mild* preeclampsia is controversial and depends on the duration of gestation. If preeclampsia develops near term, and if fetal maturity is certain, induction of labor is advised. However, if mild preeclampsia develops earlier in gestation, experts disagree about what to do. Suggested measures include bed rest, prolonged hospitalization, treatment with antihypertensive drugs, and prophylaxis with an anticonvulsant. Studies to evaluate these strategies have generally failed to demonstrate benefits from any of them, including treatment with antihypertensive drugs.

The definitive intervention for *severe* preeclampsia is delivery. However, making the choice to induce labor presents a dilemma. Since preeclampsia can deteriorate rapidly, with grave consequences for mother and fetus, immediate delivery is recommended. However, if the fetus is not sufficiently ma-

ture, immediate delivery could threaten its life. Hence the dilemma: Do we deliver the fetus immediately, which would eliminate risk for the mother but present a serious risk for the fetus—or do we postpone delivery, which would reduce risk for the fetus but greatly increase risk for the mother? If the woman elects to postpone delivery, then BP can be lowered with drugs. Because severe preeclampsia can be life threatening, treatment must be done in a tertiary care center to permit close monitoring of mother and fetus. The major objective is to prevent maternal cerebral complications (eg, hemorrhage, encephalopathy). The drug of choice for lowering BP is *hydralazine* (5 mg by IV bolus); dosing may be repeated 3 times at 20-minute intervals.

Because preeclampsia can (rarely) evolve into eclampsia, an antiseizure drug may be given for prophylaxis. *Magnesium sulfate* is the drug of choice. In one study, prophylaxis with magnesium sulfate reduced the risk of eclampsia by 58% and the risk of death by 45%. Dosing consists of a 10-gm IM loading dose followed by 5 gm IM every 4 hours for maintenance.

If eclampsia develops, magnesium sulfate is the preferred drug for seizure control. Dosing consists of a 4-gm IV loading dose followed by 5 gm IM injected into alternate buttocks every 4 hours for maintenance. To ensure therapeutic effects and prevent toxicity, blood levels of magnesium should be monitored. The target range is 4 to 7 mEq/L (the normal range for magnesium is 1.5 to 2 mEq/L).

Can drugs help prevent preeclampsia in women at risk? Yes. When started before 16 weeks of gestation, low-dose *aspirin* reduces risk by about 50%. Similarly, *L-arginine* (combined with antioxidant vitamins) can also help. By contrast, several other preparations—magnesium, zinc, vitamin C, vitamin E, fish oil, and diuretics—appear to offer no protection at all.

KEY POINTS

- Hypertension is defined as systolic BP greater than 140 mm Hg or diastolic BP greater than 90 mm Hg.
- Primary hypertension (essential hypertension), defined as hypertension with no identifiable cause, is the most common form of hypertension.
- Untreated hypertension can lead to heart disease, kidney disease, and stroke.
- In patients older than 50, elevated *systolic* BP represents a greater cardiovascular risk than elevated *diastolic* BP.
- The goal of antihypertensive therapy is to decrease morbidity and mortality without decreasing quality of life. For most patients, this goal is achieved by maintaining BP below 140/90 mm Hg, or below 130/80 mm Hg for those with diabetes or chronic kidney disease.
- To reduce BP, two kinds of treatment may be used: drug therapy and lifestyle modification (weight reduction, smoking cessation, reduction of salt and alcohol intake, following the DASH diet, and increasing aerobic exercise).
- The baroreceptor reflex, the kidneys, and the RAAS can oppose our attempts to lower BP with drugs. We can counteract the baroreceptor reflex with a beta blocker, the kidneys with a diuretic, and the RAAS with an ACE inhibitor, ARB, DRI, or aldosterone antagonist.
- Thiazide diuretics (eg, hydrochlorothiazide, chlorthalidone) and loop diuretics (eg, furosemide) reduce BP in two ways: they reduce blood volume (by promoting diuresis) and they reduce arterial resistance (by an unknown mechanism).
- Loop diuretics should be reserved for (1) patients who need greater diuresis than can be achieved with thiazides and (2) patients with a low GFR (because thiazides don't work when GFR is low).
- Beta blockers (eg, propranolol) appear to lower BP primarily by reducing peripheral vascular resistance; the mechanism is unknown. They may also lower BP by decreasing myocardial contractility and suppressing reflex tachycardia (through beta₁ blockade in the heart), and by decreasing renin release (through beta₁ blockade in the kidney).
- Calcium channel blockers (eg, diltiazem, nifedipine) reduce BP by promoting dilation of arterioles.

- ACE inhibitors, ARBs, and DRIs lower BP by preventing angiotensin II–mediated vasoconstriction and aldosterone-mediated volume expansion. ACE inhibitors work by blocking the formation of angiotensin II, whereas ARBs block the actions of angiotensin II. DRIs prevent formation of angiotensin I, and thereby shut down the entire RAAS.
- Aldosterone antagonists lower BP by preventing aldosterone-mediated retention of sodium and water in the kidney.
- Patients with stage 1 hypertension can often be treated with one drug, whereas those with stage 2 hypertension usually require two or more drugs.
- Thiazide diuretics are preferred drugs for initial therapy of uncomplicated hypertension.
- When a combination of drugs is used for hypertension, each drug should have a different mechanism of action.
- Dosages of antihypertensive drugs should be low initially and then gradually increased. This approach minimizes adverse effects and permits baroreceptors to reset to a lower pressure.
- Lack of patient adherence is the major cause of treatment failure in antihypertensive therapy.
- Adherence is difficult to achieve because (1) hypertension has no symptoms (so drug benefits aren't obvious); (2) hypertension progresses slowly (so patients think they can postpone treatment); and (3) treatment is complex and expensive, continues lifelong, and can cause adverse effects.
- A severe hypertensive emergency exists when diastolic BP exceeds 120 mm Hg and there is ongoing end-organ damage.
- Nitroprusside (IV) is a drug of choice for hypertensive emergencies.
- Hypertension is the most common complication of pregnancy.
- Methyldopa is a drug of choice for treating chronic hypertension of pregnancy.

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Summary of Major Nursing Implications*

ANTIHYPERTENSIVE DRUGS

Preadministration Assessment

Therapeutic Goal

The goal of antihypertensive therapy is to prevent the long-term sequelae of hypertension (heart disease, kidney disease, stroke) while minimizing drug effects that can reduce quality of life. For most patients, BP should be reduced to less than 140/90 mm Hg or less than 130/80 mm Hg for those with diabetes or chronic kidney disease.

Baseline Data

The following tests should be done in all patients: BP; electrocardiogram; complete urinalysis; hemoglobin and hematocrit; and blood levels of sodium, potassium, calcium, creatinine, glucose, uric acid, triglycerides, and cholesterol (total, LDL, and HDL cholesterol).

Identifying High-Risk Patients

When taking the patient's drug history, attempt to identify drugs that can raise BP or that can interfere with the effects of antihypertensive drugs. Some drugs of concern are listed below under *Minimizing Adverse Interactions*.

The patient history should identify comorbid conditions that either contraindicate use of specific agents (eg, asthma and AV block contraindicate use of beta blockers) or require that drugs be used with special caution (eg, thiazide diuretics must be used with caution in patients with gout or diabetes). For risk factors that pertain to specific antihypertensive drugs, refer to the chapters in which those drugs are discussed.

Implementation: Administration

Routes

All drugs for chronic hypertension are administered orally.

Dosage

To minimize adverse effects, dosages should be low initially and then gradually increased. It is counterproductive to employ high initial dosages that produce a rapid fall in pressure while also producing intense undesired responses that can discourage adherence. After 12 months of successful treatment, dosage reductions should be tried.

Implementation: Measures to Enhance Therapeutic Effects

Lifestyle Modifications

In hypertensive patients, lifestyle changes can reduce BP and increase responsiveness to antihypertensive drugs. These changes should be tried for 6 to 12 months before implementing drug therapy and should continue even if drugs are required.

Weight Reduction. Help overweight patients develop an exercise program and a restricted-calorie diet. The goal is a body mass index in the normal range (18.5 to 24.9).

Sodium Restriction. Encourage patients to consume no more than 6 gm of salt (2.4 gm of sodium) daily and provide them with information on the salt content of foods.

DASH Diet. Encourage patients to adopt a diet rich in fruits, vegetables, and low-fat dairy products, and low in total fat, unsaturated fat, and cholesterol.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Alcohol Restriction. Encourage patients to limit alcohol consumption to 1 ounce/day (for most men) and 0.5 ounce/day (for women and lighter weight men). One ounce of ethanol is equivalent to about two mixed drinks, two glasses of wine, or two cans of beer.

Exercise. Encourage patients with a sedentary lifestyle to perform 30 to 45 minutes of aerobic exercise (eg, walking, jogging, swimming, bicycling) most days of the week.

Smoking Cessation. Strongly encourage patients to quit smoking. Teach patients about aids for smoking cessation (eg, nicotine patch, bupropion, varenicline).

Promoting Adherence

Nonadherence is the major cause of treatment failure. Achieving adherence is difficult for several reasons: hypertension is devoid of overt symptoms; drugs don't make people feel better (but can make them feel worse); regimens can be complex and expensive; complications of hypertension take years to develop, thereby providing a misguided rationale for postponing treatment; and treatment usually lasts lifelong.

Provide Patient Education. Educate patients about the long-term consequences of hypertension and the ability of lifestyle changes and drug therapy to decrease morbidity and prolong life. Inform patients that drugs do not cure hypertension, and therefore must usually be taken lifelong.

Encourage Self-Monitoring. Make certain that patients know the treatment goal (usually reduction of BP to less than 140/90 mm Hg) and teach them to monitor and chart their own BP. This will increase their involvement and help them see the benefits of treatment.

Minimize Adverse Effects. Adverse drug effects are an obvious deterrent to adherence. Measures to reduce undesired effects are discussed below, under *Minimizing Adverse Effects*.

Establish a Collaborative Relationship. Encourage patients to be active partners in setting treatment goals, creating a treatment program, and evaluating progress.

Simplify the Regimen. An antihypertensive regimen can consist of several drugs taken multiple times a day. Once an effective regimen has been established, attempt to switch to once-a-day or twice-a-day dosing. If an appropriate combination product is available (eg, a fixed-dose combination of a thiazide diuretic plus an ACE inhibitor), substitute the combination product for its components.

Other Measures. Additional measures to promote adherence include providing positive reinforcement when treatment goals are achieved, involving family members in the treatment program, scheduling office visits at convenient times, following up on patients who miss an appointment, and devising a program that is effective but keeps costs low.

Ongoing Evaluation and Interventions

Evaluating Treatment

Monitor BP periodically. The usual goal is to reduce it to less than 140/90 mm Hg. **Teach patients to self-monitor their BP and to maintain a BP record.**

Minimizing Adverse Effects

General Considerations. The fundamental strategy for decreasing adverse effects is to tailor the regimen to the sensitivities of the patient. If a drug causes objectionable effects, a more acceptable drug should be substituted.

Inform patients about the potential side effects of treatment and encourage them to report objectionable responses.

Avoid drugs that can exacerbate comorbid conditions. For example, don't give beta blockers to patients who have bradycardia, AV block, or asthma. Table 47-8 lists drugs to avoid in patients with specific disorders.

Initiate therapy with low doses and increase them gradually.

Adverse Effects of Specific Drugs. For measures to minimize adverse effects of specific antihypertensive drugs (eg, beta blockers, diuretics, ACE inhibitors), refer to the chapters in which those drugs are discussed.

Minimizing Adverse Interactions

When taking the patient history, identify drugs that can raise BP or interfere with the effects of antihypertensive drugs. Drugs of concern include oral contraceptives, nonsteroidal anti-inflammatory drugs, glucocorticoids, appetite suppressants, tricyclic antidepressants, monoamine oxidase inhibitors, cyclosporine, erythropoietin, alcohol (in large quantities), and nasal decongestants and other cold remedies.

Antihypertensive regimens frequently contain two or more drugs, thereby posing a potential risk of adverse interactions (eg, ACE inhibitors can increase the risk of hyperkalemia caused by potassium-sparing diuretics). For interactions that pertain to specific antihypertensive drugs, refer to the chapters in which those drugs are discussed.

*Patient education information is highlighted as blue text.

Drugs for Heart Failure

Pathophysiology of Heart Failure

Overview of Drugs Used to Treat Heart Failure

Diuretics

Drugs That Inhibit the RAAS

Beta Blockers

Digoxin

Inotropic Agents (Other Than Digoxin)

Vasodilators (Other Than ACE Inhibitors and ARBs)

Digoxin, a Cardiac Glycoside

Management of Heart Failure



Box 48–1. Attention Ladies: Digoxin May Be Hazardous to Your Health

Heart failure is a disease with two major forms: (1) heart failure with left ventricular (LV) systolic dysfunction, and (2) diastolic heart failure, also known as heart failure with preserved LV ejection fraction. In this chapter, discussion is limited to the first form. Accordingly, for the rest of this chapter, the term *heart failure* (HF) will be used to denote the first form only.

Heart failure is a progressive, often fatal disorder characterized by ventricular dysfunction, reduced cardiac output, insufficient tissue perfusion, and signs of fluid retention (eg, peripheral edema, shortness of breath). The disease affects nearly 5 million Americans and, every year, is responsible for 12 to 15 million office visits, 6.5 million hospital days, and about 300,000 deaths. Of those who have HF, 24% are likely to die within 1 year, and 65% within 5 years. Heart failure is primarily a disease of the elderly, affecting 2% to 3% of those at age 65 and more than 80% of those over age 80. In 2008, direct and indirect healthcare costs of HF were estimated at more than \$35 billion. With improved evaluation and care, many hospitalizations could be prevented, quality of life could be improved, and life expectancy could be extended.

In the past, HF was commonly referred to as *congestive heart failure*. This term was used because HF frequently causes fluid accumulation (congestion) in the lungs and peripheral tissues. However, because many patients do not have signs of pulmonary or systemic congestion, the term *heart failure* is now preferred.

Drugs recommended for treatment include diuretics, inhibitors of the renin-angiotensin-aldosterone system (RAAS), beta blockers, and digoxin. In this chapter, only digoxin is discussed at length. The other drugs are presented at length in previous chapters, and hence discussion here is limited to their use in heart failure.

In order to understand HF and its treatment, you need a basic understanding of hemodynamics. In particular, you need to understand the role of venous pressure, afterload, and Starling's mechanism in determining cardiac output. You also need to understand the roles of the baroreceptor reflex, the RAAS, and the kidneys in regulating arterial pressure. If your understanding of these concepts is a little hazy, you can refresh your memory by reading Chapter 43 (Review of Hemodynamics).

PATHOPHYSIOLOGY OF HEART FAILURE

Heart failure is a syndrome in which the heart is unable to pump sufficient blood to meet the metabolic needs of tissues. The syndrome is characterized by signs of *inadequate tissue perfusion* (fatigue, shortness of breath, exercise intolerance) and/or signs of *volume overload* (venous distention, peripheral and pulmonary edema). The major underlying causes of HF are chronic hypertension and myocardial infarction. Other causes include valvular heart disease, coronary artery disease, congenital heart disease, dysrhythmias, and aging of the myocardium. In its earliest stage, HF is asymptomatic. As failure progresses, fatigue and shortness of breath develop. As cardiac performance declines further, blood backs up behind the failing ventricles, causing venous distention, peripheral edema, and pulmonary edema. Heart failure is a chronic disorder that requires continuous treatment with drugs.

Cardiac Remodeling

In the initial phase of failure, the heart undergoes remodeling, a process in which the ventricles dilate (grow larger), hypertrophy (increase in wall thickness), and become more spherical (less cylindrical). These alterations in cardiac geometry increase wall stress and reduce LV ejection fraction. Remodeling occurs in response to cardiac injury, brought on by infarction and other causes. The remodeling process is driven primarily by neurohormonal systems, including the sympathetic nervous system (SNS) and the RAAS. In addition to promoting remodeling, neurohormonal factors promote cardiac fibrosis and myocyte death. The net result of these pathologic changes—remodeling, fibrosis, and cell death—is progressive decline in cardiac output. As a rule, cardiac remodeling precedes development of symptoms, and continues after they appear. As a result, cardiac performance continues to decline.

Physiologic Adaptations to Reduced Cardiac Output

In response to reductions in cardiac pumping ability, the body undergoes several adaptive changes. Some of these help improve tissue perfusion; others compound existing problems.

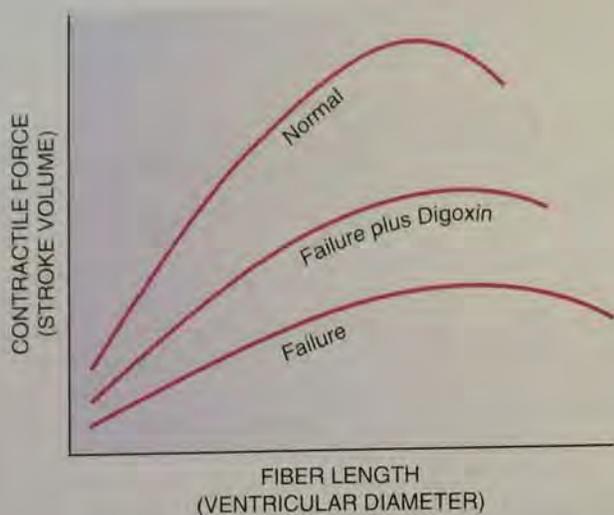


Figure 48-1 • Relationship of ventricular diameter to contractile force.

In the normal heart and the failing heart, increased fiber length produces increased contractile force. However, for any given fiber length, contractile force in the failing heart is much less than in the healthy heart. By increasing cardiac contractility, digoxin shifts the relationship between fiber length and stroke volume in the failing heart toward that in the normal heart.

Cardiac Dilation. Dilation of the heart is characteristic of HF. Cardiac dilation results from a combination of increased venous pressure (see below) and reduced contractile force. Reduced contractility lowers the amount of blood ejected during systole, causing end-systolic volume to rise. The increase in venous pressure increases diastolic filling, which causes the heart to expand even further.

Because of Starling's mechanism, the increase in heart size that occurs in HF helps improve cardiac output. That is, as the heart fails and its volume expands, contractile force increases, causing a corresponding increase in stroke volume. However, please note that the maximal contractile force that can be developed by the failing heart is considerably lower than the maximal force of the healthy heart. This limitation is reflected in the curve for the failing heart shown in Figure 48-1.

If cardiac dilation is insufficient to maintain cardiac output, other factors come into play. As discussed below, these are not always beneficial.

Increased Sympathetic Tone. Heart failure causes arterial pressure to fall. In response, the baroreceptor reflex increases sympathetic output to the heart, veins, and arterioles. At the same time, parasympathetic effects on the heart are reduced. The consequences of increased sympathetic tone are summarized below.

- **Increased heart rate.** Acceleration of heart rate increases cardiac output, thereby helping improve tissue perfusion. However, if heart rate increases too much, there will be insufficient time for complete ventricular filling, and hence cardiac output will fall.
- **Increased contractility.** Increased myocardial contractility has the obvious benefit of increasing cardiac output. The only detriment is an increase in cardiac oxygen demand.

- **Increased venous tone.** Elevation of venous tone increases venous pressure, and thereby increases ventricular filling. Because of Starling's mechanism, increased filling increases stroke volume. Unfortunately, if venous pressure is excessive, blood will back up behind the failing ventricles, thereby aggravating pulmonary and peripheral edema. Furthermore, excessive filling pressure can dilate the heart so much that stroke volume will begin to decline (see Fig. 48-1).
- **Increased arteriolar tone.** Elevation of arteriolar tone increases arterial pressure, thereby increasing perfusion of vital organs. Unfortunately, increased arterial pressure also means the heart must pump against greater resistance. Since cardiac reserve is minimal in HF, the heart may be unable to meet this challenge, and output may fall.

Water Retention and Increased Blood Volume. *Mechanisms.* Water retention results from two mechanisms. First, reduced cardiac output causes a reduction in renal blood flow, which in turn decreases glomerular filtration rate (GFR). As a result, urine production is decreased and water is retained. Retention of water increases blood volume.

Second, HF activates the RAAS. Activation occurs in response to reduced blood pressure and reduced renal blood flow. Once activated, the RAAS promotes water retention by increasing circulating levels of *aldosterone* and *angiotensin II*. Aldosterone acts directly on the kidneys to promote retention of sodium and water. Angiotensin II causes constriction of renal blood vessels, which decreases renal blood flow, and thereby further decreases urine production. In addition, angiotensin II causes constriction of systemic arterioles and veins, and thereby increases venous and arterial pressure.

Consequences. As with other adaptive responses to HF, increased blood volume can be beneficial or harmful. Increased blood volume increases venous pressure, and thereby increases venous return. As a result, ventricular filling and stroke volume are increased. The resultant increase in cardiac output can improve tissue perfusion. However, as noted, if venous pressure is too high, edema of the lungs and periphery may result. More importantly, *if the increase in cardiac output is insufficient to maintain adequate kidney function, renal retention of water will progress unabated. The resultant accumulation of fluid will cause severe cardiac, pulmonary, and peripheral edema—and, ultimately, death.*

Natriuretic Peptides. In response to stretching of the atria and dilation of the ventricles, the heart releases two natriuretic peptides: atrial natriuretic peptide (ANP) and B-natriuretic peptide (BNP). As discussed in Chapter 43, these hormones promote dilation of arterioles and veins, and also promote loss of sodium and water through the kidneys. Hence, they tend to counterbalance vasoconstriction caused by the SNS and angiotensin II, as well as retention of sodium and water caused by the RAAS. However, as HF progresses, the effects of ANP and BNP eventually become overwhelmed by the effects of the SNS and RAAS.

Levels of circulating BNP are an important index of cardiac status in HF patients, and hence can be a predictor of long-term survival. High levels of BNP indicate poor cardiac health, and hence predict a lower chance of survival. Conversely, low levels of BNP indicate better cardiac health, and hence predict a higher chance of survival. This information can be helpful when assessing the hospitalized patient at dis

charge: The lower the BNP level, the greater the chances of long-term survival.

The Vicious Cycle of "Compensatory" Physiologic Responses

As discussed above, reduced cardiac output leads to compensatory responses: (1) cardiac dilation, (2) activation of the SNS, (3) activation of the RAAS, and (4) retention of water and expansion of blood volume. Although these responses represent the body's attempt to compensate for reduced cardiac output, they can actually make matters worse: Excessive heart rate can reduce ventricular filling; excessive arterial pressure can lower cardiac output; and excessive venous pressure can cause pulmonary and peripheral edema. Hence, as depicted in Figure 48-2, the "compensatory" responses can create a self-sustaining cycle of maladaptation that further impairs cardiac output and tissue perfusion. If cardiac output becomes too low to maintain sufficient production of urine, the resultant accumulation of water will eventually be fatal. The actual cause of death is complete cardiac failure secondary to excessive cardiac dilation and cardiac edema.

Signs and Symptoms of Heart Failure

The prominent signs and symptoms of HF are a direct consequence of the pathophysiology just described. Decreased tissue perfusion results in reduced exercise tolerance, fatigue, and shortness of breath; shortness of breath may also reflect pulmonary edema. Increased sympathetic tone produces tachycardia. Increased ventricular filling, reduced systolic ejection, and myocardial hypertrophy result in cardiomegaly (increased heart size). The combination of increased venous tone plus increased blood volume helps cause pulmonary edema, peripheral edema, hepatomegaly (increased liver size), and distention of the jugular veins. Weight gain results from fluid retention.

Classification of Heart Failure Severity

There are two major schemes for classifying HF severity. One scheme, established by the New York Heart Association (NYHA), classifies HF based on the functional limitations it causes. A newer scheme, proposed jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA), is based on the observation that HF is a progressive disease that moves through stages of increasing severity.

The NYHA scheme, which has four classes, can be summarized as follows:

- Class I—No limitation of ordinary physical activity
- Class II—Slight limitation of physical activity: normal activity produces fatigue, dyspnea, palpitations, or angina
- Class III—Marked limitation of physical activity: even mild activity produces symptoms
- Class IV—Symptoms occur at rest

The ACC/AHA scheme, which also has four stages, can be summarized as follows:

- Stage A—At high risk for HF but without structural heart disease or symptoms of HF
- Stage B—Structural heart disease but without symptoms of HF
- Stage C—Structural heart disease with prior or current symptoms of HF

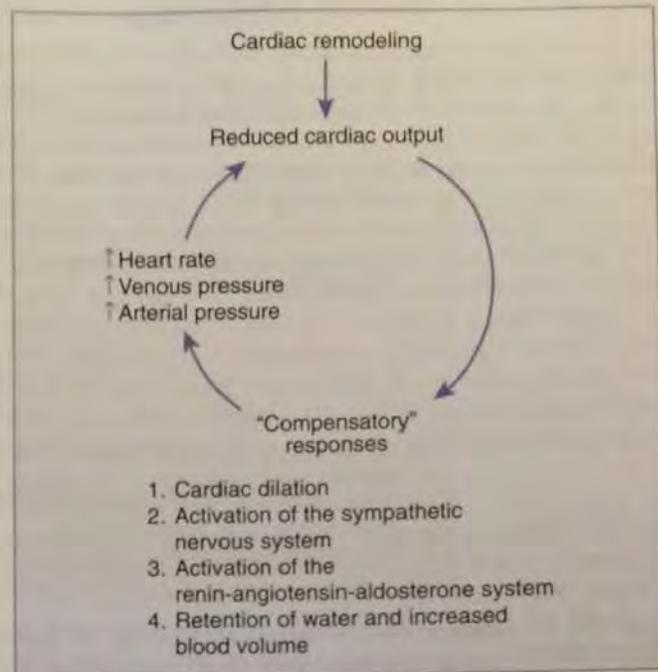


Figure 48-2 • The vicious cycle of maladaptive compensatory responses to a failing heart.

- Stage D—Advanced structural heart disease with marked symptoms of HF at rest, and requiring specialized interventions (eg, heart transplant, mechanical assist device)

The ACC/AHA scheme was unveiled in treatment guidelines issued in 2001. The 2005 version of that document—*ACC/AHA 2005 Guideline Update for the Evaluation and Management of Chronic Heart Failure in the Adult*—and its 2009 focused update are discussed below under *Management of Heart Failure*.

Please note that the ACC/AHA scheme is intended to complement the NYHA scheme, not replace it. The relationship between the two is shown graphically in Figure 48-3.

OVERVIEW OF DRUGS USED TO TREAT HEART FAILURE

For routine therapy, heart failure is treated with three types of drugs: (1) diuretics, (2) agents that inhibit the RAAS, and (3) beta blockers. Other agents (eg, digoxin, dopamine, hydralazine) may be used as well.

Diuretics

Diuretics are first-line drugs for all patients with signs of volume overload or with a history of volume overload. By reducing blood volume, these drugs can decrease venous pressure, arterial pressure (afterload), pulmonary edema, peripheral edema, and cardiac dilation. However, excessive diuresis must be avoided: If blood volume drops too low, cardiac output and blood pressure may fall precipitously, thereby further compromising tissue perfusion. For the most part, benefits of diuretics are limited to symptom reduction. As a rule, these drugs

ACC/AHA Stage	NYHA Functional Classification
A At high risk for HF but without structural heart disease or symptoms of HF	
B Structural heart disease but without symptoms of HF	I Asymptomatic
C Structural heart disease with prior or current symptoms of HF	II Symptomatic with moderate exertion
	III Symptomatic with minimal exertion
D Advanced structural heart disease with marked symptoms of HF at rest despite maximal medical therapy. Specialized interventions (e.g., heart transplant, mechanical assist device) required	IV Symptomatic at rest

Figure 48-3 ■ American College of Cardiology/American Heart Association (ACC/AHA) Stage and New York Heart Association (NYHA) Classification of Heart Failure.

do not prolong survival. The basic pharmacology of the diuretics is discussed in Chapter 41.

Thiazide Diuretics. The thiazide diuretics (eg, hydrochlorothiazide) produce moderate diuresis. These oral agents are used for long-term therapy of HF when edema is not too great. Since thiazides are ineffective when GFR is low, these drugs cannot be used if cardiac output is greatly reduced. The principal adverse effect of the thiazides is *hypokalemia*, which increases the risk of *digoxin-induced dysrhythmias* (see below).

High-Ceiling (Loop) Diuretics. The loop diuretics (eg, furosemide) produce profound diuresis. In contrast to the thiazides, these drugs can promote fluid loss even when GFR is low. Hence, loop diuretics are preferred to thiazides when cardiac output is greatly reduced. Administration may be oral or IV. Because they can mobilize large volumes of water, and because they work when GFR is low, loop diuretics are drugs of choice for patients with severe HF. Like the thiazides, these drugs can cause *hypokalemia*, thereby increasing the risk of *digoxin toxicity*. In addition, loop diuretics can cause severe *hypotension* secondary to excessive volume reduction.

Potassium-Sparing Diuretics. In contrast to the thiazides and loop diuretics, the potassium-sparing diuretics (eg, spironolactone, triamterene) promote only scant diuresis. In patients with HF, these drugs are employed to counteract potassium loss caused by thiazide and loop diuretics, thereby lowering the risk of *digoxin-induced dysrhythmias*. Not surprisingly, the principal adverse effect of the potassium-sparing drugs is *hyperkalemia*. Because *angiotensin-converting enzyme (ACE) inhibitors* and *angiotensin II receptor blockers (ARBs)* also carry a risk of hyperkalemia, caution is needed if these drugs are combined with a potassium-sparing diuretic. Accordingly, when therapy with an ACE inhibitor or ARB is initiated, the potassium-sparing diuretic should be discontinued. It can be resumed later if needed.

One potassium-sparing diuretic—spironolactone—prolongs survival in patients with HF primarily by blocking receptors for aldosterone, not by causing diuresis. This drug and a related

agent—eplerenone—are discussed below under *Aldosterone Antagonists*.

Drugs That Inhibit the RAAS

The RAAS plays an important role both in cardiac remodeling and in the hemodynamic changes that occur in response to reduced cardiac output. Accordingly, agents that inhibit the RAAS can be highly beneficial. Four groups of drugs are available: ACE inhibitors, ARBs, direct renin inhibitors (DRIs), and aldosterone antagonists. Of the four, the ACE inhibitors have been studied most thoroughly in HF. The basic pharmacology of the RAAS inhibitors is presented in Chapter 44.

ACE Inhibitors

ACE inhibitors (eg, captopril, enalapril) are a cornerstone of HF therapy. These drugs can improve functional status and prolong life. In one trial, the 2-year mortality rate for patients taking enalapril was 47% lower than the rate for patients taking placebo. Other large, controlled trials have shown similar benefits. Accordingly, in the absence of specific contraindications, all patients with HF should receive one of these drugs. Although ACE inhibitors can be used alone, they are usually combined with a beta blocker and a diuretic.

How do ACE inhibitors help? They block production of angiotensin II, decrease release of aldosterone, and suppress degradation of kinins. As a result, they improve hemodynamics and favorably alter cardiac remodeling.

Hemodynamic Benefits. By suppressing production of angiotensin II, ACE inhibitors cause dilation of arterioles and veins and they decrease release of aldosterone. Resulting benefits in HF are as follows:

- *Arteriolar dilation* improves regional blood flow in the kidneys and other tissues and, by reducing afterload, it increases stroke volume and cardiac output. Increased renal blood flow promotes excretion of sodium and water.

- *Venous dilation* reduces venous pressure, and thereby reduces pulmonary congestion, peripheral edema, preload, and cardiac dilation.
- *Suppression of aldosterone release* enhances excretion of sodium and water, while causing retention of potassium.

Interestingly, suppression of angiotensin II production diminishes over time, suggesting that long-term benefits are the result of some other action.

Impact on Cardiac Remodeling. With continued use, ACE inhibitors have a favorable impact on cardiac remodeling. Elevation of kinins is largely responsible. This statement is based in part on the observation that, in experimental models, giving a kinin receptor blocker decreases beneficial effects on remodeling. Also, we know that suppression of angiotensin II production diminishes over time, and hence reduced angiotensin II cannot fully explain long-term benefits.

Adverse Effects. The principal adverse effects of the ACE inhibitors are *hypotension* (secondary to arteriolar dilation), *hyperkalemia* (secondary to decreased aldosterone release), *intractable cough*, and *angioedema*. In addition, these drugs can cause *renal failure in patients with bilateral renal artery stenosis*. If taken during pregnancy—especially the second and third trimesters—ACE inhibitors can cause *fetal injury*. Accordingly, if pregnancy occurs, these drugs should be discontinued. Because of their ability to elevate potassium levels, ACE inhibitors should be used with caution in patients taking potassium supplements or a potassium-sparing diuretic (eg, spironolactone, triamterene).

Dosage. Adequate dosage is critical: Higher dosages are associated with increased survival. Results of the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial indicate that the doses needed to increase survival are higher than those needed to produce hemodynamic changes. Unfortunately, in everyday practice, dosages are often too low: Providers frequently prescribe dosages that are large enough to produce hemodynamic benefits, but are still too low to prolong life. Target dosages associated with increased survival are summarized in Table 48-1. These dosages should be used unless side effects make them intolerable.

Angiotensin II Receptor Blockers

In patients with HF, the effects of ARBs are similar to those of ACE inhibitors—but not identical. Hemodynamic effects of both groups are much the same. Clinical trials have shown that ARBs improve LV ejection fraction, reduce HF symptoms, increase exercise tolerance, decrease hospitalization, enhance quality of life, and, most importantly, reduce mortality. However, because ARBs do not increase levels of kinins, their effects on cardiac remodeling are less favorable than those of ACE inhibitors. For this reason, and because clinical experience with ACE inhibitors is much greater than with ARBs, ACE inhibitors are generally preferred. For now, ARBs should be reserved for HF patients who cannot tolerate ACE inhibitors, usually owing to intractable cough. (Because ARBs do not increase bradykinin levels, they do not cause cough.)

Aldosterone Antagonists

In patients with HF, aldosterone antagonists—*spironolactone* [Aldactone] and *eplerenone* [Inspra]—can reduce symptoms, decrease hospitalizations, and prolong life. These benefits were first demonstrated with spironolactone in the Randomized Aldactone Evaluation Study (RALES). Similar results were later obtained with eplerenone. Current guidelines recommend adding an aldosterone antagonist to standard HF therapy (ie, a diuretic, an ACE inhibitor or ARB, and a beta blocker), but only in patients with moderately severe or severe symptoms.

How do aldosterone antagonists help? Primarily by blocking aldosterone receptors in the heart and blood vessels. To understand these effects, we need to review the role of aldosterone in HF. In the past, researchers believed that all aldosterone did was promote renal retention of sodium (and water) in exchange for excretion of potassium. However, we now know that aldosterone has additional—and more harmful—effects. Among these are

- Promotion of myocardial remodeling (which impairs pumping)
- Promotion of myocardial fibrosis (which increases the risk of dysrhythmias)

TABLE 48-1 ■ Inhibitors of the Renin-Angiotensin-Aldosterone System Used in Heart Failure

Drug	Initial Daily Dose	Maximum Daily Dose
ACE Inhibitors		
Captopril [Capoten]	25 mg 3 times	50–150 mg 3 times
Enalapril [Vasotec]	2.5 mg once	10–20 mg twice
Fosinopril [Monopril]	5–10 mg once	40 mg once
Lisinopril [Zestril, Prinivil]	2.5–5 mg once	20–40 mg once
Quinapril [Accupril]	5 mg twice	20 mg twice
Ramipril [Altace]	1.25–2.5 mg twice	10 mg once
Trandolapril [Mavik]	1 mg once	4 mg once
Angiotensin II Receptor Blockers		
Candesartan [Atacand]	4 mg once	32 mg once
Losartan [Cozaar]	12.5–25 mg once	150 mg once
Valsartan [Diovan]	40 mg twice	160 mg twice
Aldosterone Antagonists		
Eplerenone [Inspra]	25 mg once	50 mg once
Spironolactone [Aldactone]	12.5–25 mg once	25 mg once

- Activation of the SNS and suppression of norepinephrine uptake in the heart (both of which can promote dysrhythmias and ischemia)
- Promotion of vascular fibrosis (which decreases arterial compliance)
- Promotion of baroreceptor dysfunction

During HF, activation of the RAAS causes levels of aldosterone to rise. In some patients, levels reach 20 times normal. As aldosterone levels grow higher, harmful effects increase, and prognosis becomes progressively worse.

Drugs can reduce the impact of aldosterone by either decreasing aldosterone production or blocking aldosterone receptors. ACE inhibitors, ARBs, and DRIs decrease aldosterone production; spironolactone and eplerenone block aldosterone receptors. Although ACE inhibitors and ARBs can reduce aldosterone production, they do not block it entirely. Furthermore, production is suppressed only for a relatively short time. Hence, when ACE inhibitors or ARBs are used alone, detrimental effects of aldosterone can persist. However, when an aldosterone antagonist is added to the regimen, any residual effects are eliminated. As a result, symptoms of HF are improved and life is prolonged.

Aldosterone antagonists have one major adverse effect: *hyperkalemia*. The underlying cause is renal retention of potassium. Risk is increased by renal impairment and by using an ACE inhibitor or ARB. To minimize risk, potassium levels and renal function should be measured at baseline and periodically thereafter. Potassium supplements should be discontinued.

Spironolactone—but not eplerenone—poses a significant risk of *gynecomastia* (breast enlargement) in men, a condition that can be both cosmetically troublesome and painful. In the RALES trial, 10% of males experienced painful breast enlargement.

Direct Renin Inhibitors

As discussed in Chapter 44, DRIs can shut down the entire RAAS. In theory, their benefits in HF should equal those of the ACE inhibitors and ARBs. At this time, only one DRI is available. This drug—*aliskiren* [Tekturna]—is approved for hypertension, but is not yet approved for HF.

Beta Blockers

The role of beta blockers in HF continues to evolve. Until the mid-1990s, HF was considered an absolute contraindication to these drugs. After all, blockade of cardiac β_1 -adrenergic receptors *reduces* contractility—an effect that is clearly detrimental, given that contractility is already compromised in the failing heart. However, it is now clear that, with careful control of dosage, beta blockers can improve patient status. Controlled trials have shown that three beta blockers—*carvedilol* [Coreg], *bisoprolol* [Zebeta], and *sustained-release metoprolol* [Toprol XL]—when added to conventional therapy, can improve LV ejection fraction, increase exercise tolerance, slow progression of HF, reduce the need for hospitalization, and, most importantly, prolong survival. Accordingly, beta blockers are now recommended for most patients. These drugs can even be used in patients with severe disease (NYHA Class IV), provided the patient is euvolemic and hemodynamically stable. Although the mechanism underlying

benefits is uncertain, likely possibilities include protecting the heart from excessive sympathetic stimulation and protecting against dysrhythmias. Because excessive beta blockade can reduce contractility, doses must be very low initially and then gradually increased. Full benefits may not be seen for 1 to 3 months. Among patients with HF, the principal adverse effects are (1) fluid retention and worsening of HF, (2) fatigue, (3) hypotension, and (4) bradycardia or heart block. The basic pharmacology of the beta blockers is discussed in Chapter 18.

Digoxin

Digoxin belongs to a class of drugs known as *cardiac glycosides*, agents best known for their *positive inotropic actions*, that is, their ability to increase myocardial contractile force. By increasing contractile force, digoxin can increase cardiac output. In addition, it can alter the electrical activity of the heart, and it can favorably affect neurohormonal systems. Unfortunately, although digoxin can reduce symptoms of HF, it does not prolong life. Used widely in the past, *digoxin is considered a second-line agent today*. The pharmacology of digoxin is discussed at length later.

Inotropic Agents (Other Than Digoxin)

In addition to digoxin, we have two other types of inotropic drugs: *sympathomimetics* and phosphodiesterase (PDE) inhibitors. Unlike digoxin, which can be taken orally, these other inotropics must be given by IV infusion. Accordingly, their use is restricted to acute care of hospitalized patients. Because digoxin can be given PO, it is the only inotropic agent suited for long-term therapy.

Sympathomimetic Drugs: Dopamine and Dobutamine

The basic pharmacology of dopamine and dobutamine is presented in Chapter 17. Discussion here is limited to their use in HF. Both drugs are administered by IV infusion.

Dopamine. Dopamine is a catecholamine that can activate (1) β_1 -adrenergic receptors in the heart, (2) dopamine receptors in the kidney, and (3) at high doses, α_1 -adrenergic receptors in blood vessels. Activation of β_1 receptors increases myocardial contractility, thereby improving cardiac performance. β_1 activation also increases heart rate, creating a risk of tachycardia. Activation of dopamine receptors dilates renal blood vessels, thereby increasing renal blood flow and urine output. Activation of α_1 receptors increases vascular resistance (afterload), and can thereby reduce cardiac output. Dopamine is administered by continuous infusion. Constant monitoring of blood pressure, the electrocardiogram (ECG), and urine output is required. Dopamine is employed as a short-term rescue measure for patients with severe, acute cardiac failure.

Dobutamine. Dobutamine is a synthetic catecholamine that causes selective activation of β_1 -adrenergic receptors. By doing so, the drug can increase myocardial contractility, and can thereby improve cardiac performance. Like dopamine, dobutamine can cause tachycardia. In contrast to dopamine, dobutamine does not activate α_1 receptors, and therefore does not increase vascular resistance. As a result, the drug is generally preferred to dopamine for short-term treatment of acute HF. Administration is by continuous infusion.

Phosphodiesterase Inhibitors

Inamrinone. Inamrinone, formerly known as *amrinone*, has been called an *inodilator* because it increases myocardial contractility and promotes vasodilation. Increased contractility results from intracellular accumulation of cyclic AMP (cAMP) secondary to inhibition of phosphodiesterase type 3 (PDE3), an enzyme that degrades cAMP. The mechanism underlying vasodilation is unclear. Comparative studies indicate that improvements in cardiac function elicited by inamrinone are superior to those elicited by dopamine or dobutamine. Like dopamine and dobutamine, inamrinone is administered by IV infusion, and hence is not suited for outpatient use. Inamrinone is indicated only for short-term (2- to 3-day) treatment of HF in patients who have not responded to RAAS inhibitors, diuretics, and digoxin. The drug should be protected from light and should not be mixed with glucose-containing solutions. Constant monitoring is required. The initial dose is 0.75 mg/kg IV

administered over 2 to 3 minutes. The maintenance infusion is 5 to 10 mcg/kg/min.

Milrinone. Like inamrinone, milrinone is an inodilator. Increased contractility results from accumulation of cAMP secondary to inhibition of PDE3. Milrinone is administered by IV infusion and is indicated only for short-term therapy of severe HF. Dosing is complex.

Vasodilators (Other Than ACE Inhibitors and ARBs) Isosorbide Dinitrate Plus Hydralazine

For treatment of HF, isosorbide dinitrate (ISDN) and hydralazine are usually combined. The combination represents an alternative to ACE inhibitors or ARBs. However, ACE inhibitors and ARBs are generally preferred.

Isosorbide dinitrate [Isordil, others] belongs to the same family as nitroglycerin. Like nitroglycerin, ISDN causes selective dilation of veins. In patients with severe, refractory HF, the drug can reduce congestive symptoms and improve exercise capacity. In addition to its hemodynamic actions, ISDN may inhibit abnormal myocyte growth, and hence may retard cardiac remodeling. Principal adverse effects are *orthostatic hypotension* and *reflex tachycardia*. The basic pharmacology of ISDN and other organic nitrates is discussed in Chapter 51 (Drugs for Angina Pectoris).

Hydralazine [Apresoline] causes selective dilation of arterioles. By doing so, the drug can improve cardiac output and renal blood flow. For treatment of HF, hydralazine is always used in combination with ISDN, since hydralazine by itself is not very effective. Principal adverse effects are *hypotension*, *tachycardia*, and a syndrome that resembles *systemic lupus erythematosus*. The basic pharmacology of hydralazine is discussed in Chapter 46 (Vasodilators).

In 2005, the Food and Drug Administration approved *BiDil*, a fixed-dose combination of hydralazine and isosorbide dinitrate, for treating HF—but only in African Americans, making *BiDil* the first medication approved for a specific ethnic group. Can *BiDil* help people in other ethnic groups? Probably, but data are lacking: The manufacturer only tested the product in blacks. As discussed in Chapter 8 (under the heading *Race*), testing was limited to blacks primarily because of regulatory and market incentives, not because there were data suggesting it wouldn't work for others. Of course, now that *BiDil* is approved, clinicians may prescribe it for anyone they see fit. Each *BiDil* tablet contains 37.5 mg hydralazine and 20 mg isosorbide dinitrate. The recommended dosage is 1 or 2 tablets 3 times a day.

Intravenous Vasodilators for Acute Care

Nitroglycerin. Intravenous nitroglycerin is a powerful *venodilator* that produces a dramatic reduction in venous pressure. Effects have been described as being equivalent to “pharmacologic phlebotomy.” In HF, nitroglycerin is used to relieve acute severe pulmonary edema. Principal adverse effects are *hypotension* and resultant *reflex tachycardia*. The basic pharmacology of nitroglycerin is discussed in Chapter 51 (Drugs for Angina Pectoris).

Sodium Nitroprusside. Sodium nitroprusside [Nitropress] acts rapidly to dilate arterioles and veins. Arteriolar dilation reduces afterload and thereby increases cardiac output. Venodilation reduces venous pressure and thereby decreases pulmonary and peripheral congestion. The drug is indicated for short-term therapy of severe refractory HF. The principal adverse effect is *profound hypotension*. Blood pressure must be monitored continuously. The basic pharmacology of nitroprusside is discussed in Chapter 46 (Vasodilators).

Nesiritide. Nesiritide [Nattrecor] is a synthetic form of human BNP indicated only for short-term, IV therapy of hospitalized patients with acutely decompensated HF, characterized by increased pulmonary capillary wedge pressure (PCWP) and dyspnea at rest. Nesiritide is produced by recombinant DNA technology and has the same amino acid sequence as naturally occurring BNP. The drug was approved in 2001, after a relatively small trial—*Vasodilation in the Management of Acute Congestive Heart Failure (VMAC)*—showed a modest decrease in dyspnea and PCWP. However, after ten years of use, and over \$1 billion in sales, a much larger trial—*Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF)*—failed to show *any* benefit: The incidence of dyspnea, rehospitalization, and 30-day mortality was the same for patients receiving nesiritide as it was for patients receiving placebo. Worse yet, although nesiritide offered no benefit, it nearly doubled the incidence of hypotension. These results led the authors to conclude that “Nesiritide cannot be recommended for routine use in the broad population of patients with heart failure.”

Mechanism of Action. Nesiritide affects hemodynamics by three mechanisms: suppression of the RAAS, suppression of sympathetic outflow

from the central nervous system (CNS), and direct dilation of arterioles and veins. In patients with HF, benefits derive primarily from direct vasodilation. To promote vasodilation, nesiritide binds to receptors on vascular smooth muscle (VSM), and thereby stimulates production of cyclic GMP (cGMP), a second messenger that causes VSM to relax. This mechanism is similar to that of nitroglycerin, which also stimulates cGMP production. However, whereas nitroglycerin acts primarily on veins, nesiritide dilates arterioles as well. By dilating arterioles and veins, nesiritide reduces both preload and afterload. The net result is a decrease in PCWP and increased cardiac output. Also, by dilating afferent renal arterioles, nesiritide increases GFR, and thereby increases excretion of sodium and water. The result is a reduction in blood volume, which further reduces cardiac preload.

Pharmacokinetics. With continuous infusion, nesiritide achieves steady-state levels that are 3 to 6 times greater than the level of endogenous BNP present at baseline. Nesiritide is eliminated by three mechanisms: (1) proteolytic cleavage by endopeptidases present on the luminal surface of blood vessels; (2) binding to clearance receptors on the surface of cells, followed by cellular uptake and proteolytic cleavage; and (3) renal filtration. The drug's half-life is short, about 18 minutes.

Adverse Effects. The principal adverse effect is symptomatic *hypotension*. In the ASCEND-HF trial, hypotension developed in 26.6% of patients receiving nesiritide, compared with 15.3% of those receiving placebo. The risk of hypotension is increased by high doses of nesiritide and by concurrent use of ACE inhibitors and other vasodilators. In addition to causing hypotension, nesiritide can cause ventricular tachycardia (3%), headache (8%), back pain (4%), dizziness (3%), and nausea (4%). An analysis of several clinical trials suggested that nesiritide may cause renal damage. However, ASCEND-HF revealed no evidence of renal harm.

Preparations, Dosage, and Administration. Nesiritide [Nattrecor] is available in 1.5-mg, single-use vials. The powder must be dissolved and then diluted to a final concentration of 6 mcg/mL. Dosing consists of an initial IV bolus (2 mcg/kg) followed by continuous infusion (0.01 mcg/kg/min), typically lasting 48 hours or less. If symptomatic hypotension develops, the infusion should be slowed or stopped.

DIGOXIN, A CARDIAC GLYCOSIDE

Digoxin [Lanoxin] belongs to a family of drugs known as *cardiac glycosides*. These drugs are prepared by extraction from *Digitalis purpurea* (purple foxglove) and *Digitalis lanata* (Greek foxglove), and hence are also known as *digitalis glycosides*. In the United States, digoxin is the only cardiac glycoside available. Glycosides available in the past include *digitoxin*, *deslanoside*, and *powdered digitalis leaf*.

Digoxin has profound effects on the mechanical and electrical properties of the heart. In addition, it has important neurohormonal effects. In patients with HF, benefits derive from increased myocardial contractility and from effects on neurohormonal systems as well.

Digitalis is a dangerous drug. Why? Because, at doses close to therapeutic, it can cause severe dysrhythmias. Owing to its prodysrhythmic actions, digoxin must be used with respect, caution, and skill.

Digoxin is indicated for HF and for control of dysrhythmias (see Chapter 49). When used for HF, digoxin can reduce symptoms, increase exercise tolerance, and decrease hospitalizations. However, the drug does *not* prolong life. Furthermore, when used by *women*, it may actually *shorten* life (Box 48-1). Because benefits are limited to symptomatic relief, and because the risk of toxicity is substantial, *digoxin is now considered a second-line drug for treating HF*.

Chemistry

Digoxin consists of three components: a steroid nucleus, a lactone ring, and three molecules of digitoxose (a sugar). It is because of the sugars that digoxin is known as a glycoside. The region of the molecule composed of the steroid nucleus plus the lactone ring (ie, the region without the sugar mole-

si

ATTENTION LADIES: DIGOXIN MAY BE HAZARDOUS TO YOUR HEALTH

Researchers who conducted a re-analysis of older data discovered that, for *women* with heart failure, digoxin may do more harm than good. In 1997, the Digitalis Investigation Group¹ (DIG) reported the results of a large, randomized, placebo-controlled trial designed to assess the impact of digoxin on morbidity and mortality in patients with heart failure. The study enrolled 6801 patients (men and women) with heart failure and followed them for an average of 37 months. They all took an ACE inhibitor and a diuretic; half also received digoxin and the other half received a placebo. The result? Digoxin improved symptoms and decreased hospitalizations, but did not reduce mortality. The overall death rate was 35%, regardless of whether patients took digoxin or placebo. However, the data were not analyzed for possible gender-related effects. Accordingly, in 2002, Rathore et al.² performed a retrospective analysis of the DIG data to determine whether digoxin had different effects in men and women. What did their analysis reveal? Among men, digoxin had no significant impact on mortality, mirroring the overall mortality seen in 1997. However, among *women*, digoxin produced a small, but significant *increase* in mortality: After 37 months, the death rate was 28.9% for women taking placebo compared with 33.1% for those taking digoxin—an increase of 4.2%.

Why did digoxin increase the mortality rate in women, but not in men? We don't know. Possibilities include sex-based differences in autonomic function, muscle metabolism, signal

transduction, or myocardial cell growth and function. However, there may be a more simple answer: Among the women who died, digoxin plasma levels may have been excessive. It is well established that digoxin can be lethal at high levels. In the DIG trial, digoxin levels were measured only in randomly selected patients, and hence Rathore et al. lacked the data needed to determine whether deaths were related to high drug levels. If high digoxin levels were indeed responsible for the observed mortality increase, then the take-home message is obvious: We must keep digoxin doses low.

The Rathore et al. study suggests that, for female patients, the benefits of digoxin therapy (primarily a small [4%] decrease in the risk of hospitalization) may not justify the risk (possible drug-induced death). Until more is known, prudence dictates using digoxin in women with increased caution. As a rule, the drug should be reserved for patients who have not responded adequately to first-line medicines: ACE inhibitors or ARBs, diuretics, and beta blockers. Furthermore, digoxin levels should be kept as low as possible (0.5 to 0.8 ng/mL is a reasonable initial target). Finally, although the re-analysis underscores the potential dangers of digoxin, we mustn't forget that the drug *can* benefit many patients—especially those with heart failure combined with atrial fibrillation. Accordingly, we shouldn't withhold digoxin indiscriminately. Nor should we discontinue it without careful consideration, since doing so might lead to hemodynamic decompensation.

¹The Digitalis Investigation Group: The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 336:525–533, 1997.

²Rathore SS, Wang Y, Krumholz H: Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 347:1403–1411, 2002.

cules) is responsible for the pharmacologic effects of digoxin. The sugars only increase solubility.

Mechanical Effects on the Heart

Digoxin exerts a *positive inotropic action* on the heart. That is, the drug *increases the force of ventricular contraction*, and can thereby increase cardiac output.

Mechanism of Inotropic Action. Digoxin increases myocardial contractility by inhibiting an enzyme known as *sodium, potassium-ATPase* (Na^+, K^+ -ATPase). By way of an indirect process described below, inhibition of Na^+, K^+ -ATPase promotes calcium accumulation within myocytes. The calcium then augments contractile force by facilitating the interaction of myocardial contractile proteins: actin and myosin.

To understand how inhibition of Na^+, K^+ -ATPase causes intracellular calcium to rise, we must first understand the normal role of Na^+, K^+ -ATPase in myocytes. That role is illustrated in Figure 48-4. As indicated, when an action potential passes along the myocyte membrane (sarcolemma), Na^+ ions and Ca^{++} ions enter the cell, and K^+ ions exit. Once the action potential has passed, these ion fluxes must be reversed, so that the original ionic balance of the cell can be restored. Na^+, K^+ -ATPase is critical to this process. As shown in Figure 48-4, Na^+, K^+ -ATPase acts as a “pump” to draw extracellular K^+ ions into the cell, while simultaneously extruding intracellular Na^+ . The energy required for pumping Na^+ and K^+ is provided by the breakdown of ATP—hence the name Na^+, K^+ -ATPase. To complete the normalization of

cellular ionic composition, Ca^{++} ions must leave the cell. Extrusion of Ca^{++} is accomplished through an exchange process in which extracellular Na^+ ions are taken into the cell while Ca^{++} ions exit. This exchange of Na^+ for Ca^{++} is a passive (energy-independent) process.

We can now answer the question, how does inhibition of Na^+, K^+ -ATPase increase intracellular Ca^{++} ? By inhibiting Na^+, K^+ -ATPase, digoxin prevents the myocyte from restoring its proper ionic composition following the passage of an action potential. Inhibition of Na^+, K^+ -ATPase blocks uptake of K^+ and extrusion of Na^+ . Hence, with each successive action potential, intracellular K^+ levels decline and intracellular Na^+ levels rise. It is this rise in Na^+ that leads to the rise in intracellular Ca^{++} . In the presence of excess intracellular Na^+ , further Na^+ entry is suppressed. Since Na^+ entry is suppressed, the passive exchange of Ca^{++} for Na^+ cannot take place, and hence Ca^{++} accumulates within the cell.

Relationship of Potassium to Inotropic Action. Potassium ions compete with digoxin for binding to Na^+, K^+ -ATPase. This competition is of great clinical significance. Because potassium competes with digoxin, when potassium levels are low, binding of digoxin to Na^+, K^+ -ATPase increases. This increase can produce excessive inhibition of Na^+, K^+ -ATPase with resultant toxicity. Conversely, when levels of potassium are high, inhibition of Na^+, K^+ -ATPase by digoxin is reduced, causing a reduction in the therapeutic response. Because an increase in potassium can impair therapeutic responses, whereas a decrease in potassium can cause

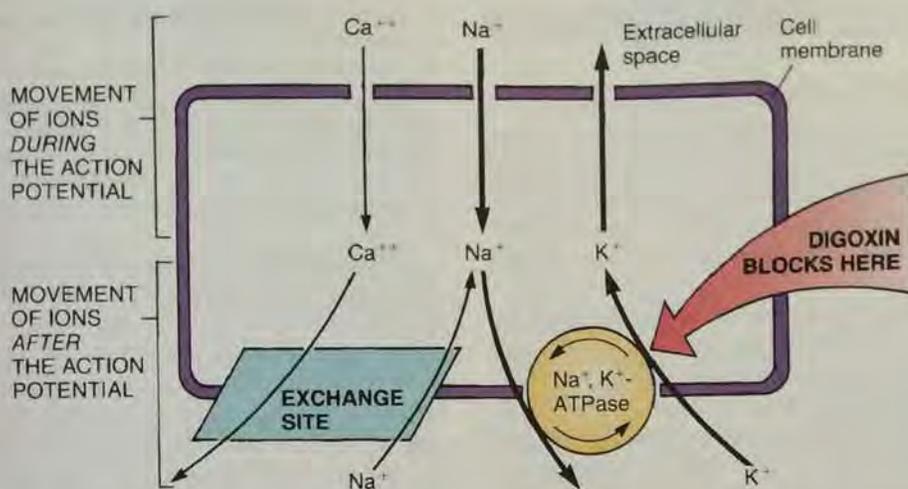


Figure 48-4 • Ion fluxes across the cardiac cell membrane.

During the action potential, Na^+ and Ca^{++} enter the cardiac cell and K^+ exits. Following the action potential, Na^+ , K^+ -ATPase pumps Na^+ out of the cell and takes up K^+ . Ca^{++} leaves the cell in exchange for the uptake of Na^+ . By inhibiting Na^+, K^+ -ATPase, digoxin prevents the extrusion of Na^+ , causing Na^+ to accumulate inside the cell. The resulting buildup of intracellular Na^+ suppresses the Na^+ - Ca^{++} exchange process, thereby causing intracellular levels of Ca^{++} to rise.

toxicity, it is imperative that potassium levels be kept within the normal physiologic range: 3.5 to 5 mEq/L.

Hemodynamic Benefits in Heart Failure

Increased Cardiac Output. In patients with HF, increased myocardial contractility increases cardiac output. As shown in Figure 48-1, by increasing contractility, digoxin shifts the relationship of fiber length to stroke volume in the failing heart toward that in the healthy heart. Consequently, at any given heart size, the stroke volume of the failing heart increases, causing cardiac output to rise.

Consequences of Increased Cardiac Output. As a result of increased cardiac output, three major secondary responses occur: (1) sympathetic tone declines, (2) urine production increases, and (3) renin release declines. These responses can reverse virtually all signs and symptoms of HF. However, they do not correct the underlying problem of cardiac remodeling.

Decreased Sympathetic Tone. By increasing contractile force and cardiac output, digoxin increases arterial pressure. In response, sympathetic nerve traffic to the heart and blood vessels is reduced via the baroreceptor reflex. (Recall that a compensatory increase in sympathetic tone had taken place because of HF.)

The decrease in sympathetic tone has several beneficial effects. First, heart rate is reduced, thereby allowing more complete ventricular filling. Second, afterload is reduced (because of reduced arteriolar constriction), thereby allowing more complete ventricular emptying. Third, venous pressure is reduced (because of reduced venous constriction), thereby reducing cardiac distention, pulmonary congestion, and peripheral edema.

Increased Urine Production. The increase in cardiac output increases renal blood flow, and thereby increases production of urine. The resultant loss of water reduces blood volume, which in turn reduces cardiac distention, pulmonary congestion, and peripheral edema.

Decreased Renin Release. In response to increased arterial pressure, renin release declines, causing levels of aldosterone and angiotensin II to decline as well. The decrease in angiotensin II decreases vasoconstriction, thereby further reducing afterload and venous pressure. The decrease in aldosterone reduces retention of sodium and water, which reduces blood volume, which in turn further reduces venous pressure.

Summary of Hemodynamic Effects. In summary, we can see that, through direct and indirect mechanisms, digoxin has the potential to reverse all of the overt manifestations of HF: cardiac output improves, heart rate decreases, heart size declines, constriction of arterioles and veins decreases, water retention reverses, blood volume declines, peripheral and pulmonary edema decrease, and weight is lost (owing to water loss). In addition, exercise tolerance improves and fatigue is reduced. There is, however, one important caveat: Although digoxin can produce substantial improvement in HF symptoms, it does not prolong life.

Neurohormonal Benefits in Heart Failure

At dosages below those needed for positive inotropic effects, digoxin can modulate the activity of neurohormonal systems. The underlying mechanism is inhibition of Na^+, K^+ -ATPase.

In the kidney, digoxin can suppress renin release. How? By inhibiting Na^+, K^+ -ATPase in renal tubules, digoxin decreases tubular absorption of sodium. As a result, less sodium is presented to the distal tubule, and hence renin release is suppressed.

Through effects on the vagus nerve, digoxin can decrease sympathetic outflow from the CNS. Specifically, by inhibiting Na^+, K^+ -ATPase in vagal afferent fibers, digoxin increases the sensitivity of cardiac baroreceptors. As a result, these receptors discharge more readily, thereby signaling the CNS to reduce sympathetic traffic to the periphery.

How important are these effects on renin and sympathetic tone? No one knows for sure. However, they are probably

just as important as inotropic effects, and perhaps even more important.

Electrical Effects on the Heart

The effects of digoxin on the electrical activity of the heart are of therapeutic and toxicologic importance. It is because of its electrical effects that digoxin is useful for treating dysrhythmias (see Chapter 49). Ironically, these same electrical effects are responsible for causing dysrhythmias, the most serious adverse effect of digoxin.

The electrical effects of digoxin can be bewildering in their complexity. Through a combination of actions, digoxin can alter the electrical activity in noncontractile tissue (sinoatrial [SA] node, atrioventricular [AV] node, Purkinje fibers) as well as in ventricular muscle. In these various regions, digoxin can alter automaticity, refractoriness, and impulse conduction. Whether these parameters are increased or decreased depends on cardiac status, digoxin dosage, and the region involved.

Although the electrical effects of digoxin are many and varied, only a few are clinically significant. These are discussed below.

Mechanisms for Altering Electrical Activity of the Heart.

Digoxin alters the electrical properties of the heart by inhibiting Na^+, K^+ -ATPase and by enhancing vagal influences on the heart. By inhibiting Na^+, K^+ -ATPase, digoxin alters the distribution of ions (Na^+ , K^+ , Ca^{++}) across the cardiac cell membrane. This change in ion distribution can alter the electrical responsiveness of the cells involved. Since hypokalemia intensifies inhibition of Na^+, K^+ -ATPase, hypokalemia intensifies alterations in cardiac electrical properties.

Digoxin acts in two ways to enhance vagal effects on the heart. First, the drug acts in the CNS to increase the firing rate of vagal fibers that innervate the heart. Second, digoxin increases the responsiveness of the SA node to acetylcholine (the neurotransmitter released by the vagus). The net result of these vagotonic effects is (1) decreased automaticity of the SA node, and (2) decreased conduction through the AV node.

Effects on Specific Regions of the Heart. In the SA node, digoxin decreases automaticity (by the vagotonic mechanisms just mentioned). In the AV node, digoxin decreases conduction velocity and prolongs the effective refractory period. These effects, which can promote varying degrees of AV block, result primarily from the drug's vagotonic actions. In Purkinje fibers, digoxin-induced inhibition of Na^+, K^+ -ATPase results in increased automaticity; this increase can generate ectopic foci that, in turn, can cause ventricular dysrhythmias. In the ventricular myocardium, digoxin acts to shorten the effective refractory period and (possibly) increase automaticity.

Adverse Effects I: Cardiac Dysrhythmias

Dysrhythmias are the most serious adverse effect of digoxin. They result from altering the electrical properties of the heart. Fortunately, when used in the dosages recommended today, dysrhythmias are uncommon.

What kinds of dysrhythmias can occur? Digoxin can mimic practically all types of dysrhythmias. Atrioventricular block with escape beats is among the most common. Ventricular flutter and ventricular fibrillation are the most dangerous.

Because serious dysrhythmias are a potential consequence of therapy, all patients should be evaluated frequently for changes in heart rate and rhythm. If significant changes occur, digoxin should be withheld and the prescriber consulted. Outpatients should be taught to monitor their pulses and instructed to report any significant changes in rate or regularity.

Mechanism of Ventricular Dysrhythmia Generation. Digoxin-induced ventricular dysrhythmias result from a combination of four factors:

- Decreased automaticity of the SA node
- Decreased impulse conduction through the AV node

- Spontaneous discharge of Purkinje fibers (caused in part by increased automaticity)
- Shortening of the effective refractory period in ventricular muscle

Increased Purkinje fiber discharge and shortening of the ventricular effective refractory period predispose the ventricles to developing ectopic beats. Potential ectopic beats become manifest because the effects of digoxin on the SA and AV nodes decrease the ability of the normal pacemaker to drive the ventricles, thereby allowing ventricular ectopic beats to take over.

Predisposing Factors. Hypokalemia. The most common cause of dysrhythmias in patients receiving digoxin is hypokalemia secondary to the use of diuretics. Less common causes include vomiting and diarrhea. Hypokalemia promotes dysrhythmias by increasing digoxin-induced inhibition of Na^+, K^+ -ATPase, which in turn leads to increased automaticity of Purkinje fibers. Because low potassium can precipitate dysrhythmias, it is imperative that serum potassium levels be kept within the normal range. If diuretic therapy causes potassium levels to fall, a potassium-sparing diuretic (eg, spironolactone) can be prescribed to correct the problem. Potassium supplements may be used too. Patients should be taught to recognize symptoms of hypokalemia (eg, muscle weakness) and instructed to notify the prescriber if these develop.

Elevated Digoxin Levels. Digoxin has a narrow therapeutic range: Drug levels only slightly higher than therapeutic greatly increase the risk of toxicity. Possible causes of excessive digoxin levels include (1) intentional or accidental overdose, (2) increased digoxin absorption, and (3) decreased digoxin elimination.

If digoxin levels are kept within the optimal therapeutic range—now considered to be 0.5 to 0.8 ng/mL—the chances of a dysrhythmia will be reduced. However, it is important to note that careful control over drug levels does not eliminate the risk. As discussed above, there is only a loose relationship between digoxin levels and clinical effects. As a result, some patients may experience dysrhythmias even when drug levels are within what is normally considered a safe range.

Heart Disease. The ability of digoxin to cause dysrhythmias is greatly increased by the presence of heart disease. Doses of digoxin that have no adverse effects on healthy volunteers can precipitate serious dysrhythmias in patients with HF. The probability and severity of a dysrhythmia are directly related to the severity of the underlying disease. Since heart disease is the reason for taking digoxin, it should be no surprise that people taking the drug are at risk of dysrhythmias.

Diagnosing Digoxin-Induced Dysrhythmias. Diagnosis is not easy. Why? Largely because the failing heart is prone to spontaneous dysrhythmias. Hence, when a dysrhythmia occurs, we cannot simply assume that digoxin is the cause. The possibility that the dysrhythmia is the direct result of heart disease must be considered. Compounding diagnostic difficulties is the poor correlation between plasma digoxin levels and dysrhythmia onset. Because of this loose association, the presence of an apparently excessive digoxin level does not necessarily indicate that digoxin is responsible for the problem. Laboratory data required for diagnosis include digoxin level, serum electrolytes, and an ECG. Ultimately, diagnosis is based on experience and clinical judgment. Resolution of the dysrhythmia following digoxin withdrawal confirms the diagnosis.

Managing Digoxin-Induced Dysrhythmias. With proper treatment, digoxin-induced dysrhythmias can almost

always be controlled. Basic management measures are as follows:

- *Withdraw digoxin and potassium-wasting diuretics.* For many patients, no additional treatment is needed. To help ensure that medication is stopped, a written order to withhold digoxin should be made.
- *Monitor serum potassium.* If the potassium level is low or nearly normal, potassium (IV or PO) should be administered. Potassium displaces digoxin from Na^+, K^+ -ATPase and thereby helps reverse toxicity. However, if potassium levels are high or if AV block is present, no more potassium should be given. Under these conditions, more potassium may cause complete AV block.
- Some patients may require an antidysrhythmic drug. *Phenytoin* and *lidocaine* are most effective. Quinidine, another antidysrhythmic drug, can cause plasma levels of digoxin to rise, and hence should not be used.
- Patients who develop bradycardia or AV block can be treated with atropine. (Atropine blocks the vagal influences that underlie bradycardia and AV block.) Alternatively, electronic pacing may be employed.
- When overdose is especially severe, digoxin levels can be lowered using *Fab antibody fragments* [Digibind, Digifab]. Following IV administration, these fragments bind digoxin, and thereby prevent it from acting. Treatment is expensive: A full neutralizing dose costs \$2000 to \$3000. *Cholestyramine* and *activated charcoal*, agents that also bind digoxin, can be administered orally to suppress absorption of digoxin from the GI tract.

Adverse Effects II: Noncardiac Adverse Effects

The principal noncardiac toxicities of digoxin concern the GI system and the CNS. Since adverse effects on these systems frequently precede development of dysrhythmias, symptoms involving the GI tract and CNS can provide advance warning of more serious toxicity. Accordingly, patients should be taught to recognize these effects and instructed to notify the prescriber if they occur.

Anorexia, nausea, and vomiting are the most common GI side effects. These responses result primarily from stimulation of the chemoreceptor trigger zone of the medulla. Digoxin rarely causes diarrhea.

Fatigue is the most frequent CNS effect. *Visual disturbances* (eg, blurred vision, yellow tinge to vision, appearance of halos around dark objects) are also relatively common.

Adverse Effects III: Measures to Reduce Adverse Effects

Patient education can help reduce the incidence of toxicity. Patients should be warned about digoxin-induced dysrhythmias and instructed to take their medication exactly as prescribed. In addition, they should be informed about symptoms of developing toxicity (altered heart rate or rhythm, visual or GI disturbances) and instructed to notify the prescriber if these develop. If a potassium supplement or potassium-sparing diuretic is part of the regimen, it should be taken exactly as ordered.

Drug Interactions

Digoxin is subject to a large number of significant drug interactions. Some are pharmacodynamic and some are pharmacokinetic. Several important interactions are dis-

TABLE 48-2 ■ Drug Interactions with Digoxin

Drug	Effect
Pharmacodynamic Interactions	
Thiazide diuretics Loop diuretics	Promote potassium loss and thereby increase the risk of digoxin-induced dysrhythmias
Beta blockers Verapamil Diltiazem	Decrease contractility and heart rate
Sympathomimetics	Increase contractility and heart rate
Pharmacokinetic Interactions	
Cholestyramine Kaolin-pectin Neomycin Sulfasalazine	Decrease digoxin levels by decreasing digoxin absorption or bioavailability
Aminoglycosides Antacids Colestipol Azithromycin Clarithromycin Erythromycin Omeprazole Tetracycline	Increase digoxin levels by increasing digoxin absorption or bioavailability
Alprazolam Amiodarone Captopril Diltiazem Nifedipine Nitrendipine Propafenone Quinidine Verapamil	Increase digoxin levels by decreasing excretion of digoxin, altering distribution of digoxin, or both

cussed below. A summary of interactions is presented in Table 48-2.

Diuretics. *Thiazide diuretics* and *loop diuretics* promote loss of potassium, and thereby increase the risk of digoxin-induced dysrhythmias. Accordingly, when digoxin and these diuretics are used concurrently, serum potassium levels must be monitored and maintained within the normal range (3.5 to 5 mEq/L). If hypokalemia develops, potassium levels can be restored with potassium supplements, a potassium-sparing diuretic, or both.

ACE Inhibitors and ARBs. These drugs can increase potassium levels, and can thereby decrease therapeutic responses to digoxin. Exercise caution if an ACE inhibitor or ARB is combined with potassium supplements or a potassium-sparing diuretic.

Sympathomimetics. Sympathomimetic drugs (eg, dopamine, dobutamine) act on the heart to increase the rate and force of contraction. The increase in contractile force can add to the positive inotropic effects of digoxin. These complementary actions can be beneficial. In contrast, the ability of sympathomimetics to increase heart rate may be detrimental in that the risk of a tachydysrhythmia is increased.

Quinidine. Quinidine is an antidysrhythmic drug that can cause plasma levels of digoxin to rise. Quinidine increases digoxin levels by (1) displacing digoxin from tissue binding sites and (2) reducing renal excretion of digoxin. By elevating

levels of free digoxin, quinidine can promote digoxin toxicity. Accordingly, concurrent use of quinidine and digoxin should be avoided.

Verapamil. Verapamil, a calcium channel blocker, can significantly increase plasma levels of digoxin. If the combination is employed, digoxin dosage must be reduced. In addition, verapamil can suppress myocardial contractility, and can thereby counteract the benefits of digoxin.

Pharmacokinetics

Absorption. Absorption with digoxin tablets is variable, ranging between 60% and 80%, and can be decreased by certain foods and drugs. Meals high in bran can decrease absorption significantly, as can cholestyramine, kaolin-pectin, and certain other drugs (see Table 48-2). Of note, taking digoxin with meals decreases the rate of absorption but not the extent.

In the past, there was considerable variability in the absorption of digoxin from tablets prepared by different manufacturers. This variability resulted from differences in the rate and extent of tablet dissolution. Because of this variable bioavailability, it had been recommended that patients not switch between different digoxin brands. Today, bioavailability of digoxin in tablets produced by different companies is fairly uniform, making brands of digoxin more interchangeable than in the past. However, given the narrow therapeutic range of digoxin, some authorities still recommend that patients not switch between brands of digoxin tablets—even when prescriptions are written generically—except with the approval and supervision of the prescriber.

Distribution. Digoxin is distributed widely and crosses the placenta. High levels are achieved in cardiac and skeletal muscle, owing largely to binding to Na^+, K^+ -ATPase. About 23% of digoxin in plasma is bound to proteins, mainly albumin.

Elimination. Digoxin is eliminated primarily by renal excretion. Hepatic metabolism is minimal. Because digoxin is eliminated by the kidneys, renal impairment can lead to toxic accumulation. Accordingly, dosage must be reduced if kidney function declines. Because digoxin is not metabolized to a significant extent, changes in liver function do not affect digoxin levels.

Half-Life and Time to Plateau. The half-life of digoxin is about 1.5 days. Hence, in the absence of a loading dose, about 6 days (four half-lives) are required to reach plateau. When use of the drug is discontinued, another 6 days are required for digoxin stores to be eliminated.

Single-Dose Time Course. Effects of a single oral dose begin 30 minutes to 2 hours after administration and peak within 4 to 6 hours. Effects of IV digoxin begin rapidly (within 5 to 30 minutes) and peak in 1 to 4 hours.

A Note on Plasma Digoxin Levels. Most hospitals are equipped to measure plasma levels of digoxin. The optimal range is 0.5 to 0.8 ng/mL. Levels above 1 ng/mL offer no additional benefits, but do increase the risk of toxicity. Knowledge of plasma levels can be useful for

- Establishing dosage
- Monitoring compliance
- Diagnosing toxicity
- Determining the cause of therapeutic failure

Once a stable blood level has been achieved, routine measurement of digoxin levels can be replaced with an an-

nual measurement. Additional measurements may be useful when

- Digoxin dosage is changed
- Symptoms of HF intensify
- Kidney function deteriorates
- Signs of toxicity appear
- Drugs that can affect digoxin levels are added to or deleted from the regimen

Although knowledge of digoxin plasma levels can aid the clinician, it must be understood that the extent of this aid is limited. The correlation between plasma levels of digoxin and clinical effects—both therapeutic and adverse—is not very tight: Drug levels that are safe and effective for patient A may be subtherapeutic for patient B and toxic for patient C. Because of interpatient variability, knowledge of digoxin levels does not permit precise predictions of therapeutic effects or toxicity. Hence, information regarding drug levels must not be relied on too heavily. Rather, this information should be seen as but one factor among several to be considered when evaluating clinical responses.

Preparations, Dosage, and Administration

Preparations. Digoxin is available in three formulations:

- Tablets—0.125 and 0.25 mg
- Pediatric elixir—0.05 mg/mL
- Solution for injection—0.1 and 0.25 mg/mL

Administration. Digoxin can be administered orally and intravenously. Intramuscular administration should be avoided, owing to a risk of tissue damage and severe pain. Prior to dosing, the rate and regularity of the heartbeat should be determined. If heart rate is less than 60 beats/min or if a change in rhythm is detected, digoxin should be withheld and the prescriber notified. When digoxin is given IV, cardiac status should be monitored continuously for 1 to 2 hours.

Dosage in Heart Failure. Most patients can be treated with initial and maintenance dosages of 0.125 mg/day. Doses above 0.25 mg/day are rarely used or needed. The target plasma drug level is 0.5 to 0.8 ng/mL.

Digitalization. The term *digitalization* refers to the use of a loading dose to achieve high plasma levels of digoxin quickly. (As noted, 6 days are needed for drug levels to reach plateau if no loading dose is employed.) Although digitalization was common in the past, the practice is now considered both unnecessary and inappropriate.

MANAGEMENT OF HEART FAILURE

Our discussion of HF management is based on recommendations in the *ACC/AHA 2005 Guideline Update for the Evaluation and Management of Chronic Heart Failure in the Adult* and on an update—*Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults*—issued in 2009. As noted earlier, these guidelines approach HF as a progressive disease that advances through four stages of increasing severity. Management for each stage is discussed below.

These management measures are consistent with those in another guideline—*HFSA 2006 Comprehensive Heart Failure Practice Guideline*—issued by the Heart Failure Society of America. (In addition to discussing heart failure with LV systolic dysfunction [ie, the form of heart failure that we've been discussing], the HFSA guidelines address other issues, including acutely decompensated heart failure, heart failure with preserved LV ejection fraction [diastolic heart failure], and heart failure in special populations.)

Stage A

By definition, patients in ACC/AHA Stage A have no symptoms of HF and no structural or functional cardiac abnormalities—but they do have behaviors or conditions strongly associated with developing HF. Important among these are hypertension, coronary artery disease, diabetes, family history of cardiomyopathy, and a personal history of alcohol abuse, rheumatic fever, or treatment with a cardiotoxic drug (eg, doxorubicin, trastuzumab).

Management is directed at reducing risk. Hypertension, hyperlipidemia, and diabetes should be controlled, as should ventricular rate in patients with supraventricular tachycardias. An ACE inhibitor or ARB can be useful for patients with diabetes, atherosclerosis, or hypertension. Patients should cease behaviors that increase HF risk, especially smoking and alcohol abuse. (Excessive, chronic consumption of alcohol is a leading cause of cardiomyopathy. In patients with HF, acute alcohol consumption can suppress contractility.) There is no evidence that getting regular exercise can prevent development of HF, although exercise does have other health benefits. Routine use of dietary supplements to prevent structural heart disease is not recommended.

Stage B

Like patients in Stage A, those in Stage B have no signs or symptoms of HF, but they do have structural heart disease that is strongly associated with development of HF. Among these structural changes are LV hypertrophy or fibrosis, LV dilation or hypocontractility, valvular heart disease, and previous myocardial infarction.

The goal of management is to prevent development of symptomatic HF. The approach is to implement measures that can prevent further cardiac injury and thereby retard the progression of remodeling and LV dysfunction. Specific measures include all those discussed above for Stage A. In addition, treatment with an ACE inhibitor plus a beta blocker is recommended for all patients with a reduced ejection fraction, history of myocardial infarction, or both. For patients who cannot tolerate ACE inhibitors, an ARB may be used instead. As in Stage A, there is no evidence that using dietary supplements or getting regular exercise can help prevent progression to symptomatic HF.

Stage C

Patients in Stage C have symptoms of HF and also have structural heart disease. As discussed earlier, symptoms include dyspnea, fatigue, peripheral edema, and distention of the jugular veins. Treatment has four major goals: (1) relief of pulmonary and peripheral congestive symptoms, (2) improvement of functional capacity and quality of life, (3) slowing of cardiac remodeling and progression of LV dysfunction, and (4) prolongation of life. Treatment measures include those recommended for Stages A and B, plus those discussed below.

Drug Therapy

Drug therapy of HF has changed dramatically over the past 15 to 20 years. Formerly, digoxin was a mainstay of treatment. Today, its role is secondary. First-line therapy now consists of three drugs: a diuretic, an ACE inhibitor or ARB, and a beta

blocker. As a rule, digoxin is added only when symptoms cannot be managed with the preferred agents.

Diuretics. All patients with evidence of fluid retention should restrict salt intake and use a diuretic. Diuretics are the only reliable means of correcting fluid overload. Furthermore, these drugs produce symptomatic improvement faster than any other drugs. If renal function is good, a thiazide diuretic will work. However, if renal function is significantly impaired, as it is in most patients, a loop diuretic will be needed. Efficacy of diuresis is best assessed by daily measurement of body weight. Once fluid overload has been corrected, diuretic therapy should continue to prevent recurrence. Diuretics should not be used alone. Rather, for most patients, they should be combined with an ACE inhibitor (or ARB) plus a beta blocker. Since aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the effects of diuretics, these agents should be avoided. As noted, although diuretics reduce symptoms, they do not prolong survival.

ACE Inhibitors and ARBs. In the absence of specific contraindications (eg, pregnancy), all patients with Stage C HF should receive an ACE inhibitor. If fluid retention is evident, a diuretic should be used as well. Symptomatic improvement may take weeks or even months to develop. However, even in the absence of symptomatic improvement, ACE inhibitors may prolong life. Dosage should be sufficient to reduce mortality (see Table 48-1).

For patients who cannot tolerate ACE inhibitors (owing to intractable cough or angioedema), ARBs are considered a reasonable alternative. However, it is important to note that clinical experience with ARBs is less than with ACE inhibitors, and that ACE inhibitors have a more favorable effect on cardiac remodeling.

Aldosterone Antagonists. Adding an aldosterone antagonist (spironolactone or eplerenone) to standard therapy (ie, diuretic, ACE inhibitor or ARB, and a beta blocker) is reasonable in patients with moderately severe or severe symptoms of HF following a heart attack. However, aldosterone antagonists must not be used if kidney function is impaired or serum potassium is elevated. Monitoring renal function and potassium levels is imperative.

Beta Blockers. In the absence of specific contraindications, all patients with Stage C HF should receive an approved beta blocker (eg, carvedilol). As with ACE inhibitors, symptomatic improvement may not be evident for months. Nonetheless, life may be prolonged even in the absence of clinical improvement.

Digoxin. Digoxin may be used in combination with ACE inhibitors (or ARBs), diuretics, and beta blockers to improve clinical status. However, although digoxin can reduce symptoms, it does not prolong life. The usual dosage is 0.125 mg/day. Adjustments are based on clinical response. Digoxin may be started early to help improve symptoms, or it may be reserved for patients who have not responded adequately to a diuretic, ACE inhibitor or ARB, and beta blocker.

Isosorbide Dinitrate/Hydralazine. Adding ISDN/hydralazine is recommended to improve outcomes in self-described African Americans who have moderate to severe symptoms despite optimal therapy with ACE inhibitors, beta blockers, and diuretics. For all other patients who continue to have symptoms despite treatment with standard therapy, adding ISDN/hydralazine to the regimen is considered

reasonable. For patients who cannot tolerate ACE inhibitors or ARBs, substitution of ISDN/hydralazine is considered reasonable.

Drugs to Avoid

Patients in Stage C should avoid three classes of drugs: anti-dysrhythmics, calcium channel blockers (CCBs), and NSAIDs (eg, aspirin). Reasons for not using these drugs are as follows:

- **Antidysrhythmic agents**—These drugs have cardiosuppressant and pro-dysrhythmic actions that can make HF worse. Only two agents—amiodarone [Cordarone] and dofetilide [Tikosyn]—have been proven not to reduce survival.
- **Calcium channel blockers**—These drugs can make HF worse and may increase the risk of adverse cardiovascular events. Only the vasoselective CCBs have been shown not to reduce survival.
- **NSAIDs**—These drugs promote sodium retention and peripheral vasoconstriction. Both actions can make HF worse. In addition, NSAIDs can reduce the efficacy and intensify the toxicity of diuretics and ACE inhibitors. Hence, even though aspirin has beneficial effects on coagulation, it should still be avoided.

Device Therapy

Implanted Cardioverter-Defibrillators. Cardiac arrest and fatal ventricular dysrhythmias are relatively common complications of HF. Accordingly, implantable cardioverter-defibrillators are now recommended for primary or secondary prevention to reduce mortality in selected patients.

Cardiac Resynchronization. When the left and right ventricles fail to contract at the same time, cardiac output is further compromised. Synchronized contractions can be restored with a biventricular pacemaker. In clinical trials, cardiac resynchronization improved exercise tolerance and quality of life and reduced all-cause mortality.

Exercise Training

In the past, bed rest was recommended owing to concern that physical activity might accelerate progression of LV dysfunction. However, we now know that inactivity is actually detrimental: It reduces conditioning, worsens exercise intolerance, and contributes to HF symptoms. Conversely, studies have shown that exercise training can improve clinical status, increase exercise capacity, and improve quality of life. Accordingly, exercise training should be considered for all stable patients.

Evaluating Treatment

Evaluation is based on symptoms and physical findings. Reductions in dyspnea on exertion, paroxysmal nocturnal dyspnea, and orthopnea (difficulty breathing, except in the upright position) indicate success. The physical examination

should assess for reductions in jugular distention, edema, and rales. Success is also indicated by increased capacity for physical activity. Accordingly, patients should be interviewed to determine improvements in the maximal activity they can perform without symptoms, the type of activity that regularly produces symptoms, and the maximal activity they can tolerate. (Activity is defined as walking, stair climbing, activities of daily living, or any other activity that is appropriate.) Successful treatment should also improve health-related quality of life in general. Hence the interview should look for improvements in sleep, sexual function, outlook on life, cognitive function (alertness, memory, concentration), and ability to participate in usual social, recreational, and work activities.

Routine measurement of ejection fraction or maximal exercise capacity is not recommended. Although the degree of reduction in ejection fraction measured at the beginning of therapy is predictive of outcome, improvement in the ejection fraction does not necessarily indicate the prognosis has changed.

As noted earlier, a reduction in circulating BNP indicates improvement. The lower BNP is, the better the odds of long-term survival.

Stage D

Patients in Stage D have advanced structural heart disease and marked symptoms of HF at rest, despite treatment with maximal dosages of medications used in Stage C. Repeated and prolonged hospitalization is common. For eligible candidates, the best long-term solution is a heart transplant. An implantable LV mechanical assist device can be used as a "bridge" in patients awaiting a transplant and to prolong life in those who are not transplant eligible.

Management focuses largely on control of fluid retention, which underlies most signs and symptoms. Intake and output should be monitored closely, and the patient should be weighed daily. Fluid retention can usually be treated with a loop diuretic, perhaps combined with a thiazide. If volume overload becomes severe, the patient should be hospitalized and given an IV diuretic. If needed, IV dopamine or IV dobutamine can be added to increase renal blood flow, thereby enhancing diuresis. Patients should not be discharged until a stable and effective oral diuretic regimen has been established.

What about beta blockers and ACE inhibitors? These agents may be tried, but doses should be low and responses monitored with care. Why? Because, in Stage D, beta blockers pose a significant risk of making HF worse, and ACE inhibitors may induce profound hypotension or renal failure.

When severe symptoms persist despite application of all recommended therapies, options for end-of-life care should be discussed with the patient and family.

KEY POINTS

- Heart failure with LV systolic dysfunction, referred to simply as *heart failure* (HF) in this chapter, is characterized by ventricular dysfunction, reduced cardiac output, signs of inadequate tissue perfusion (fatigue, shortness of breath, exercise intolerance), and signs of fluid overload (venous distention, peripheral edema, pulmonary edema).
- The initial phase of HF consists of cardiac remodeling—a process in which the ventricles dilate (grow larger), hypertrophy (increase in wall thickness), and become more spherical—coupled with cardiac fibrosis and myocyte death. As a result of these changes, cardiac output is reduced.
- Reduced cardiac output leads to compensatory responses: (1) activation of the SNS, (2) activation of the RAAS, and (3) retention of water and expansion of blood volume. As a result of volume expansion, cardiac dilation increases.
- If the compensatory responses are not sufficient to maintain adequate production of urine, body water will continue to accumulate, eventually causing death (from complete cardiac failure secondary to excessive cardiac dilation and cardiac edema).
- There are three major groups of drugs for heart failure: diuretics, ACE inhibitors or ARBs, and beta blockers. Digoxin, which had been used widely in the past, may be added as indicated.
- Diuretics are first-line drugs for all patients with fluid overload. By reducing blood volume, these drugs can decrease venous pressure, arterial pressure, pulmonary edema, peripheral edema, and cardiac dilation.
- Although diuretics can reduce symptoms of HF, they do not prolong survival.
- Thiazide diuretics are ineffective when GFR is low, and hence cannot be used if cardiac output is greatly reduced.
- Loop diuretics are effective even when GFR is low, and hence are preferred to thiazides for most patients.
- Thiazide diuretics and loop diuretics can cause hypokalemia, and can thereby increase the risk of digoxin-induced dysrhythmias.
- Potassium-sparing diuretics are used to counteract potassium loss caused by thiazide diuretics and loop diuretics.
- Potassium-sparing diuretics can cause hyperkalemia. By doing so, they can increase the risk of hyperkalemia in patients taking ACE inhibitors or ARBs.
- In patients with HF, ACE inhibitors improve functional status and reduce mortality. In the absence of specific contraindications, all patients should get one.
- ACE inhibitors block formation of angiotensin II, promote accumulation of kinins, and reduce aldosterone release. As a result, these drugs cause dilation of veins and arterioles, promote renal excretion of water, and favorably alter cardiac remodeling.
- By dilating arterioles, ACE inhibitors (1) improve regional blood flow in the kidneys and other tissues and (2) reduce cardiac afterload, which causes stroke volume and cardiac output to rise.
 - By dilating veins, ACE inhibitors reduce venous pressure, which in turn reduces pulmonary congestion, peripheral edema, preload, and cardiac dilation.
 - By suppressing aldosterone release, ACE inhibitors increase excretion of sodium and water, and decrease excretion of potassium.
 - By increasing levels of kinins (and partly by decreasing levels of angiotensin II), ACE inhibitors can favorably alter cardiac remodeling.
 - Major side effects of ACE inhibitors are hypotension, hyperkalemia, cough, angioedema, and birth defects.
 - ARBs share the beneficial hemodynamic effects of ACE inhibitors, but not the beneficial effects on cardiac remodeling.
 - In patients with HF, ARBs should be reserved for patients intolerant of ACE inhibitors (usually owing to cough).
 - In patients with HF, aldosterone antagonists (eg, spironolactone, eplerenone) reduce symptoms and prolong life. Benefits derive from blocking aldosterone receptors in the heart and blood vessels.
 - Isosorbide dinitrate (which dilates veins) plus hydralazine (which dilates arterioles) can be used in place of an ACE inhibitor (or ARB) if an ACE inhibitor (or ARB) cannot be used.
 - BiDil, a fixed-dose combination of hydralazine and isosorbide dinitrate, is approved specifically for treating HF in blacks.
 - Beta blockers can prolong survival in patients with HF, and hence are considered first-line therapy.
 - To avoid excessive cardiodepression, beta blocker dosage must be very low initially and then gradually increased.
 - Digoxin and other inotropic agents increase the force of myocardial contraction, and thereby increase cardiac output.
 - Of the available inotropic agents, digoxin is the only one that is both effective and safe when used *orally*, and hence the only one suitable for long-term use.
 - Digoxin increases contractility by inhibiting myocardial Na^+, K^+ -ATPase, thereby (indirectly) increasing intracellular calcium, which in turn facilitates the interaction of actin and myosin.
 - Potassium competes with digoxin for binding to Na^+, K^+ -ATPase. Hence, if potassium levels are low, excessive inhibition of Na^+, K^+ -ATPase can occur, resulting in toxicity. Conversely, if potassium levels are high, insufficient inhibition can occur, resulting in therapeutic failure. Accordingly, it is imperative to keep potassium levels in the normal physiologic range: 3.5 to 5 mEq/L.
 - By increasing cardiac output, digoxin can reverse all of the overt manifestations of HF: cardiac output improves, heart rate decreases, heart size declines, constriction of arterioles and veins decreases, water retention reverses, blood volume declines, peripheral and pulmonary edema decrease, weight is lost (owing to water loss), and exercise tolerance improves. Unfortunately, although digoxin can improve symptoms, it does not prolong life.

- In patients with HF, benefits of digoxin are not due solely to improved cardiac output: Neurohormonal effects are important too.
- Digoxin causes dysrhythmias by altering the electrical properties of the heart (secondary to inhibition of Na^+/K^+ -ATPase).
- The most common reason for digoxin-related dysrhythmias is diuretic-induced hypokalemia.
- If a severe digoxin overdose is responsible for dysrhythmias, digoxin levels can be lowered using Fab antibody fragments [Digibind].
- In addition to dysrhythmias, digoxin can cause GI effects (anorexia, nausea, vomiting) and CNS effects (fatigue, visual disturbances). Gastrointestinal and CNS effects often precede dysrhythmias, and therefore can provide advance warning of serious toxicity.
- Digoxin has a narrow therapeutic range.
- Digoxin is eliminated by renal excretion.
- Although routine monitoring of digoxin levels is generally unnecessary, monitoring can be helpful when dosage

is changed, symptoms of HF intensify, kidney function declines, signs of toxicity appear, or drugs that affect digoxin levels are added to or deleted from the regimen.

- Maintenance doses of digoxin are based primarily on observation of the patient. Doses should be large enough to minimize symptoms of HF but not so large as to cause adverse effects.
- Maintenance doses of digoxin must be reduced if renal function declines.
- Therapy of Stage C HF has four major goals: (1) relief of pulmonary and peripheral congestion, (2) improvement of functional status and quality of life, (3) retarding progression of cardiac remodeling and LV dysfunction, and (4) prolongation of life.
- For routine therapy, Stage C HF is treated with a diuretic, an ACE inhibitor or an ARB, and a beta blocker.

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Summary of Major Nursing Implications*

DIGOXIN

Preadministration Assessment

Therapeutic Goal

Digoxin is used to treat HF and dysrhythmias. Be sure to confirm which disorder the drug has been ordered for.

Baseline Data

Assess for signs and symptoms of HF, including fatigue, weakness, cough, breathing difficulty (orthopnea, dyspnea on exertion, paroxysmal nocturnal dyspnea), jugular distention, and edema.

Determine baseline values for maximal activity without symptoms, activity that regularly causes symptoms, and maximal tolerated activity.

Laboratory tests should include an ECG, serum electrolytes, measurement of ejection fraction, and evaluation of kidney function.

Identifying High-Risk Patients

Digoxin is *contraindicated* for patients experiencing ventricular fibrillation, ventricular tachycardia, or digoxin toxicity.

Exercise *caution* in the presence of conditions that can predispose the patient to serious adverse responses to digoxin, such as hypokalemia, partial AV block, advanced HF, or renal impairment.

Implementation: Administration

Routes

Oral, slow IV injection.

Administration

Oral. Determine heart rate and rhythm prior to administration. If heart rate is less than 60 beats/min or if a change in rhythm is detected, withhold digoxin and notify the prescriber.

Warn patients not to “double up” on doses in attempts to compensate for missed doses.

Intravenous. Monitor cardiac status closely for 1 to 2 hours following IV injection.

Promoting Adherence

Because digoxin has a narrow therapeutic range, rigid adherence to the prescribed dosage is essential. **Inform patients that failure to take digoxin exactly as prescribed may lead to toxicity or therapeutic failure.** If poor adherence is suspected, serum drug levels may help in assessing the extent of nonadherence.

Implementation: Measures to Enhance Therapeutic Effects

Advise patients to limit salt intake to 2 gm/day, and to avoid excessive fluids. Advise patients who drink alcohol to consume no more than one drink each day. Advise obese pa-

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

tients to adopt a reduced-calorie diet. Help patients establish an appropriate program of regular, mild exercise (eg, walking, cycling). Precipitating factors for HF (eg, hypertension, valvular heart disease) should be corrected.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Evaluation is based on symptoms and physical findings. Assess for reductions in orthopnea, dyspnea on exertion, paroxysmal nocturnal dyspnea, neck vein distention, edema, and rales, and for increased capacity for physical activity. In addition, assess for improvements in sleep, sexual function, outlook on life, cognitive function, and ability to participate in social, recreational, and work activities.

Plasma BNP levels reflect cardiac status: The lower the level, the better the odds for long-term survival.

Measurement of plasma drug levels can help determine the cause of therapeutic failure. The optimal range for digoxin is 0.5 to 0.8 ng/mL.

Minimizing Adverse Effects

Cardiotoxicity. Dysrhythmias are the most serious adverse effect of digoxin.

Monitor hospitalized patients for alterations in heart rate or rhythm, and withhold digoxin if significant changes develop.

Inform outpatients about the danger of dysrhythmias. Teach them to monitor their pulses for rate and rhythm, and instruct them to notify the prescriber if significant changes occur. Provide the patient with an ECG rhythm strip; this can be used by providers unfamiliar with the patient (eg, when the patient is traveling) to verify suspected changes in rhythm.

Hypokalemia, usually diuretic induced, is the most frequent underlying cause of dysrhythmias. Monitor serum potassium concentrations. If hypokalemia develops, potassium levels can be raised with potassium supplements, a potassium-sparing diuretic, or both. **Teach patients to recognize early signs of hypokalemia (eg, muscle weakness), and**

instruct them to notify the prescriber if these develop. Severe vomiting and diarrhea can increase potassium loss; exercise caution if these events occur.

To treat digoxin-induced dysrhythmias: (1) withdraw digoxin and diuretics (make sure that a written order for digoxin withdrawal is made); (2) administer potassium (unless potassium levels are above normal or AV block is present); (3) administer an antidysrhythmic drug (phenytoin or lidocaine, but not quinidine) if indicated; (4) manage bradycardia with atropine or electrical pacing; and (5) treat with Fab fragments if toxicity is life threatening.

Noncardiac Effects. *Nausea, vomiting, anorexia, fatigue, and visual disturbances* (blurred or yellow vision) frequently foreshadow more serious toxicity (dysrhythmias) and should be reported immediately. **Inform patients about these early indications of toxicity, and instruct them to notify the prescriber if they develop.**

Minimizing Adverse Interactions

Diuretics. *Thiazide diuretics and loop diuretics* increase the risk of dysrhythmias by promoting potassium loss. Monitor potassium levels. If hypokalemia develops, it should be corrected with potassium supplements, a potassium-sparing diuretic, or both.

ACE Inhibitors and ARBs. These drugs can elevate potassium levels, and can thereby decrease therapeutic responses to digoxin. Exercise caution if an ACE inhibitor or ARB is combined with potassium supplements or a potassium-sparing diuretic.

Sympathomimetic Agents. Sympathomimetic drugs (eg, dopamine, dobutamine) stimulate the heart, thereby increasing the risk of tachydysrhythmias and ectopic pacemaker activity. When sympathomimetics are combined with digoxin, monitor closely for dysrhythmias.

Quinidine. Quinidine can elevate plasma levels of digoxin. If quinidine is employed concurrently with digoxin, digoxin dosage must be reduced. Do not use quinidine to treat digoxin-induced dysrhythmias.

*Patient education information is highlighted as blue text.

INTRODUCTION TO CARDIAC ELECTROPHYSIOLOGY, DYSRHYTHMIAS, AND THE ANTIDYSRHYTHMIC DRUGS

Electrical Properties of the Heart

Impulse Conduction: Pathways and Timing

Cardiac Action Potentials

The Electrocardiogram

Generation of Dysrhythmias

Disturbances of Automaticity

Disturbances of Conduction

Classification of Antidysrhythmic Drugs

Prodysrhythmic Effects of Antidysrhythmic Drugs

Overview of Common Dysrhythmias and Their Treatment

Supraventricular Dysrhythmias

Ventricular Dysrhythmias

Principles of Antidysrhythmic Drug Therapy

PHARMACOLOGY OF THE ANTIDYSRHYTHMIC DRUGS

Class I: Sodium Channel Blockers

Class IA Agents

Class IB Agents

Class IC Agents

Class II: Beta Blockers

Class III: Potassium Channel Blockers (Drugs That Delay Repolarization)

Amiodarone

Dronedarone

Sotalol

Dofetilide

Ibutilide

Class IV: Calcium Channel Blockers

Other Antidysrhythmic Drugs

Adenosine

Digoxin

NONDRUG TREATMENT OF DYSRHYTHMIAS

Implantable Cardioverter-Defibrillators

Radiofrequency Catheter Ablation

There are two basic types of dysrhythmias: *tachydysrhythmias* (dysrhythmias in which heart rate is increased) and *bradydysrhythmias* (dysrhythmias in which heart rate is slowed). In this chapter, we only consider the tachydysrhythmias. This is by far the largest group of dysrhythmias and the group that responds best to drugs. We do not discuss the bradydysrhythmias because they are few in number and are commonly treated with electronic pacing. When drugs are indicated, atropine (see Chapter 14) and isoproterenol (see Chapter 17) are usually the agents of choice.

It is important to appreciate that virtually all of the drugs used to treat dysrhythmias can also *cause* dysrhythmias. These drugs can create new dysrhythmias and worsen existing ones. Because of these prodysrhythmic actions, antidysrhythmic drugs should be employed only when the benefits of treatment clearly outweigh the risks.

For two reasons, use of antidysrhythmic drugs is declining. First, research has shown that some of these agents actually *increase* the risk of death. Second, nonpharmacologic therapies—especially implantable defibrillators and radiofrequency ablation—have begun to replace drugs as the preferred treatment for many dysrhythmia types.

A note on terminology: Dysrhythmias are also known as *arrhythmias*. Since the term *arrhythmia* denotes an *absence* of cardiac rhythm, whereas *dysrhythmia* denotes an *abnormal* rhythm, dysrhythmia would seem the more appropriate term.

INTRODUCTION TO CARDIAC ELECTROPHYSIOLOGY, DYSRHYTHMIAS, AND THE ANTIDYSRHYTHMIC DRUGS

In this section we discuss background information that will help you understand the actions and uses of antidysrhythmic drugs. We begin by reviewing the electrical properties of the heart and the electrocardiogram. Next, we discuss how dysrhythmias are generated. After that, we discuss classification of the antidysrhythmic drugs as well as the ability of these drugs to *cause* dysrhythmias. We conclude by discussing the major dysrhythmias and the basic principles that guide antidysrhythmic therapy.

ELECTRICAL PROPERTIES OF THE HEART

Dysrhythmias result from alteration of the electrical impulses that regulate cardiac rhythm—and antidysrhythmic drugs control rhythm by correcting or compensating for these alterations. Accordingly, in order to understand both the generation and treatment of dysrhythmias, we must first understand the electrical properties of the heart. Therefore, we begin the chapter by reviewing (1) pathways and timing of impulse

A dysrhythmia is defined as *an abnormality in the rhythm of the heartbeat*. In their mildest forms, dysrhythmias have only modest effects on cardiac output. However, in their most severe forms, dysrhythmias can so disable the heart that no blood is pumped at all. Because of their ability to compromise cardiac function, dysrhythmias are associated with a high degree of morbidity and mortality.

conduction, (2) cardiac action potentials, and (3) basic elements of the electrocardiogram (ECG).

Impulse Conduction: Pathways and Timing

For the heart to pump effectively, contraction of the atria and ventricles must be coordinated. Coordination is achieved through precise timing and routing of impulse conduction. In the healthy heart, impulses originate in the sinoatrial (SA) node, spread rapidly through the atria, pass slowly through the atrioventricular (AV) node, and then spread rapidly through the ventricles via the His-Purkinje system (Fig. 49-1).

SA Node. Under normal circumstances, the SA node serves as the pacemaker for the heart. Pacemaker activity results from spontaneous phase 4 depolarization (see below). Because cells of the sinus node usually discharge faster than other cells that display automaticity, the SA node normally dominates all other potential pacemakers.

After the SA node discharges, impulses spread rapidly through the atria along the *internodal pathways*. This rapid conduction allows the atria to contract in unison.

AV Node. Impulses originating in the atria must travel through the AV node to reach the ventricles. In the healthy heart, impulses arriving at the AV node are delayed before going on to excite the ventricles. This delay provides time for blood to fill the ventricles prior to ventricular contraction.

His-Purkinje System. The fibers of the His-Purkinje system consist of specialized conducting tissue. The function of these fibers is to conduct electrical excitation very rapidly to all parts of the ventricles. Stimulation of the His-Purkinje system is caused by impulses leaving the AV node. These impulses are conducted rapidly down the bundle of His, enter the right and left bundle branches, and then distribute to the many fine branches of the Purkinje fibers (see Fig. 49-1). Because impulses travel quickly through this system, all regions of the ventricles are stimulated almost simultaneously, producing synchronized ventricular contraction with resultant forceful ejection of blood.

Cardiac Action Potentials

Cardiac cells can initiate and conduct action potentials, consisting of self-propagating waves of depolarization followed by repolarization. As in neurons, cardiac action potentials are generated by the movement of ions into and out of cells. These ion fluxes take place by way of specific channels in the cell membrane. In the resting cardiac cell, negatively charged ions cover the inner surface of the cell membrane while positively charged ions cover the external surface. Because of this separation of charge, the cell membrane is said to be *polarized*. Under proper conditions, channels in the cell membrane open, allowing positively charged ions to rush in. This influx eliminates the charge difference across the cell membrane, and hence the cell is said to depolarize. Following depolarization, positively charged ions are extruded from the cell, causing the cell to return to its original polarized state.

In the heart, two kinds of action potentials occur: *fast potentials* and *slow potentials*. These potentials differ with respect to the mechanisms by which they are generated, the kinds of cells in which they occur, and the drugs to which they respond.

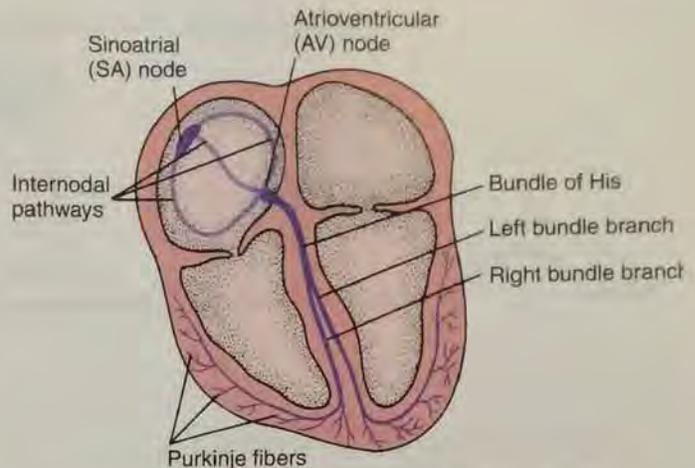


Figure 49-1 • Cardiac conduction pathways.

Profiles of fast and slow potentials are depicted in Figure 49-2. Please note that action potentials in this figure represent the electrical activity of *single cardiac cells*. Such single-cell recordings, which are made using experimental preparations, should not be confused with the ECG, which is made using surface electrodes, and hence reflects the electrical activity of the entire heart.

Fast Potentials

Fast potentials occur in fibers of the *His-Purkinje system* and in *atrial and ventricular muscle*. These responses serve to conduct electrical impulses rapidly throughout the heart.

As indicated in panel A of Figure 49-2, fast potentials have five distinct phases, labeled 0, 1, 2, 3, and 4. As we discuss each phase, we focus on its ionic basis and its relationship to the actions of antidysrhythmic drugs.

Phase 0. In phase 0, the cell undergoes *rapid depolarization* in response to *influx of sodium ions*. Phase 0 is important in that the speed of phase 0 depolarization determines the velocity of impulse conduction. Drugs that decrease the rate of phase 0 depolarization (by blocking sodium channels) slow impulse conduction through the His-Purkinje system and myocardium.

Phase 1. During phase 1, rapid (but partial) repolarization takes place. Phase 1 has no relevance to antidysrhythmic drugs.

Phase 2. Phase 2 consists of a prolonged plateau in which the membrane potential remains relatively stable. During this phase, *calcium* enters the cell and promotes contraction of atrial and ventricular muscle. Drugs that reduce calcium entry during phase 2 do *not* influence *cardiac rhythm*. However, since calcium influx is required for contraction, these drugs *can* reduce myocardial contractility.

Phase 3. In phase 3, rapid repolarization takes place. This repolarization is caused by *extrusion of potassium* from the cell. Phase 3 is relevant in that delay of repolarization prolongs the action potential duration, and thereby prolongs the effective refractory period (ERP). (The ERP is the time during which a cell is unable to respond to excitation and initiate a new action potential. Hence, extending the ERP prolongs the minimum interval between two propagating responses.) Phase 3 repolarization can be delayed by drugs that block potassium channels.

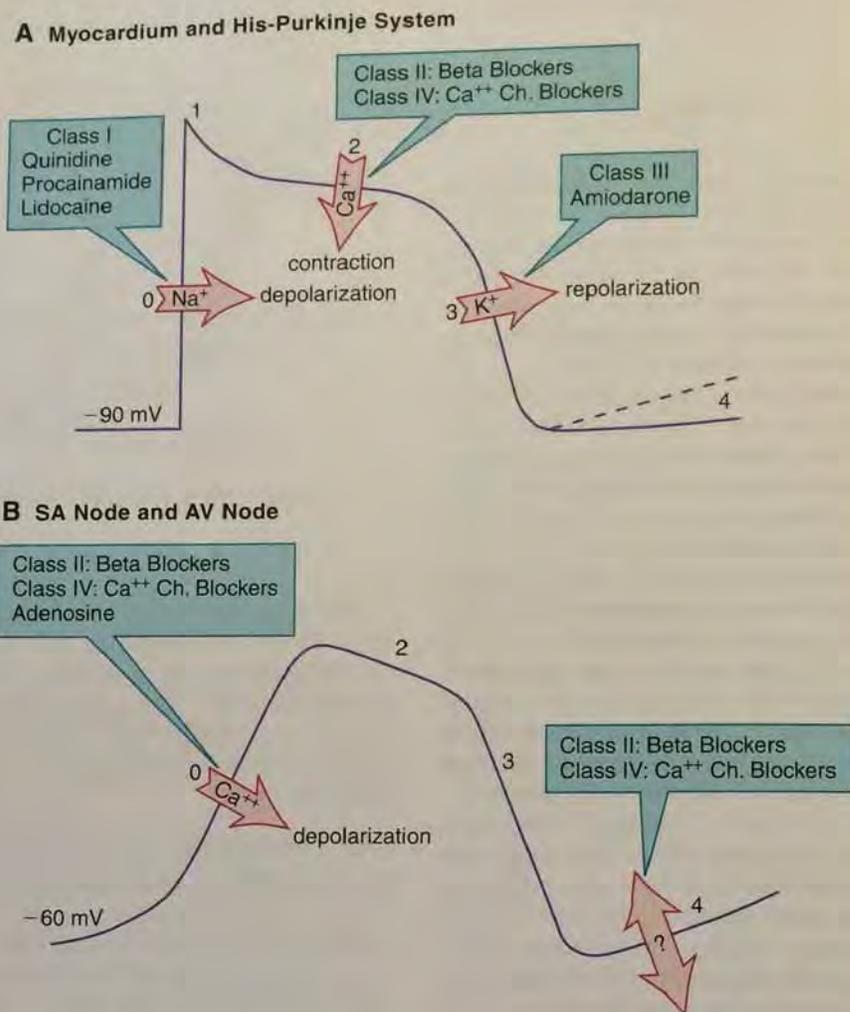


Figure 49-2 ■ Ion fluxes during cardiac action potentials and effects of antidysrhythmic drugs.

A, Fast potential of the His-Purkinje system and atrial and ventricular myocardium. Blockade of sodium influx by class I drugs slows conduction in the His-Purkinje system. Blockade of calcium influx by beta blockers and calcium channel blockers decreases contractility. Blockade of potassium efflux by class III drugs delays repolarization and thereby prolongs the effective refractory period. **B**, Slow potential of the sinoatrial (SA) node and atrioventricular (AV) node. Blockade of calcium influx by beta blockers, calcium channel blockers, and adenosine slows AV conduction. Beta blockers and calcium channel blockers decrease SA nodal automaticity (phase 4 depolarization); the ionic basis of this effect is not understood.

Phase 4. During phase 4, two types of electrical activity are possible: (1) the membrane potential may remain *stable* (solid line in Fig. 49-2A), or (2) the membrane may undergo *spontaneous depolarization* (dashed line). In cells undergoing spontaneous depolarization, the membrane potential gradually rises until a threshold potential is reached. At this point, rapid phase 0 depolarization takes place, setting off a new action potential. Hence, it is phase 4 depolarization that gives cardiac cells *automaticity* (ie, the ability to initiate an action potential through self-excitation). The capacity for self-excitation makes potential pacemakers of all cells that have it.

Under normal conditions, His-Purkinje cells undergo very slow spontaneous depolarization, and myocardial cells do not undergo any. However, under pathologic conditions, significant phase 4 depolarization may occur in all of these cells,

and especially in Purkinje fibers. When this happens, a dysrhythmia can result.

Slow Potentials

Slow potentials occur in cells of the *SA node* and *AV node*. The profile of a slow potential is depicted in Figure 49-2B. Like fast potentials, slow potentials are generated by ion fluxes. However, the specific ions involved are not the same for every phase.

From a physiologic and pharmacologic perspective, slow potentials have three features of special significance: (1) phase 0 depolarization is slow and mediated by calcium influx, (2) these potentials conduct slowly, and (3) spontaneous phase 4 depolarization in the SA node normally determines heart rate.

Phase 0. Phase 0 (depolarization phase) of slow potentials differs significantly from phase 0 of fast potentials. As we can see from Figure 49-2, whereas phase 0 of fast potentials is caused by a *rapid influx of sodium*, phase 0 of slow potentials is caused by *slow influx of calcium*. Because calcium influx is slow, the rate of depolarization is slow; and because depolarization is slow, these potentials conduct slowly. This explains why impulse conduction through the AV node is delayed. Phase 0 of the slow potential is of therapeutic significance in that drugs that suppress calcium influx during phase 0 can slow (or stop) AV conduction.

Phases 1, 2, and 3. Slow potentials lack a phase 1 (see Fig. 49-2B). Phases 2 and 3 of the slow potential are not significant with respect to the actions of antidysrhythmic drugs.

Phase 4. Cells of the SA node and AV node undergo spontaneous phase 4 depolarization. The ionic basis of this phenomenon is complex and incompletely understood.

Under normal conditions, the rate of phase 4 depolarization in cells of the SA node is faster than in all other cells of the heart. As a result, the SA node discharges first and determines heart rate. Hence, the SA node is referred to as the *cardiac pacemaker*.

As indicated in Figure 49-2B, two classes of drugs (beta blockers and calcium channel blockers) can suppress phase 4 depolarization. By doing so, these agents can decrease automaticity in the SA node.

The Electrocardiogram

The ECG provides a graphic representation of cardiac electrical activity. The ECG can be used to identify dysrhythmias and monitor responses to therapy. (Note: In referring to the electrocardiogram, two abbreviations may be used: EKG and ECG. Some people prefer EKG over ECG. Why? Because ECG sounds much like EEG [electroencephalogram] when spoken aloud, whereas EKG does not.)

The major components of an ECG are illustrated in Figure 49-3. As we can see, three features are especially prominent: the P wave, the QRS complex, and the T wave. The P wave is caused by *depolarization in the atria*. Hence, the P wave corresponds to atrial contraction. The QRS complex is caused by *depolarization of the ventricles*. Hence, the QRS complex corresponds to ventricular contraction. If conduction through the ventricles is slowed, the QRS complex will widen. The T wave is caused by *repolarization of the ventricles*. Hence, this wave is not associated with overt physical activity of the heart.

In addition to the features just described, the ECG has three other components of interest: the PR interval, the QT interval, and the ST segment. The PR interval is defined as the time between the onset of the P wave and the onset of the QRS complex. Lengthening of this interval indicates a delay in conduction through the AV node. Several drugs increase the PR interval. The QT interval is defined as the time between the onset of the QRS complex and completion of the T wave. This interval is prolonged by drugs that delay ventricular repolarization. The ST segment is the portion of the ECG that lies between the end of the QRS complex and the beginning of the T wave. Digoxin depresses the ST segment.

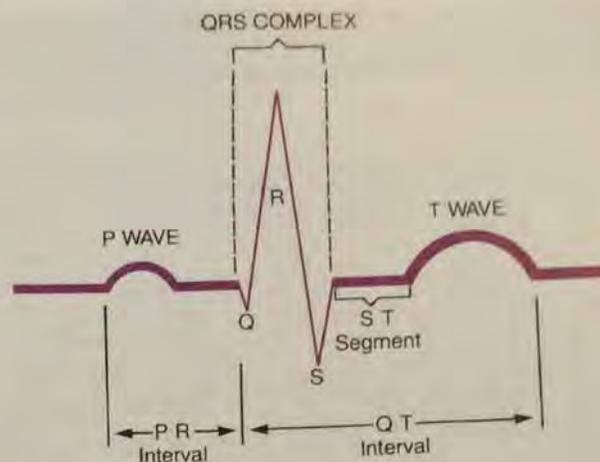


Figure 49-3 • The electrocardiogram.

GENERATION OF DYSRHYTHMIAS

Dysrhythmias arise from two fundamental causes: *disturbances of impulse formation* (automaticity) and *disturbances of impulse conduction*. One or both of these disturbances underlie all dysrhythmias. Factors that may alter automaticity or conduction include hypoxia, electrolyte imbalance, cardiac surgery, reduced coronary blood flow, myocardial infarction, and antidysrhythmic drugs.

Disturbances of Automaticity

Disturbances of automaticity can occur in any part of the heart. Cells normally capable of automaticity (cells of the SA node, AV node, and His-Purkinje system) can produce dysrhythmias if their normal rate of discharge changes. In addition, dysrhythmias may be produced if tissues that do not normally express automaticity (atrial and ventricular muscle) develop spontaneous phase 4 depolarization.

Altered automaticity in the SA node can produce tachycardia or bradycardia. Excessive discharge of sympathetic neurons that innervate the SA node can augment automaticity to such a degree that sinus tachycardia results. Excessive vagal (parasympathetic) discharge can suppress automaticity to such a degree that sinus bradycardia results.

Increased automaticity of Purkinje fibers is a common cause of dysrhythmias. The increase can be brought on by injury and by excessive stimulation of Purkinje fibers by the sympathetic nervous system. If Purkinje fibers begin to discharge faster than the SA node, they will escape control by the SA node; potentially serious dysrhythmias can result.

Under special conditions, automaticity may develop in cells of atrial and ventricular muscle. If these cells fire faster than the SA node, dysrhythmias will result.

Disturbances of Conduction

Atrioventricular Block. Impaired conduction through the AV node produces varying degrees of AV block. If impulse conduction is delayed (but not prevented entirely), the block is termed *first degree*. If some impulses pass through

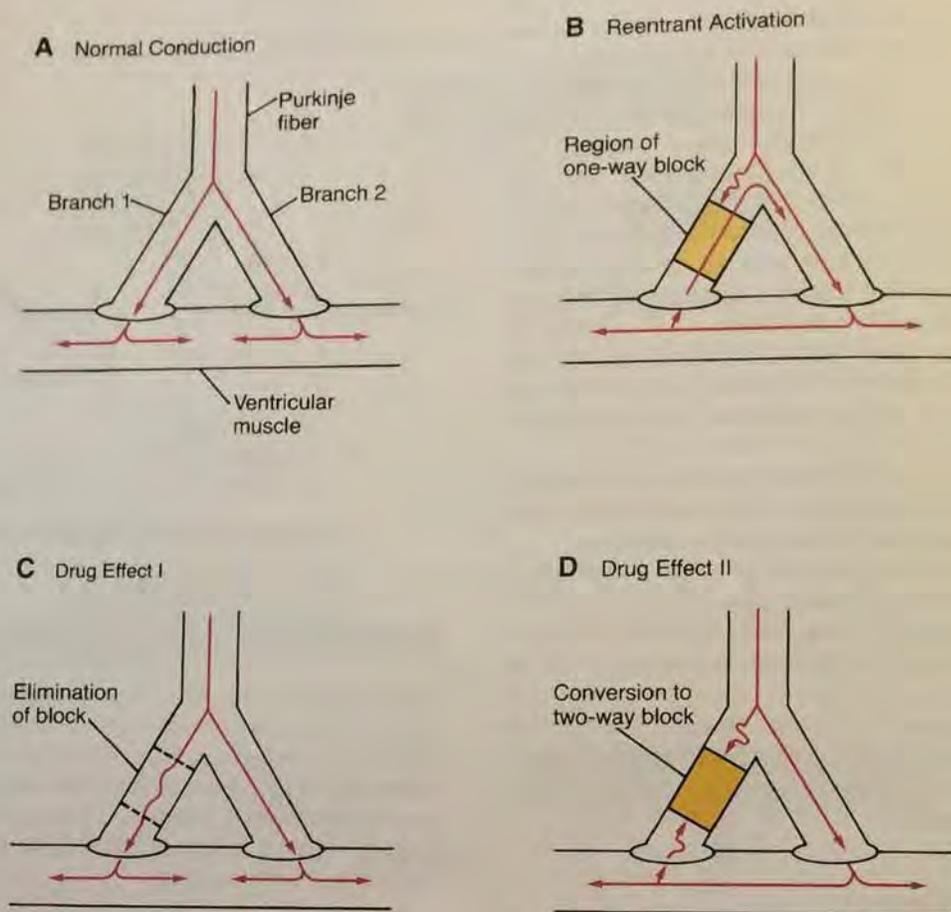


Figure 49-4 ■ Reentrant activation: mechanism and drug effects.

A, In normal conduction, impulses from the branched Purkinje fiber stimulate the strip of ventricular muscle in two places. Within the muscle, waves of excitation spread from both points of excitation, meet between the Purkinje fibers, and cease further travel. **B**, In the presence of one-way block, the strip of muscle is excited at only one location. Impulses spreading from this area meet no impulses coming from the left and, therefore, can travel far enough to stimulate branch 1 of the Purkinje fiber. This stimulation passes back up the fiber, past the region of one-way block, and then stimulates branch 2, causing reentrant activation. **C**, Elimination of reentry by a drug that improves conduction in the sick branch of the Purkinje fiber. **D**, Elimination of reentry by a drug that further suppresses conduction in the sick branch, thereby converting one-way block into two-way block.

the node but others do not, the block is termed *second degree*. If all traffic through the AV node stops, the block is termed *third degree*.

Reentry (Recirculating Activation). Reentry, also referred to as recirculating activation, is a generalized mechanism by which dysrhythmias can be produced. Reentry causes dysrhythmias by establishing a localized, self-sustaining circuit capable of repetitive cardiac stimulation. Reentry results from a unique form of conduction disturbance. The mechanism of reentrant activation and the effects of drugs on this process are described below.

The mechanism for establishing a reentrant circuit is depicted in Figure 49-4, panels *A* and *B*. In the figure, the inverted Y-shaped structure represents a branched Purkinje fiber terminating on a strip of ventricular muscle, which appears as a horizontal bar. Normal impulse conduction is shown in Figure 49-4*A*. As indicated by the arrows, impulses travel down both branches of the Purkinje fiber to cause excitation of the muscle at two locations. Impulses created within the muscle travel in both directions (to the right and left) away from their sites of origin. Those impulses that are moving toward each other

meet midway between the two branches of the Purkinje fiber. Since in the wake of both impulses the muscle is in a refractory state, neither impulse can proceed further, and hence both impulses stop.

Figure 49-4*B* depicts a reentrant circuit. The shaded area in branch 1 of the Purkinje fiber represents a region of one-way conduction block. This region prevents conduction of impulses downward (toward the muscle) but does not prevent impulses from traveling upward. (Impulses can travel back up the block because impulses in muscle are very strong, and hence are able to pass the block, whereas impulses in the Purkinje fiber are weaker, and hence are unable to pass.) A region of one-way block is essential for reentrant activation.

How does one-way block lead to reentrant activation? As an impulse travels down the Purkinje fiber, it is stopped in branch 1 but continues unimpeded in branch 2. Upon reaching the tip of branch 2, the impulse stimulates the muscle. As described above, the impulse in the muscle travels to the right and to the left away from its site of origin. However, in this new situation, as the impulse travels toward the impaired branch of the Purkinje fiber, it meets no impulse coming from the other direction, and hence continues on, resulting in stimulation of the terminal end of branch 1. This stimulation causes an impulse to travel backward up the Purkinje fiber. Since blockade of conduction is unidirectional, the impulse passes through the region of block and then back down into branch 2, causing reentrant activation of this branch. Under

proper conditions, the impulse will continue to cycle indefinitely, resulting in repetitive ectopic beats.

There are two mechanisms by which drugs can abolish a reentrant dysrhythmia. First, drugs can improve conduction in the sick branch of the Purkinje fiber, and can thereby eliminate the one-way block (Fig. 49-4C). Alternatively, drugs can suppress conduction in the sick branch, thereby converting one-way block into two-way block (Fig. 49-4D).

CLASSIFICATION OF ANTIDYSRHYTHMIC DRUGS

According to the Vaughan Williams classification scheme, the antidysrhythmic drugs fall into five groups (Table 49-1). As the table shows, there are four major classes of antidysrhythmic drugs (classes I, II, III, and IV) and a fifth group that includes adenosine and digoxin. Membership in classes I through IV is determined by effects on ion movements during slow and fast potentials (see Fig. 49-2).

Class I: Sodium Channel Blockers

Class I drugs block cardiac sodium channels (see Fig. 49-2A). By doing so, these drugs slow impulse conduction in the atria, ventricles, and His-Purkinje system. Class I constitutes the largest group of antidysrhythmic drugs.

Class II: Beta Blockers

Class II consists of beta-adrenergic blocking agents. As suggested by Figure 49-2, these drugs reduce calcium entry (during fast and slow potentials) and they depress phase 4 depolarization (in slow potentials only). Beta blockers have three prominent effects on the heart:

- In the SA node, they reduce automaticity.
- In the AV node, they slow conduction velocity.
- In the atria and ventricles, they reduce contractility.

Cardiac effects of the beta blockers are nearly identical to those of the calcium channel blockers.

Class III: Potassium Channel Blockers (Drugs That Delay Repolarization)

Class III drugs block potassium channels (Fig. 49-2A), and thereby delay repolarization of fast potentials. By delaying repolarization, these drugs prolong both the action potential duration and the effective refractory period.

Class IV: Calcium Channel Blockers

Only two calcium channel blockers—verapamil and diltiazem—are employed as antidysrhythmics. As indicated in Figure 49-2, calcium channel blockade has the same impact on cardiac action potentials as does beta blockade. Accordingly, verapamil, diltiazem, and beta blockers have nearly identical effects on cardiac function—namely, reduction of automaticity in the SA node, delay of conduction through the AV node, and reduction of myocardial contractility. Antidysrhythmic benefits derive from suppressing AV nodal conduction.

Other Antidysrhythmic Drugs

Adenosine and digoxin do not fit into the four major classes of antidysrhythmic drugs. Both drugs suppress dysrhythmias by decreasing conduction through the AV node and reducing automaticity in the SA node.

TABLE 49-1 ■ Vaughan Williams Classification of Antidysrhythmic Drugs

Class I: Sodium Channel Blockers

Class IA

- Quinidine
- Procainamide [Procan★, generic in U.S.]
- Disopyramide [Norpace, Rythmodan★]

Class IB

- Lidocaine [Xylocaine]
- Phenytoin [Dilantin]
- Mexiletine [Mexitil]

Class IC

- Flecainide [Tambocor]
- Propafenone [Rythmol, Rythmol SR]

Class II: Beta Blockers

- Propranolol [Inderal, Inderal LA]
- Acebutolol [Sectral]
- Esmolol [Brevibloc, Brevibloc Double Strength]

Class III: Potassium Channel Blockers (Drugs That Delay Repolarization)

- Amiodarone [Cordarone, Pacerone]
- Dronedarone [Multaq]
- Dofetilide [Tikosyn]
- Ibutilide [Corvert]
- Sotalol [Betapace, Betapace AF]

Class IV: Calcium Channel Blockers

- Diltiazem [Cardizem, Dilacor-XR, Tiazac, others]
- Verapamil [Calan, Covera-HS, Isoptin SR, Verelan]

Other Antidysrhythmic Drugs

- Adenosine [Adenocard]
- Digoxin [Lanoxin]

PRODYSRHYTHMIC EFFECTS OF ANTIDYSRHYTHMIC DRUGS

Virtually all of the drugs used to treat dysrhythmias have prodysrhythmic (proarrhythmic) effects. That is, *all of these drugs can worsen existing dysrhythmias and generate new ones*. This ability was documented dramatically in the Cardiac Arrhythmia Suppression Trial (CAST), in which use of class IC drugs (encainide and flecainide) to prevent dysrhythmias after myocardial infarction actually *doubled the rate of mortality*. Because of their prodysrhythmic actions, antidysrhythmic drugs should be used only when dysrhythmias are symptomatically significant, and only when the potential benefits clearly outweigh the risks. Applying this guideline, it would be inappropriate to give antidysrhythmic drugs to a patient with nonsustained ventricular tachycardia, since this dysrhythmia does not significantly reduce cardiac output. Conversely, when a patient is facing death from ventricular fibrillation, any therapy that might work must be tried. In this case, the risk of prodysrhythmic effects is clearly outweighed by the potential benefits of stopping the fibrillation. Regardless of the particular circumstances of drug use, all patients must be followed closely.

Of the mechanisms by which drugs can cause dysrhythmias, one deserves special mention: prolongation of the QT interval. As discussed in Chapter 7, drugs that prolong the

QT interval increase the risk of *torsades de pointes*, a dysrhythmia that can progress to fatal ventricular fibrillation. All class IA and class III agents cause QT prolongation, and hence must be used with special caution.

OVERVIEW OF COMMON DYSRHYTHMIAS AND THEIR TREATMENT

The common dysrhythmias can be divided into two major groups: *supraventricular dysrhythmias* and *ventricular dysrhythmias*. In general, ventricular dysrhythmias are more dangerous than supraventricular dysrhythmias. With either type, intervention is required only if the dysrhythmia interferes with effective ventricular pumping. Treatment often proceeds in two phases: (1) *termination* of the dysrhythmia (with electrical countershock, drugs, or both), followed by (2) *long-term suppression* with drugs. Dysrhythmias can also be treated with an implantable cardioverter-defibrillator or by destroying small areas of cardiac tissue using radiofrequency (RF) catheter ablation.

It is important to appreciate that drug therapy of dysrhythmias is highly empiric (ie, based largely on the response of the patient and not on scientific principles). In practice, this means that, even after a dysrhythmia has been identified, we cannot predict with certainty just which drugs will be effective. Frequently, trials with several drugs are required before control of rhythm is achieved. In the discussion below, only first-choice drugs are considered.

Supraventricular Dysrhythmias

Supraventricular dysrhythmias are dysrhythmias that arise in areas of the heart above the ventricles (atria, SA node, AV node). Supraventricular dysrhythmias per se are not especially harmful. Why? Because dysrhythmic activity within the atria does not significantly reduce cardiac output (except in patients with valvular disorders and heart failure). Supraventricular tachydysrhythmias *can* be dangerous, however, in that atrial impulses are likely to traverse the AV node, resulting in excitation of the ventricles. If the atria drive the ventricles at an excessive rate, diastolic filling will be incomplete and cardiac output will decline. Hence, when treating supraventricular tachydysrhythmias, the objective is frequently one of slowing ventricular rate (by blocking impulse conduction through the AV node) and not elimination of the dysrhythmia itself. Of course, if treatment did abolish the dysrhythmia, this outcome would not be unwelcome. Acute treatment of supraventricular dysrhythmias is accomplished with vagotonic maneuvers, direct-current (DC) cardioversion, and certain drugs: class II agents, class IV agents, adenosine, and digoxin.

Atrial Fibrillation. Atrial fibrillation is the most common sustained dysrhythmia, affecting about 2.2 million people in the United States. The disorder is caused by multiple atrial ectopic foci firing randomly; each focus stimulates a small area of atrial muscle. This chaotic excitation produces a highly irregular atrial rhythm. Depending upon the extent of impulse transmission through the AV node, ventricular rate may be very rapid or nearly normal.

In addition to compromising cardiac performance, atrial fibrillation carries a high risk of stroke. Why? Because in patients with atrial fibrillation, some blood can become trapped in the atria (rather than flowing straight through to the

ventricles), thereby permitting formation of a clot. When normal sinus rhythm is restored, the clot may become dislodged, and then may travel to the brain to cause stroke.

Treatment of atrial fibrillation has two goals: improvement of ventricular pumping and prevention of stroke. Pumping can be improved by either (1) restoring normal sinus rhythm or (2) slowing ventricular rate. The preferred method is to slow ventricular rate. How? By *long-term* therapy with a beta blocker (atenolol or metoprolol) or a cardioselective calcium channel blocker (diltiazem or verapamil), both of which impede conduction through the AV node. If episodes of atrial fibrillation are infrequent (eg, less than 12 a year), they can be managed with PRN flecainide or propafenone. This so-called pill-in-the-pocket approach is analogous to treating infrequent attacks of angina with sublingual nitroglycerin. For patients who elect to restore normal rhythm, options are DC cardioversion, short-term treatment with drugs (eg, amiodarone, sotalol), or RF ablation of the dysrhythmia source.

To prevent stroke, most patients are treated with warfarin. For those undergoing treatment to restore normal sinus rhythm, warfarin should be taken for 3 to 4 weeks prior to the procedure and for several weeks after. For those taking an antidysrhythmic drug long term to control ventricular rate, warfarin must be taken long term too. Alternatives to warfarin include two new oral anticoagulants—dabigatran [Pradaxa] and rivaroxaban [Xarelto]—and antiplatelet drugs (either aspirin alone or aspirin plus clopidogrel).

Atrial Flutter. Atrial flutter is caused by an ectopic atrial focus discharging at a rate of 250 to 350 times a minute. Ventricular rate is considerably slower, however, because the AV node is unable to transmit impulses at this high rate. Typically, one atrial impulse out of two reaches the ventricles. The treatment of choice is DC cardioversion, which almost always converts atrial flutter to normal sinus rhythm. Cardioversion may also be achieved with IV ibutilide. To prevent the dysrhythmia from recurring, patients may need long-term therapy with drugs—either a class IC agent (flecainide or propafenone) or a class III agent (amiodarone, dronedarone, sotalol, dofetilide).

There are two alternatives to cardioversion: (1) RF ablation of the dysrhythmia focus and (2) control of ventricular rate with drugs. As with atrial fibrillation, ventricular rate is controlled with drugs that suppress AV conduction: verapamil, diltiazem, or a beta blocker.

Like atrial fibrillation, atrial flutter poses a risk of stroke, which can be reduced by treatment with warfarin.

Sustained Supraventricular Tachycardia (SVT). Sustained SVT is usually caused by an AV nodal reentrant circuit. Heart rate is increased to 150 to 250 beats/min. SVT often responds to interventions that increase vagal tone, such as carotid sinus massage or the Valsalva maneuver. If these are ineffective, an IV beta blocker or calcium channel blocker can be tried. With these drugs, ventricular rate will be slowed even if the dysrhythmia persists. Once the dysrhythmia has been controlled, beta blockers and/or calcium channel blockers can be taken orally to prevent recurrence. As a last resort, amiodarone can be used for prevention.

Ventricular Dysrhythmias

In contrast to atrial dysrhythmias, which are generally benign, ventricular dysrhythmias can cause significant disruption of cardiac pumping. Accordingly, the usual objective is to abol-

ish the dysrhythmia. Cardioversion is often the treatment of choice. When antidysrhythmic drugs are indicated, agents in class I or class III are usually employed.

Sustained Ventricular Tachycardia. Ventricular tachycardia arises from a single, rapidly firing ventricular ectopic focus, typically located at the border of an old infarction. The focus drives the ventricles at a rate of 150 to 250 beats/min. Since the ventricles cannot pump effectively at these rates, immediate intervention is required. Cardioversion is the treatment of choice. If cardioversion fails to normalize rhythm, IV amiodarone should be administered; lidocaine and procainamide are alternatives. For long-term management, drugs (eg, sotalol, amiodarone) or an implantable cardioverter-defibrillator (ICD) may be employed.

Ventricular Fibrillation. Ventricular fibrillation is a life-threatening emergency that requires immediate treatment. This dysrhythmia results from the asynchronous discharge of multiple ventricular ectopic foci. Because many different foci are firing, and because each focus initiates contraction in its immediate vicinity, localized twitching takes place all over the ventricles, making coordinated ventricular contraction impossible. As a result, the pumping action of the heart stops. In the absence of blood flow, the patient becomes unconscious and cyanotic. If heartbeat is not restored rapidly, death soon follows. Electrical countershock (defibrillation) is applied to eliminate fibrillation and restore cardiac function. If necessary, IV lidocaine can be used to enhance the effects of defibrillation. Procainamide may also be helpful. Amiodarone can be used for long-term suppression. As an alternative, an ICD may be employed.

Ventricular Premature Beats (VPBs). VPBs are beats that occur before they should in the cardiac cycle. These beats are caused by ectopic ventricular foci. VPBs may arise from a single ectopic focus or from several foci. In the absence of additional signs of heart disease, VPBs are benign and not usually treated. However, in the presence of acute myocardial infarction, VPBs may predispose the patient to ventricular fibrillation. In this case, therapy is required. A beta blocker is the agent of choice. Because VPBs are associated with a premature QRS complex on the ECG, this dysrhythmia is also known as *premature ventricular complexes*.

Digoxin-Induced Ventricular Dysrhythmias. Digoxin toxicity can mimic practically all types of dysrhythmias. Varying degrees of AV block are among the most common. Ventricular flutter and ventricular fibrillation are the most dangerous. Digoxin causes dysrhythmias by increasing automaticity in the atria, ventricles, and His-Purkinje system, and by decreasing conduction through the AV node.

With proper treatment, digoxin-induced dysrhythmias can almost always be controlled. Treatment is discussed at length in Chapter 48. If antidysrhythmic drugs are required, lidocaine and phenytoin are the agents of choice. In patients with digoxin toxicity, DC cardioversion may bring on ventricular fibrillation. Accordingly, this procedure should be used only when absolutely required.

Torsades de Pointes. Torsades de pointes is an atypical, rapid, undulating ventricular tachydysrhythmia that can evolve into potentially fatal ventricular fibrillation. The main factor associated with development of torsades de pointes is prolongation of the QT interval, which can be caused by a variety of drugs (see Table 7-2 in Chapter 7), including class IA and class III antidysrhythmic agents. Acute management consists

of IV magnesium plus cardioversion for sustained ventricular tachycardia.

PRINCIPLES OF ANTIDYSRHYTHMIC DRUG THERAPY

Balancing Risks and Benefits

Therapy with antidysrhythmic drugs is based on a simple but important concept: Treat only if there is a clear benefit—and then only if the benefit outweighs the risks. As a rule, this means that intervention is needed only when the dysrhythmia interferes with ventricular pumping.

Treatment offers two potential benefits: reduction of symptoms and reduction of mortality. Symptoms that can be reduced include palpitations, angina, dyspnea, and faintness. For most antidysrhythmic drugs, there is little or no evidence of reduced mortality. In fact, mortality may actually increase.

Antidysrhythmic therapy carries considerable risk. Because of their *pro-dysrhythmic actions*, antidysrhythmic drugs can exacerbate existing dysrhythmias and generate new ones. Examples abound: toxic doses of digoxin can generate a wide variety of dysrhythmias; drugs that prolong the QT interval can cause torsades de pointes; many drugs can cause ventricular ectopic beats; several drugs (quinidine, flecainide, propafenone) can cause atrial flutter; and one drug—flecainide—can produce incessant ventricular tachycardia. Because of their pro-dysrhythmic actions, antidysrhythmic drugs can *increase mortality*. Other adverse effects include heart failure and third-degree AV block (caused by calcium channel blockers and beta blockers), as well as many noncardiac effects, including severe diarrhea (quinidine), a lupus-like syndrome (procainamide), and pulmonary toxicity (amiodarone).

Properties of the Dysrhythmia to Be Considered

Sustained Versus Nonsustained Dysrhythmias. As a rule, nonsustained dysrhythmias require intervention only when they are symptomatic; in the absence of symptoms, treatment is usually unnecessary. In contrast, sustained dysrhythmias can be dangerous; hence, the benefits of treatment generally outweigh the risks.

Asymptomatic Versus Symptomatic Dysrhythmias. No study has demonstrated a benefit to treating dysrhythmias that are asymptomatic or minimally symptomatic. In contrast, therapy may be beneficial for dysrhythmias that produce symptoms (palpitations, angina, dyspnea, faintness).

Supraventricular Versus Ventricular Dysrhythmias. Supraventricular dysrhythmias are generally benign. The primary harm comes from driving the ventricles too rapidly to allow adequate filling. The goal of treatment is to either (1) terminate the dysrhythmia or (2) prevent excessive atrial beats from reaching the ventricles (using a beta blocker, calcium channel blocker, or digoxin). In contrast to supraventricular dysrhythmias, ventricular dysrhythmias frequently interfere with pumping. Accordingly, the goal of treatment is to terminate the dysrhythmia and prevent its recurrence.

Phases of Treatment

Treatment has two phases: acute and long term. The goal of acute treatment is to terminate the dysrhythmia. For many dysrhythmias, termination is accomplished with DC cardioversion (electrical countershock) or vagotonic maneuvers (eg, carotid

sinus massage), rather than drugs. The goal of long-term therapy is to prevent dysrhythmias from recurring. Quite often, the risks of long-term prophylactic therapy outweigh the benefits.

Long-Term Treatment: Drug Selection and Evaluation

Selecting a drug for long-term therapy is largely empiric. There are many drugs that might be employed, and we usually can't predict which one is going to work. Hence, finding an effective drug is done by trial and error.

Drug selection can be aided with electrophysiologic testing. In these tests, a dysrhythmia is generated artificially by programmed electrical stimulation of the heart. If a candidate drug is able to suppress the electrophysiologically induced dysrhythmia, it may also work against the real thing.

Holter monitoring can be used to evaluate treatment. A Holter monitor is a portable ECG device that is worn by the patient around-the-clock. If Holter monitoring indicates that dysrhythmias are still occurring with the present drug, a different drug should be tried.

Minimizing Risks

Several measures can help minimize risk. These include

- Starting with low doses and increasing them gradually.
- Using a Holter monitor during initial therapy to detect danger signs—especially QT prolongation, which can precede torsades de pointes.
- Monitoring plasma drug levels. Unfortunately, although drug levels can be good predictors of noncardiac toxicity (eg, quinidine-induced nausea), they are less helpful for predicting adverse cardiac effects.

PHARMACOLOGY OF THE ANTIDYSRHYTHMIC DRUGS

As discussed above, the antidysrhythmic drugs fall into four main groups—classes I, II, III, and IV—plus a fifth group that includes adenosine and digoxin. The pharmacology of these drugs is presented below, and summarized in Table 49-2.

TABLE 49-2 • Properties of Antidysrhythmic Drugs

Drug	Usual Route	Effects on the ECG	Major Antidysrhythmic Applications
Class IA			
Quinidine	PO	Widens QRS, prolongs QT	Broad spectrum: used for long-term suppression of ventricular and supraventricular dysrhythmias
Procainamide	PO	Widens QRS, prolongs QT	Broad spectrum: similar to quinidine, but toxicity makes it less desirable for long-term use
Disopyramide	PO	Widens QRS, prolongs QT	Ventricular dysrhythmias
Class IB			
Lidocaine	IV	No significant change	Ventricular dysrhythmias
Mexiletine	PO	No significant change	Ventricular dysrhythmias
Phenytoin	PO	No significant change	Digoxin-induced ventricular dysrhythmias
Class IC			
Flecainide	PO	Widens QRS, prolongs PR	Maintenance therapy of supraventricular dysrhythmias
Propafenone	PO	Widens QRS, prolongs PR	Maintenance therapy of supraventricular dysrhythmias
Class II			
Propranolol	PO	Prolongs PR, bradycardia	Dysrhythmias caused by excessive sympathetic activity; control of ventricular rate in patients with supraventricular tachydysrhythmias
Acebutolol	PO	Prolongs PR, bradycardia	Premature ventricular beats
Esmolol	IV	Prolongs PR, bradycardia	Control of ventricular rate in patients with supraventricular tachydysrhythmias
Class III			
Amiodarone	PO	Prolongs QT and PR, widens QRS	Life-threatening ventricular dysrhythmias, atrial fibrillation*
Dronedarone	PO	Prolongs QT and PR, widens QRS	Atrial flutter, atrial fibrillation
Sotalol	IV	Prolongs QT and PR, bradycardia	Life-threatening ventricular dysrhythmias, atrial fibrillation/ flutter
Dofetilide	PO	Prolongs QT	Highly symptomatic atrial dysrhythmias
Ibutilide	IV	Prolongs QT	Atrial flutter, atrial fibrillation
Class IV			
Verapamil	PO	Prolongs PR, bradycardia	Control of ventricular rate in patients with supraventricular tachydysrhythmias
Diltiazem	IV	Prolongs PR, bradycardia	Same as verapamil
Others			
Adenosine	IV	Prolongs PR	Termination of paroxysmal supraventricular tachycardia
Digoxin	PO	Prolongs PR, depresses ST	Control of ventricular rate in patients with supraventricular tachydysrhythmias

*Amiodarone is widely used for atrial fibrillation, but it is not approved for this use.

CLASS I: SODIUM CHANNEL BLOCKERS

Class I antidysrhythmic drugs block cardiac sodium channels. By doing so, they decrease conduction velocity in the atria, ventricles, and His-Purkinje system.

There are three subgroups of class I agents. Drugs in all three groups block sodium channels. In addition, class IA agents delay repolarization, whereas class IB agents accelerate repolarization. Class IC agents have pronounced prodysrhythmic actions.

The class I drugs are similar in action and structure to the local anesthetics. In fact, one of these drugs—lidocaine—has both local anesthetic and antidysrhythmic applications. Because of their relationship to the local anesthetics, class I agents are sometimes referred to as *local anesthetic antidysrhythmic agents*.

Class IA Agents

Quinidine

Quinidine is the oldest, best studied, and most widely used class IA drug. Accordingly, quinidine will serve as our prototype for the group. Like other antidysrhythmic agents, quinidine has prodysrhythmic actions.

Chemistry and Source. Quinidine is similar to quinine in structure and actions. The natural source of both drugs is the bark of the South American cinchona tree. Accordingly, these agents are referred to as *cinchona alkaloids*. Like quinine, quinidine has antimalarial and antipyretic properties.

Effects on the Heart. By blocking sodium channels, quinidine slows impulse conduction in the atria, ventricles, and His-Purkinje system. In addition, the drug delays repolarization at these sites, apparently by blocking potassium channels. Both actions contribute to suppression of dysrhythmias.

Quinidine is strongly *anticholinergic* (atropine-like) and blocks vagal input to the heart. The resultant increase in SA nodal automaticity and AV conduction can drive the ventricles at an excessive rate. To prevent excessive ventricular stimulation, patients are usually pretreated with digoxin, verapamil, or a beta blocker, all of which suppress AV conduction.

Effects on the ECG. Quinidine has two pronounced effects on the ECG. The drug widens the QRS complex (by slowing depolarization of the ventricles) and prolongs the QT interval (by delaying ventricular repolarization).

Therapeutic Uses. Quinidine is a broad-spectrum agent active against *supraventricular* and *ventricular dysrhythmias*. The drug's principal indication is long-term suppression of dysrhythmias, including SVT, atrial flutter, atrial fibrillation, and sustained ventricular tachycardia. To prevent quinidine from increasing ventricular rate, patients are usually pretreated with an AV nodal blocking agent (digoxin, verapamil, beta blocker). An analysis of older studies indicates that quinidine may actually increase mortality in patients with atrial flutter and atrial fibrillation.

In addition to its antidysrhythmic applications, quinidine is a drug of choice for severe *malaria* (see Chapter 98).

Pharmacokinetics. Quinidine is rapidly absorbed after oral dosing. Peak responses to quinidine sulfate develop in 30 to 90 minutes; responses to quinidine gluconate develop more slowly, peaking after 3 to 4 hours. Elimination is by hepatic metabolism. Accordingly, patients with liver impairment may require a reduction in dosage. Therapeutic plasma levels are 2 to 5 mcg/mL.

Adverse Effects. Diarrhea. Diarrhea and other GI symptoms develop in about 33% of patients. These reactions can be immediate and intense, frequently forcing discontinuation of treatment. Gastric upset can be reduced by administering quinidine with food.

Cinchonism. Cinchonism is characterized by tinnitus (ringing in the ears), headache, nausea, vertigo, and disturbed vision. These can develop with just one dose.

Cardiotoxicity. At high concentrations, quinidine can cause severe cardiotoxicity (sinus arrest, AV block, ventricular tachydysrhythmias, asystole). These reactions occur secondary to increased automaticity of Purkinje fibers and reduced conduction throughout all regions of the heart.

As cardiotoxicity develops, the ECG changes. Important danger signals are *widening of the QRS complex* (by 50% or more) and *excessive prolongation of the QT interval*. Notify the prescriber immediately if these changes occur.

Arterial Embolism. Embolism is a potential complication of treating atrial fibrillation. During atrial fibrillation, thrombi may form in the atria. When sinus rhythm is restored, these thrombi may be dislodged and cause embolism. To reduce the risk of embolism, warfarin (an anticoagulant) is given for 3 to 4 weeks prior to quinidine, and is maintained for an additional 4 weeks. Signs of embolism (eg, sudden chest pain, dyspnea) should be reported immediately.

Other Adverse Effects. Quinidine can cause alpha-adrenergic blockade, resulting in vasodilation and subsequent hypotension. This reaction is much more serious with IV therapy than with oral therapy. Rarely, quinidine has caused hypersensitivity reactions, including fever, anaphylactic reactions, and thrombocytopenia.

Drug Interactions. Digoxin. Quinidine can double digoxin levels. The increase is caused by displacing digoxin from plasma albumin and by decreasing digoxin elimination. When these drugs are used concurrently, digoxin dosage must be reduced. Also, patients should be monitored closely for digoxin toxicity (dysrhythmias). Because of its interaction with digoxin, quinidine is a last-choice drug for treating digoxin-induced dysrhythmias.

Other Interactions. Because of its anticholinergic actions, quinidine can intensify the effects of other atropine-like drugs; one possible result is excessive tachycardia. Phenobarbital, phenytoin, and other drugs that induce hepatic drug metabolism can shorten the half-life of quinidine by as much as 50%. Quinidine can intensify the effects of warfarin by an unknown mechanism.

Preparations, Dosage, and Administration. Preparations. Quinidine is available as two salts: *quinidine sulfate* and *quinidine gluconate*. Because these salts have different molecular weights, equal doses (on a milligram basis) do not provide equal amounts of quinidine. A 200-mg dose of quinidine sulfate is equivalent to 275 mg of quinidine gluconate. Quinidine sulfate is available in immediate-release tablets (200 and 300 mg) and sustained-release tablets (300 mg). Quinidine gluconate is available in sustained-release tablets (324 mg) and in solution (80 mg/mL) for parenteral use.

Dosage. The usual dosage of quinidine sulfate is 200 to 400 mg every 4 to 6 hours. The usual dosage of quinidine gluconate is 324 to 648 mg every 8 to 12 hours. Dosage is adjusted to produce plasma quinidine levels between 2 and 5 mcg/mL.

Administration. Quinidine is almost always administered by mouth. If time permits, a small test dose (200 mg PO or IM) should be given prior to the full therapeutic dose to assess for hypersensitivity. Intramuscular administration is painful and produces erratic absorption. Intravenous injection carries a high risk of adverse cardiovascular reactions, and hence continuous cardiovascular monitoring is required.

Procainamide

Procainamide [Procan⁺, generic only in U.S.], is similar to quinidine in actions and uses. Like quinidine, procainamide is active against a broad spectrum of dysrhythmias. Unfortunately, serious side effects frequently limit its use.

Effects on the Heart and ECG. Like quinidine, procainamide blocks cardiac sodium channels, thereby decreasing conduction velocity in the atria, ventricles, and His-Purkinje system. Also, the drug delays repolarization. In contrast to quinidine, procainamide is only weakly anticholinergic, and hence is not likely to increase ventricular rate. Effects on the ECG are the same as with quinidine: widening of the QRS complex and prolongation of the QT interval.

Therapeutic Uses. Procainamide is effective against a broad spectrum of atrial and ventricular dysrhythmias. Like quinidine, the drug can be used for long-term suppression. However, since prolonged therapy is often associated with serious adverse effects, procainamide is less desirable than quinidine for long-term use. In contrast to quinidine, procainamide can be used to terminate ventricular tachycardia and ventricular fibrillation.

Pharmacokinetics. Routes are oral, IV, and IM. Peak plasma levels develop 1 hour after oral dosing. Procainamide has a short half-life and requires more frequent dosing than quinidine.

Elimination is by hepatic metabolism and renal excretion. The major metabolite—*N*-acetylprocainamide (NAPA)—has antidysrhythmic properties of its own. NAPA is excreted by the kidneys and can accumulate to toxic levels in patients with renal impairment.

Adverse Effects. Systemic Lupus Erythematosus-like Syndrome. Prolonged treatment with procainamide is associated with severe immunologic reactions. Within a year, about 70% of patients develop antinuclear antibodies (ANAs)—antibodies directed against the patient's own nucleic acids. If procainamide is continued, between 20% and 30% of patients with ANAs go on to develop symptoms resembling those of systemic lupus erythematosus (SLE). These symptoms include pain and inflammation of the joints, pericarditis, fever, and hepatomegaly. When procainamide is withdrawn, symptoms usually slowly subside. If the patient has a life-threatening dysrhythmia for which no alternative drug is available, procainamide can be continued and the symptoms of SLE controlled with a nonsteroidal anti-inflammatory drug (eg, aspirin) or a glucocorticoid. All patients taking procainamide chronically should be tested for ANAs. If the ANA titer rises, discontinuing treatment should be considered.

Blood Dyscrasias. About 0.5% of patients develop blood dyscrasias, including neutropenia, thrombocytopenia, and agranulocytosis. Fatalities have occurred. These reactions usually develop during the first 12 weeks of treatment. Complete blood counts should be obtained weekly during this time and periodically thereafter. Also, complete blood counts should be obtained promptly at the first sign of infection, bruising, or bleeding. If blood counts indicate bone marrow suppression, procainamide should be withdrawn. Hematologic status usually returns to baseline within 1 month.

Cardiotoxicity. Procainamide has cardiotoxic actions like those of quinidine. Danger signs are QRS widening (more than 50%) and excessive QT prolongation. If these develop, the drug should be withheld and the prescriber informed.

Other Adverse Effects. Like quinidine, procainamide can cause *GI symptoms* and *hypotension*. However, these are much less prominent than with quinidine. Procainamide is a derivative of procaine (a local anesthetic), and patients with a history of procaine allergy are at high risk of having an *allergic response* to procainamide. As with quinidine, *arterial embolism* may occur during treatment of atrial fibrillation.

Preparations, Dosage, and Administration. Oral. Procainamide is available in capsules (250 and 375 mg) and sustained-release tablets (250, 500, and 1000 mg). The usual maintenance dosage is 50 mg/kg/day in divided doses. The capsules are administered every 3 to 4 hours and the sustained-release tablets every 6 hours. Dosage is adjusted to maintain plasma drug levels between 4 and 10 mcg/mL.

Parenteral. Procainamide is available in solution (500 and 1000 mg/mL) for IM and IV administration. Intramuscular injection is made deep into the gluteal muscle; dosage is 0.5 to 1 gm repeated every 4 to 8 hours.

Intravenous infusion may be performed at an initial rate of 20 mg/min (maximal loading dose is 500 to 600 mg). After the loading period, an infusion rate of 2 to 6 mg/min should be employed. Once the dysrhythmia has been controlled, the patient should be switched to oral procainamide. Three hours should elapse between terminating the infusion and the first oral dose.

Disopyramide

Disopyramide [Norpace, Rythmodan⁺] is a class I drug with actions like those of quinidine. However, because of prominent side effects, indications for disopyramide are limited.

Effects on the Heart and ECG. Cardiac effects are similar to those of quinidine. By blocking sodium channels, disopyramide decreases conduction velocity in the atria, ventricles, and His-Purkinje system. In addition, the drug delays repolarization. Anticholinergic actions are greater than those of

quinidine. In contrast to quinidine, disopyramide causes a pronounced reduction in contractility. Like quinidine, disopyramide widens the QRS complex and prolongs the QT interval.

Adverse Effects. *Anticholinergic responses* are most common. These include dry mouth, blurred vision, constipation, and urinary hesitancy or retention. Urinary retention frequently requires discontinuation of treatment.

Because of its negative inotropic effects, disopyramide can cause *severe hypotension* (secondary to reduced cardiac output) and can *exacerbate heart failure* (HF). The drug should not be administered to patients with HF or to patients taking a beta blocker. Whenever disopyramide is used, pressor drugs should be immediately available.

Therapeutic Uses. Disopyramide is indicated only for ventricular dysrhythmias (VPBs, ventricular tachycardia, ventricular fibrillation). The drug is reserved for patients who cannot tolerate safer medications (eg, quinidine, procainamide).

Preparations, Dosage, and Administration. Disopyramide [Norpace, Rythmodan⁺] is available in immediate- and extended-release capsules (100 and 150 mg). An initial loading dose (200 to 300 mg) is followed by maintenance doses (100 to 200 mg) every 6 hours.

Class IB Agents

As a group, class IB agents differ from quinidine and the other class IA agents in two respects: (1) whereas class IA agents *delay* repolarization, class IB agents *accelerate* repolarization; and (2) class IB agents have little or no effect on the ECG.

Lidocaine

Lidocaine [Xylocaine], an intravenous agent, is used only for ventricular dysrhythmias. In addition to its antidysrhythmic applications, lidocaine is employed as a local anesthetic (see Chapter 26).

Effects on the Heart and ECG. Lidocaine has three significant effects on the heart: (1) like other class I drugs, lidocaine blocks cardiac sodium channels and thereby *slows conduction* in the atria, ventricles, and His-Purkinje system; (2) the drug *reduces automaticity* in the ventricles and His-Purkinje system by a mechanism that is poorly understood; and (3) lidocaine *accelerates repolarization* (shortens the action potential duration and ERP). In contrast to quinidine and procainamide, lidocaine is devoid of anticholinergic properties. Also, lidocaine has no significant impact on the ECG: A small reduction in the QT interval may occur, but there is no QRS widening.

Pharmacokinetics. Lidocaine undergoes rapid hepatic metabolism. If the drug were administered orally, most of each dose would be inactivated on its first pass through the liver. For this reason, administration is parenteral, almost always by IV infusion.

Because lidocaine is rapidly degraded, plasma drug levels can be easily controlled: If levels climb too high, the infusion can be slowed and the liver will quickly remove excess drug from the circulation. The therapeutic range for lidocaine is 1.5 to 5 mcg/mL.

Antidysrhythmic Use. Antidysrhythmic use of lidocaine is limited to short-term therapy of *ventricular dysrhythmias*. Lidocaine is not active against supraventricular dysrhythmias.

Adverse Effects. Lidocaine is generally well tolerated. However, adverse central nervous system (CNS) effects can occur. High therapeutic doses can cause *drowsiness*, *confusion*, and *paresthesias*. Toxic doses may produce *convulsions* and *respiratory arrest*. Consequently, whenever lidocaine is used, equipment for resuscitation must be available. Convulsions can be managed with diazepam or phenytoin.

Preparations, Dosage, and Administration. Administration is parenteral only. The usual route is IV. Intramuscular injection can be used in emergencies. Blood pressure and the ECG should be monitored for signs of toxicity.

Intravenous. Lidocaine [Xylocaine] preparations intended for IV administration are clearly labeled as such. They contain no preservatives or catecholamines. (Lidocaine used for local anesthesia frequently contains epinephrine.) Preparations that contain epinephrine or another catecholamine must never be administered IV, since doing so can cause severe hypertension and life-threatening dysrhythmias.

Intravenous therapy is initiated with a loading dose followed by continuous infusion for maintenance. The usual loading dose is 50 to 100 mg (1 mg/kg) administered at a rate of 25 to 50 mg/min. An infusion rate of 1 to 4 mg/min is used for maintenance; the rate is adjusted on the basis of cardiac response. Intravenous lidocaine should be discontinued as soon as possible, usually within 24 hours. Lidocaine for IV administration is supplied in concentrated and dilute formulations. The concentrated formulations must be diluted with 5% dextrose in water.

To avoid toxicity, dosage should be reduced in patients with impaired hepatic function or impaired hepatic blood flow (eg, elderly patients; patients with cirrhosis, shock, or HF).

Intramuscular. Lidocaine is available in an automatic injection device [LidoPen Auto-Injector] for IM administration. A dose of 300 mg is injected into the deltoid muscle. This dose can be repeated in 60 to 90 minutes if necessary. The patient should be switched to IV lidocaine as soon as possible.

Phenytoin

Phenytoin [Dilantin] is an antiseizure drug that is also used to treat digoxin-induced dysrhythmias. The basic pharmacology of phenytoin is presented in Chapter 24 (Drugs for Epilepsy). Discussion here is limited to antidysrhythmic applications.

Effects on the Heart and ECG. Like lidocaine, phenytoin reduces automaticity (especially in the ventricles), and has little or no effect on the ECG. In contrast to lidocaine (and practically all other antidysrhythmic agents), phenytoin increases AV nodal conduction.

Pharmacokinetics. Phenytoin has two unfortunate kinetics properties. First, metabolism of the drug is subject to wide interpatient variation. Second, doses only slightly greater than therapeutic are likely to cause toxicity. Because of these characteristics, maintenance of therapeutic plasma levels (5 to 20 mcg/mL) is difficult.

Adverse Effects and Interactions. The most common adverse reactions are sedation, ataxia, and nystagmus. With too-rapid IV administration, phenytoin can cause hypotension, dysrhythmias, and cardiac arrest. Gingival hyperplasia is a frequent complication of long-term treatment. Phenytoin is subject to multiple undesirable drug interactions (see Chapter 24).

Antidysrhythmic Applications. Phenytoin has been used for digoxin-induced dysrhythmias and for acute and chronic suppression of ventricular dysrhythmias. The ability of phenytoin to increase AV nodal conduction can help counteract the reduction in AV conduction caused by digoxin intoxication. Phenytoin should not be used to treat atrial fibrillation or atrial flutter. Why? Because enhanced AV conduction could increase the number of atrial impulses reaching the ventricles, thereby driving the ventricles at an excessive rate.

Dosage and Administration. Phenytoin [Dilantin] can be given PO or IV. For PO therapy, a loading dose (14 mg/kg) is followed by daily maintenance doses (200 to 400 mg).

Intravenous dosing is reserved for severe, acute dysrhythmias. Blood pressure and the ECG must be monitored continuously. Phenytoin is not soluble in water and must be diluted in the medium supplied by the manufacturer. This medium is highly alkaline (pH 12) and will cause phlebitis if given by continuous infusion. Consequently, dosing is by intermittent injections. Intravenous injections must be performed slowly (50 mg/min or less), since rapid injection can cause cardiovascular collapse. Treatment is begun with a series of loading doses (50 to 100 mg every 5 minutes until the dysrhythmia has been controlled or until toxicity appears). Maintenance dosages range from 200 to 400 mg/day.

Mexiletine

Mexiletine [Mexitil] is an oral analog of lidocaine used for symptomatic ventricular dysrhythmias. Principal indications are VPBs and sustained ventricular tachycardia. Like lidocaine, mexiletine does not alter the ECG. The drug is eliminated by hepatic metabolism, and hence effects may be prolonged in patients with liver disease or reduced hepatic blood flow. The most

common adverse effects are GI (nausea, vomiting, diarrhea, constipation) and neurologic (tremor, dizziness, sleep disturbances, psychosis, convulsions). About 40% of patients find these intolerable. Like other class I agents, mexiletine has prodyssrhythmic properties. The initial dosage is 100 to 200 mg every 8 hours. The maintenance dosage is 100 to 300 mg every 6 to 12 hours. All doses should be taken with food.

Mexiletine is also used to alleviate persistent pain of diabetic neuropathy. Benefits derive from lidocaine-like anesthetic actions. Because mexiletine can cause dysrhythmias, it should not be used by diabetic patients with heart disease.

Class IC Agents

Class IC antidysrhythmics block cardiac sodium channels and thereby reduce conduction velocity in the atria, ventricles, and His-Purkinje system. In addition, these drugs delay ventricular repolarization, causing a small increase in the effective refractory period. All class IC agents can exacerbate existing dysrhythmias and create new ones. Currently, only two class IC agents are available: flecainide and propafenone.

Flecainide

Flecainide [Tambocor] is active against a variety of ventricular and supraventricular dysrhythmias. However, use is restricted largely to maintenance therapy of supraventricular dysrhythmias. Like other class IC agents, flecainide decreases cardiac conduction and increases the effective refractory period. Prominent effects on the ECG are prolongation of the PR interval and widening of the QRS complex. Excessive QRS widening indicates a need for dosage reduction. Flecainide has prodyssrhythmic effects. As a result, the drug can intensify existing dysrhythmias and provoke new ones. In patients with asymptomatic ventricular tachycardia associated with acute myocardial infarction, flecainide has caused a twofold increase in mortality. Flecainide decreases myocardial contractility and can thereby exacerbate or precipitate heart failure. Accordingly, the drug should not be combined with other agents that can decrease contractile force (eg, beta blockers, verapamil, diltiazem). Elimination is by hepatic metabolism and renal excretion. Flecainide is available in tablets (50, 100, and 150 mg) for oral dosing. Dosage is low initially (100 mg every 12 hours) and then gradually increased to a maximum of 400 mg/day. Because of its potential for serious side effects, flecainide should be reserved for severe ventricular dysrhythmias that have not responded to safer drugs. Patients should be monitored closely.

Propafenone

Propafenone [Rythmol, Rythmol SR] is similar to flecainide in actions and uses. By blocking cardiac sodium channels, the drug decreases conduction velocity in the atria, ventricles, and His-Purkinje system. In addition, it causes a small increase in the ventricular ERP. Prominent effects on the ECG are QRS widening and PR prolongation. Like flecainide, propafenone has prodyssrhythmic actions that can exacerbate existing dysrhythmias and create new ones. It is not known if propafenone, like flecainide, increases mortality in patients with asymptomatic ventricular dysrhythmias after myocardial infarction. Propafenone has beta-adrenergic blocking properties and can thereby decrease myocardial contractility and promote bronchospasm. Accordingly, the drug should be used with caution in patients with heart failure, AV block, or asthma. Noncardiac adverse effects are generally mild and include dizziness, altered taste, blurred vision, and GI symptoms (abdominal discomfort, anorexia, nausea, vomiting). Because of its prodyssrhythmic actions, propafenone should be reserved for patients who have not responded to safer drugs. Propafenone is available in immediate-release tablets (150, 225, and 300 mg) and extended-release capsules (225, 325, and 425 mg). For the immediate-release tablets, the dosage is 150 mg every 8 hours initially, and can be gradually increased to 300 mg every 8 hours.

CLASS II: BETA BLOCKERS

Class II consists of beta-adrenergic blocking agents. At this time only four beta blockers—propranolol, acebutolol, esmolol, and sotalol—are approved for treating dysrhythmias. One of these drugs—sotalol—also blocks potassium channels, and hence is discussed under class III. The basic pharmacology of the beta blockers is presented in Chapter 18. Discussion here is limited to their antidysrhythmic use.

from 25 to 110 days. Because of its slow elimination, amiodarone continues to act long after dosing has ceased.

Adverse Effects. Amiodarone produces many serious adverse effects. Furthermore, because the drug's half-life is protracted, toxicity can continue for weeks or months after drug withdrawal. To reduce adverse events, the Food and Drug Administration (FDA) requires that all patients using amiodarone be given a Medication Guide describing potential toxicities.

Pulmonary Toxicity. Lung damage—hypersensitivity pneumonitis, interstitial/alveolar pneumonitis, pulmonary fibrosis—is the greatest concern. Symptoms (dyspnea, cough, chest pain) resemble those of heart failure and pneumonia. Pulmonary toxicity develops in 2% to 17% of patients and carries a 10% risk of mortality. Patients at highest risk are those receiving long-term, high-dose therapy. A baseline chest x-ray and pulmonary function test are required. Pulmonary function should be monitored throughout treatment. If lung injury develops, amiodarone should be withdrawn.

Cardiotoxicity. Amiodarone may cause a paradoxical increase in dysrhythmic activity. In addition, by suppressing the SA and AV nodes, the drug can cause sinus bradycardia and AV block. By reducing contractility, amiodarone can precipitate heart failure.

Thyroid Toxicity. Amiodarone may cause hypothyroidism or hyperthyroidism. Accordingly, thyroid function should be assessed at baseline and periodically during treatment. Hypothyroidism can be treated with thyroid hormone supplements. Hyperthyroidism can be treated with an antithyroid drug (eg, methimazole) or thyroidectomy. Discontinuing amiodarone should be considered.

Liver Toxicity. Amiodarone can injure the liver. Accordingly, tests of liver function should be obtained at baseline and periodically throughout treatment. If circulating liver enzymes exceed 3 times the normal level, amiodarone should be discontinued. Signs and symptoms of liver injury, which are seen only rarely, include anorexia, nausea, vomiting, malaise, fatigue, itching, jaundice, and dark urine.

Ophthalmic Effects. Rarely, amiodarone has been associated with optic neuropathy and optic neuritis, sometimes progressing to blindness. However, a causal relationship has not been established. Patients who develop changes in visual acuity or peripheral vision should undergo ophthalmologic evaluation. If optic neuropathy or neuritis is diagnosed, discontinuation of amiodarone should be considered.

Virtually all patients develop corneal microdeposits. Fortunately, these deposits have little or no effect on vision, and hence rarely necessitate amiodarone cessation.

Toxicity in Pregnancy and Breast-feeding. Amiodarone crosses the placental barrier and enters breast milk, and can thereby harm the developing fetus and breast-feeding infant. Accordingly, pregnancy and breast-feeding should be avoided while using the drug and for several months after stopping it.

Dermatologic Toxicity. Patients frequently experience photosensitivity reactions (skin reactions triggered by exposure to ultraviolet radiation). To reduce risk, patients should avoid sunlamps, and should wear sunblock and protective clothing when outdoors. With frequent and prolonged sun exposure, exposed skin may turn bluish-gray. Fortunately, this discoloration resolves within months after amiodarone is discontinued.

Other Adverse Effects. Possible CNS reactions include ataxia, dizziness, tremor, mood alteration, and hallucinations. Gastrointestinal reactions (anorexia, nausea, vomiting) are common.

Drug Interactions. Amiodarone is subject to significant interactions with many drug. The result can be toxicity or reduced therapeutic effects. Accordingly, combined use with these drugs should be avoided. When it cannot, the patient should be monitored closely. Interactions of concern include the following:

- Amiodarone can increase levels of several drugs, including quinidine, procainamide, phenytoin, digoxin, diltiazem, warfarin, cyclosporine, and three statins: lovastatin, simvastatin, and atorvastatin. Dosages of these agents often require reduction.
- Amiodarone levels can be increased by grapefruit juice and by inhibitors of CYP3A4. Toxicity can result.
- Amiodarone levels can be reduced by cholestyramine (which decreases amiodarone absorption) and by agents that induce CYP3A4 (eg, St. John's wort, rifampin).
- The risk of severe dysrhythmias is increased by diuretics (because they can reduce levels of potassium and magnesium) and by drugs that prolong the QT interval, of which there are many (see Chapter 7, Table 7-2).
- Combining amiodarone with a beta blocker, verapamil, or diltiazem can lead to excessive slowing of heart rate.

Dosage. Oral amiodarone [Pacerone, Cordarone] is available in tablets (100, 200, 300, and 400 mg). Treatment should be initiated in a hospital. The following schedule is used for loading: 800 to 1600 mg daily for 1 to 3 weeks followed by 600 to 800 mg daily for 4 weeks. The daily maintenance dosage is 100 to 400 mg.

Intravenous Therapy

Therapeutic Use. Intravenous amiodarone is approved only for initial treatment and prophylaxis of recurrent ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to safer drugs. For these indications, amiodarone may be lifesaving.

In addition to its approved uses, IV amiodarone has been used with success against other dysrhythmias, including atrial fibrillation, AV nodal reentrant tachycardia, and shock-resistant ventricular fibrillation.

Effects on the Heart and ECG. In contrast to oral amiodarone, which affects multiple aspects of cardiac function, IV amiodarone affects primarily the AV node. Specifically, the drug slows AV conduction and prolongs AV refractoriness. Both effects probably result from antiadrenergic actions. The mechanism underlying antidysrhythmic effects is unknown.

Adverse Effects. The most common adverse effects are hypotension and bradycardias. Hypotension develops in 15% to 20% of patients, and may require discontinuation of treatment. Bradycardia or AV block occurs in 5% of patients; discontinuation of treatment or insertion of a pacemaker may be needed. Infusions containing more than 3 mg/mL (in 5% dextrose in water) produce a high incidence of phlebitis, and hence should be administered through a central venous line. Torsades de pointes in association with QT prolongation occurs rarely.

Dosage. Dosing is complex. During the first 24 hours, a total dose of 1050 mg is infused. After that, a maintenance infusion (0.5 mg/min) is given around-the-clock. The usual duration of treatment is 2 to 4 days. However, maintenance infusions may be continued for up to 3 weeks before switching to oral amiodarone.

Dronedarone

Dronedarone [Multaq], a derivative of amiodarone, was approved in 2009. The drug is indicated for oral therapy of *atrial flutter and paroxysmal or persistent atrial fibrillation*, but *not* permanent atrial fibrillation. The manufacturer hoped to create a drug with the high efficacy of amiodarone, but with less toxicity. Unfortunately, although dronedarone is somewhat less toxic than amiodarone, it is also less effective. Furthermore, in patients with heart failure or permanent atrial fibrillation, dronedarone doubles the risk of death. Dronedarone has a much shorter half-life than amiodarone, and hence adverse effects resolve more quickly.

Effects on the Heart and ECG. Like other class III agents, dronedarone blocks cardiac potassium channels, and thereby delays repolarization. In addition, dronedarone can block sodium channels (like class I agents), beta-adrenergic receptors (like class II agents), and calcium channels (like class IV agents). Just how these actions contribute to antidysrhythmic benefits is unclear. Prominent effects on the ECG are PR and QT prolongation, and widening of the QRS complex.

Pharmacokinetics. Oral bioavailability is low in the absence of food (4%), and higher in the presence of food (15%). Plasma levels peak 3 to 6 hours after dosing. Dronedarone undergoes extensive metabolism by hepatic CYP3A4, followed by excretion in the feces. The elimination half-life is 13 to 19 hours—much shorter than the 25 to 110 days seen with amiodarone. As a result, steady-state levels are achieved fairly quickly with dronedarone (4 to 8 days), versus 1 to 5 months with amiodarone.

Adverse Effects. The most common side effects are diarrhea (9%), weakness (7%), nausea (5%), and skin reactions (5%). In contrast to amiodarone, dronedarone does *not* cause significant thyroid toxicity, pulmonary toxicity (eg, pulmonary fibrosis, pneumonitis), or ocular toxicity (eg, corneal microdeposits, optic neuropathy)—although it can cause liver toxicity. Dronedarone can increase skin sensitivity to sunlight, but it does not cause the bluish-gray skin discoloration seen with amiodarone. Furthermore, because dronedarone has a much shorter half-life than amiodarone, adverse effects that *do* occur have a much shorter duration.

Cardiac Effects. In patients with *severe heart failure*, dronedarone doubles the risk of death, as shown in the ANDROMIDA trial. Accordingly, dronedarone is contraindicated in patients with New York Heart Association (NYHA) Class IV heart failure, and in patients with NYHA Class II or III heart failure with recent decompensation that required hospitalization.

In patients with *permanent atrial fibrillation* (as opposed to paroxysmal or persistent atrial fibrillation), dronedarone doubles the risk of death, as shown in the PALLAS trial. Accordingly, dronedarone should not be used in these patients.

Dronedarone reduces SA nodal automaticity and AV nodal conduction, posing a risk of bradycardia and heart block. Accordingly, the drug is contraindicated in patients with sick sinus syndrome or second- or third-degree AV block (unless a pacemaker is in use), and in patients with bradycardia below 50 beats/min.

Dronedarone prolongs the QT interval (by about 10 msec). Accordingly, the drug should not be used in patients with a QT interval greater than 500 msec, or in patients taking drugs or supplements that cause QT prolongation.

Liver Toxicity. Dronedarone has been associated with rare cases of severe liver injury, including two that required a liver

transplant. Accordingly, patients should be warned about signs and symptoms of liver injury (eg, anorexia, nausea, vomiting, malaise, fatigue, itching, jaundice, dark urine), and instructed to contact their provider immediately if these develop. Providers should consider monitoring for liver enzymes in blood, especially during the first 6 months of treatment.

Toxicity in Pregnancy and Breast-feeding. Dronedarone is a proven teratogen and must not be used during pregnancy. In animal studies, doses at or below the mean recommended human dose have produced visceral, skeletal, and external malformations. Accordingly, dronedarone is classified in FDA Pregnancy Risk Category X: Risks to the developing fetus clearly outweigh any possible benefit. Women of child-bearing age should be counseled about using effective contraception.

We know that dronedarone is excreted in the milk of rats, but information in lactating women is lacking. Nonetheless, owing to the potential risk to nursing infants, dronedarone is contraindicated for use by breast-feeding mothers.

Drug Interactions. Dronedarone is subject to multiple drug interactions, many involving CYP3A4.

- **Strong inhibitors of hepatic CYP3A4** (eg, ketoconazole, clarithromycin, ritonavir) can make dronedarone accumulate to dangerous levels. Accordingly, concurrent use of these inhibitors is contraindicated. Grapefruit juice, which strongly inhibits *intestinal* CYP3A4, can raise dronedarone levels threefold, and hence should also be avoided. Moderate inhibitors of hepatic CYP3A4 (eg, verapamil, diltiazem) should be used with caution.
- **Strong inducers of CYP3A4** (eg, rifampin, carbamazepine, St. John's wort) can reduce dronedarone levels by as much as 80%, and can thereby greatly reduce dysrhythmia control.
- In addition to being a substrate for CYP3A4, dronedarone can inhibit this enzyme. Accordingly, dronedarone can raise levels of other drugs that are *CYP3A4* substrates. Substrates with a narrow therapeutic range (eg, tacrolimus, sirolimus, warfarin) should be used with caution.
- Dronedarone can inhibit CYP2D6, and can thereby increase levels of *CYP2D6* substrates (eg, beta blockers, tricyclic antidepressants). Concurrent use of these agents should be done with caution.
- **Beta blockers**, which suppress the SA node and AV conduction, can intensify dronedarone-induced bradycardia, and can also increase the risk of AV block.
- Like the beta blockers, two **calcium channel blockers**—*verapamil* and *diltiazem*—also suppress the SA node and AV conduction, and hence pose the same risk as the beta blockers do. In addition, verapamil and diltiazem can inhibit CYP3A4, and can thereby raise dronedarone levels, making the risk of cardiosuppression even greater.
- **Drugs and supplements that prolong the QT interval** (eg, phenothiazines, tricyclic antidepressants, class I and class III antidysrhythmics) can intensify dronedarone-induced QT prolongation, and can thereby increase the risk of torsades de pointes. Accordingly, these drugs are contraindicated for use with dronedarone.

Summary of Contraindications. Dronedarone has the following contraindications:

- NYHA Class IV heart failure *or* NYHA Class II or III heart failure with recent decompensation requiring hospitalization.

- Permanent atrial fibrillation
- Second- or third-degree AV block or sick sinus syndrome (except in patients using a pacemaker).
- Bradycardia below 50 beats/min.
- PR interval greater than 280 msec.
- QT interval greater than 500 msec.
- Use of drugs or supplements that prolong the QT interval.
- Use of strong inhibitors of CYP3A4.
- Pregnancy.
- Breast-feeding.
- Severe liver impairment.

Preparations, Dosage, and Administration. Dronedaron [Multaq] is supplied in 400-mg tablets for oral dosing. The recommended dosage is 400 mg twice daily, taken with the morning and evening meals. Note that, unlike amiodarone, dronedaron does not require a loading dose.

Sotalol

Actions and Uses. Sotalol [Betapace, Betapace AF] is a beta blocker that also delays repolarization. Hence, the drug has combined class II and class III antidysrhythmic properties. Prodysrhythmic properties are pronounced. Sotalol was initially approved only for ventricular dysrhythmias, such as sustained ventricular tachycardia, that are considered life threatening. Later, it was approved for prophylaxis and treatment of atrial flutter and fibrillation, but only if symptoms are severe. The drug is not approved for hypertension or angina pectoris (the primary indications for other beta blockers).

Pharmacokinetics. Sotalol is administered orally and undergoes nearly complete absorption. The drug is excreted unchanged in the urine. Its half-life is 12 hours.

Adverse Effects. The major adverse effect is torsades de pointes, a serious dysrhythmia that develops in about 5% of patients. Risk is increased by hypokalemia and by other drugs that prolong the QT interval.

At therapeutic doses, sotalol produces substantial beta blockade. Hence, it can cause bradycardia, AV block, heart failure, and bronchospasm. Accordingly, the usual contraindications to beta blockers apply.

Preparations, Dosage, and Administration. Sotalol is available under two trade names: *Betapace* and *Betapace AF*. *Betapace* (80-, 120-, 160-, and 240-mg tablets) is intended for treating ventricular dysrhythmias. *Betapace AF* (80-, 120-, and 160-mg tablets) is intended for treating atrial fibrillation and atrial flutter. Although tablets are the same under both trade names, packaging differs: Packaging for *Betapace* provides information specific for treating ventricular dysrhythmias, whereas packaging for *Betapace AF* provides information specific for treating atrial dysrhythmias. For both types of dysrhythmias, treatment should start in a hospital. Dosing for both is the same: The initial dosage is 160 mg/day (in two divided doses), and the usual maintenance dosage is 160 to 320 mg/day in two or three divided doses. The dosing interval should be increased in patients with renal impairment.

Dofetilide

Therapeutic Use. Dofetilide [Tikosyn] is an oral class III antidysrhythmic indicated for restoring and maintaining normal sinus rhythm in patients with atrial flutter or atrial fibrillation. The drug causes dose-related QT prolongation and thereby poses a serious risk of torsades de pointes. Accordingly, it should be reserved for patients with highly symptomatic atrial dysrhythmias. Initial treatment requires continuous ECG monitoring in a hospital. Dosage must be carefully titrated on the basis of renal function tests. Dofetilide is available only through authorized hospitals and prescribers.

Effects on the Heart and ECG. Like other class III agents, dofetilide blocks cardiac potassium channels, and thereby delays repolarization, and hence prolongs the QT interval. Dofetilide does not affect the PR interval or widen the QRS complex, and has no effect on cardiac beta receptors or sodium channels.

Pharmacokinetics. Dofetilide is well absorbed (90%) both in the presence and absence of food. Very little is metabolized. About 80% of each dose is excreted in the urine, primarily unchanged. Renal excretion results largely from active tubular secretion, mediated by cationic pumps (ie, pumps specific for molecules that are cations). In patients with normal renal function, the drug's half-life is about 10 hours. However, in patients with renal impairment, the half-life is increased. In patients with moderate renal impairment, dosage must be reduced, in patients with severe renal impairment, dofetilide must not be used.

Adverse Effects. By increasing the QT interval, dofetilide predisposes to torsades de pointes, which can progress to fatal ventricular fibrillation. The risk is directly related to dofetilide blood levels, and is increased by hypoka-

lemia and by other drugs that cause QT prolongation. To assess risk, an ECG should be obtained at baseline, and ECG monitoring should be continuous during initial treatment. Dofetilide is contraindicated for patients with a baseline QT interval greater than 440 msec (or greater than 500 msec in patients with ventricular conduction abnormalities). Other side effects include headache (11%), chest pain (10%), and dizziness (8%).

Drug Interactions. Drugs that are excreted by renal cation pumps can interfere with the excretion of dofetilide, thereby causing its levels to rise. Accordingly, concurrent use of these drugs (eg, cimetidine, trimethoprim, ketoconazole, prochlorperazine, megestrol) is contraindicated.

Drugs that prolong the QT interval may increase the risk of dysrhythmias, and hence should be avoided. Among these are class I and class III antidysrhythmics, phenothiazines, tricyclic antidepressants, and some macrolide antibiotics.

Combining verapamil with dofetilide increases the risk of torsades de pointes, and should be avoided.

Preparations, Dosage, and Administration. Dofetilide [Tikosyn] is available in capsules (125, 250, and 500 mcg) for oral dosing. Because of the risk of dysrhythmias, treatment must be initiated in a hospital with continuous ECG monitoring for at least 3 days. Because dysrhythmia risk is directly related to plasma drug levels, which in turn are directly related to creatinine clearance (a measure of renal function), *creatinine clearance must be monitored*. Dosage should be reduced with decreasing creatinine clearance as follows: For patients with normal renal function (creatinine clearance greater than 60 mL/min), give 500 mcg twice a day; for creatinine clearance 40 to 60 mL/min, give 250 mcg twice a day; for creatinine clearance 20 to 39.9 mL/min, give 125 mcg twice a day; and for creatinine clearance below 20 mL/min, withhold dofetilide. If the QT interval becomes excessively prolonged (greater than 500 msec, or greater than 550 msec in patients with ventricular conduction abnormalities), dosage should be reduced.

Ibutilide

Ibutilide [Corvert] is an IV agent used to terminate atrial flutter and atrial fibrillation of recent onset (ie, that has been present no longer than 90 days). Conversion to sinus rhythm occurs during the infusion or within 90 minutes of its termination. Ibutilide is more effective against atrial flutter (49% to 70% success) than atrial fibrillation (22% to 43% success). Like other class III agents, ibutilide blocks potassium channels and thereby prolongs the action potential duration and QT interval. Up to 8% of patients develop torsades de pointes, frequently in association with QT prolongation. Oral doses are teratogenic and embryocidal in rats. For patients who weigh over 60 kg, the dosage is 1 mg infused over 10 minutes. If the dysrhythmia does not convert within 10 minutes of terminating the infusion, a second 1-mg infusion may be tried.

CLASS IV: CALCIUM CHANNEL BLOCKERS

Only two calcium channel blockers—*verapamil* [Calan, Covera-HS, Isoptin SR, Verelan] and *diltiazem* [Cardizem, Dilacor-XR, Tiazac, others]—are able to block calcium channels in the heart. Accordingly, they are the only calcium channel blockers used to treat dysrhythmias. Their basic pharmacology is discussed in Chapter 45. Consideration here is limited to their use against dysrhythmias.

Effects on the Heart and ECG. Blockade of cardiac calcium channels has three effects:

- Slowing of SA nodal automaticity
- Delay of AV nodal conduction
- Reduction of myocardial contractility

Note that these are identical to the effects of beta blockers, which makes sense in that beta blockers promote calcium channel closure in the heart. The principal effect on the ECG is prolongation of the PR interval, reflecting delayed AV conduction.

Therapeutic Uses. Verapamil and diltiazem have two antidysrhythmic uses. First, they can slow ventricular rate in patients with atrial fibrillation or atrial flutter. Second, they can terminate SVT caused by an AV nodal reentrant circuit. In both cases, benefits derive from suppressing AV nodal con-

duction. With IV administration, effects can be seen in 2 to 3 minutes. Verapamil and diltiazem are not active against ventricular dysrhythmias.

Adverse Effects. Although generally safe, these drugs can cause undesired effects. Blockade of cardiac calcium channels can cause *bradycardia*, *AV block*, and *heart failure*. Blockade of calcium channels in vascular smooth muscle can cause vasodilation, resulting in *hypotension* and *peripheral edema*. Blockade of calcium channels in intestinal smooth muscle can produce *constipation*.

Drug Interactions. Both verapamil and diltiazem can elevate levels of *digoxin*, thereby increasing the risk of digoxin toxicity. Also, since digoxin shares with verapamil and diltiazem the ability to decrease AV conduction, combining digoxin with either drug increases the risk of AV block.

Because verapamil, diltiazem, and *beta blockers* have nearly identical suppressant effects on the heart, combining verapamil or diltiazem with a beta blocker increases the risk of bradycardia, AV block, and heart failure.

Preparations, Dosage, and Administration. Verapamil. Dosing may be IV or oral. Intravenous therapy is preferred for initial treatment. Oral therapy is used for maintenance.

Verapamil for intravenous use is supplied in solution (5 mg/2 mL). The initial dose is 5 to 10 mg injected slowly (over 2 to 3 minutes). If the dysrhythmia persists, an additional 10 mg may be administered in 30 minutes. An IV infusion (0.375 mg/min) can be used for maintenance. Intravenous verapamil can cause serious cardiovascular effects. Accordingly, blood pressure and the ECG should be monitored, and equipment for resuscitation should be immediately available.

Verapamil for oral use is available in immediate- and sustained-release tablets. The maintenance dosage is 40 to 120 mg 3 or 4 times a day.

Diltiazem. Like verapamil, diltiazem may be given IV or PO. Intravenous therapy is preferred for initial treatment, and oral therapy is used for maintenance.

Intravenous therapy is initiated with an IV bolus (0.25 mg/kg). If the response is inadequate, a second bolus (0.35 mg/kg) may be administered in 15 minutes. If appropriate, initial therapy may be followed with a continuous IV infusion (up to 24 hours' duration) at a rate of 5 to 15 mg/hr.

OTHER ANTIDYSRHYTHMIC DRUGS

Adenosine

Adenosine [Adenocard], a naturally occurring nucleotide, is a drug of choice for terminating paroxysmal SVT. Adenosine has an extremely short half-life, and hence must be administered IV. Adverse effects are minimal because adenosine is rapidly cleared from the blood.

Effects on the Heart and ECG. Adenosine decreases automaticity in the SA node and greatly slows conduction through the AV node. The most prominent ECG change is prolongation of the PR interval, brought on by delayed AV conduction. Adenosine works in part by inhibiting cyclic AMP-induced calcium influx, thereby suppressing calcium-dependent action potentials in the SA and AV nodes.

Therapeutic Use. Adenosine is approved only for termination of paroxysmal SVT, including Wolff-Parkinson-White syndrome. The drug is not active against atrial fibrillation, atrial flutter, or ventricular dysrhythmias.

Pharmacokinetics. Adenosine has an extremely short half-life (estimated at 1.5 to 10 seconds) owing primarily to rapid uptake by cells, and partly to deactivation by circulating adenosine deaminase. Because of its rapid clearance, adenosine must be administered by IV bolus, as close to the heart as possible.

Adverse Effects. Adverse effects are short lived, lasting less than 1 minute. The most common are sinus bradycardia, dyspnea (from bronchoconstriction), hypotension and facial flushing (from vasodilation), and chest discomfort (perhaps from stimulation of pain receptors in the heart).

Drug Interactions. *Methylxanthines* (aminophylline, theophylline, caffeine) block receptors for adenosine. Hence, asthma patients taking aminophylline or theophylline need larger doses of adenosine, and even then adenosine may not work.

Dipyridamole, an antiplatelet drug, blocks cellular uptake of adenosine, and can thereby intensify its effects.

Preparations, Dosage, and Administration. Adenosine [Adenocard] is supplied in solution (3 mg/mL) for bolus IV administration. The injection should be made as close to the heart as possible, and should be followed by a saline flush. The initial dose is 6 mg. If there is no response in 1 or 2 minutes, 12 mg may be tried and repeated once. If a response is going to occur, it should happen as soon as the drug reaches the AV node.

Digoxin

Although its primary indication is heart failure, digoxin [Lanoxin] is also used to treat supraventricular dysrhythmias. The basic pharmacology of digoxin is discussed in Chapter 48. Consideration here is limited to treatment of dysrhythmias.

Effects on the Heart. Digoxin suppresses dysrhythmias by decreasing conduction through the AV node and by decreasing automaticity in the SA node. The drug decreases AV conduction by (1) a direct depressant effect on the AV node and by (2) acting in the CNS to increase vagal (parasympathetic) impulses to the AV node. Digoxin decreases automaticity of the SA node by increasing vagal traffic to the node and by decreasing sympathetic traffic. It should be noted that, although digoxin decreases automaticity in the SA node, it can increase automaticity in *Purkinje fibers*. The latter effect contributes to dysrhythmias caused by digoxin.

Effects on the ECG. By slowing AV conduction, digoxin prolongs the PR interval. The QT interval may be shortened, reflecting accelerated repolarization of the ventricles. Depression of the ST segment is common. The T wave may be depressed or even inverted. There is little or no change in the QRS complex.

Adverse Effects and Interactions. The major adverse effect is *cardiotoxicity* (dysrhythmias). Risk is increased by hypokalemia, which can result from concurrent therapy with diuretics (thiazides and high-ceiling agents). Accordingly, it is essential that potassium levels be kept within the normal range (3.5 to 5 mEq/L). The most common adverse effects are GI disturbances (anorexia, nausea, vomiting, abdominal discomfort). CNS responses (fatigue, visual disturbances) are also relatively common.

Antidysrhythmic Uses. Digoxin is used only for supraventricular dysrhythmias. The drug is inactive against ventricular dysrhythmias.

Atrial Fibrillation and Atrial Flutter. Digoxin can be used to slow ventricular rate in patients with atrial fibrillation and atrial flutter. Ventricular rate is decreased by reducing the number of atrial impulses that pass through the AV node.

Supraventricular Tachycardia. Digoxin may be employed acutely and chronically to treat SVT. Acute therapy is used to abolish the dysrhythmia. Chronic therapy is used to prevent its return. Digoxin suppresses SVT by increasing cardiac vagal tone and by decreasing sympathetic tone.

Dosage and Administration. Oral therapy is generally preferred. The initial dosage is 1 to 1.5 mg administered in three or four doses over 24 hours. The maintenance dosage is 0.125 to 0.5 mg/day.

NONDRUG TREATMENT OF DYSRHYTHMIAS

Implantable Cardioverter-Defibrillators

ICDs are surgically implanted devices that monitor and analyze cardiac rhythm and, by delivering electrical shocks to the heart, terminate any dysrhythmias that develop. Termination is accomplished with either (1) a series of pacing stimuli, which are usually imperceptible; or (2) a defibrillating shock, which can be painful. It is important to note that ICDs do not

prevent dysrhythmias. Rather, they neutralize the ones that occur. ICDs are indicated for patients with recurrent ventricular fibrillation or sustained ventricular tachycardia. For these patients, ICDs significantly reduce the risk of sudden death. The major complication associated with ICDs is mortality during surgical implantation. The mortality rate had been as high as 8%, but is declining due to use of newer techniques. ICDs cost about \$20,000 to \$25,000. The cost for implantation, including hospitalization, adds another \$30,000 to \$50,000.

Radiofrequency Catheter Ablation

Radiofrequency (RF) catheter ablation is a technique in which cardiac tissue responsible for causing a dysrhythmia is identified and destroyed. The result is often permanent cure. In preparation for RF ablation, the patient undergoes electro-

physiologic cardiac testing to identify the small region of the heart that is generating the dysrhythmia. Next, an RF catheter is placed at the site. Activation of the catheter generates RF energy, which heats, and thereby destroys, all tissue within 5 to 8 mm of the catheter tip. Destruction of the offending tissue eliminates the dysrhythmia. Success rates depend on the dysrhythmia being treated. In patients with atrial tachycardia, AV nodal reentrant tachycardia, or dysrhythmias associated with Wolff-Parkinson-White syndrome, the rate of permanent cure is between 90% and 100%. In patients with atrial flutter, initial responses are generally good, but recurrence is common. Complications develop in less than 5% of procedures. The most common complications are AV block and myocardial perforation. Complications that require intervention or that result in long-term injury occur in only 1% of patients. For treatment of atrial dysrhythmias, catheter ablation costs about \$25,000 to \$30,000.

KEY POINTS

- Dysrhythmias result from alteration of the electrical impulses that regulate cardiac rhythm. Antidysrhythmic drugs control rhythm by correcting or compensating for these alterations.
- In the healthy heart, the SA node is the pacemaker.
- Impulses originating in the SA node must travel through the AV node to reach the ventricles. Impulses arriving at the AV node are delayed before going on to excite the ventricles.
- The His-Purkinje system conducts impulses rapidly throughout the ventricles, thereby causing all parts of the ventricles to contract in near synchrony.
- The heart employs two kinds of action potentials: fast potentials and slow potentials.
- Fast potentials occur in the His-Purkinje system, atrial muscle, and ventricular muscle.
- Slow potentials occur in the SA node and AV node.
- Phase 0 of fast potentials (depolarization) is generated by rapid influx of sodium. Because depolarization is fast, these potentials conduct rapidly.
- During phase 2 of fast potentials, calcium enters myocardial cells, thereby promoting contraction.
- Phase 3 of fast potentials (repolarization) is generated by rapid extrusion of potassium.
- Phase 0 of slow potentials (depolarization) is caused by slow influx of calcium. Because depolarization is slow, these potentials conduct slowly.
- Spontaneous phase 4 depolarization—of fast or slow potentials—gives cells automaticity.
- Spontaneous phase 4 depolarization of cells in the SA node normally determines heart rate.
- The P wave of an ECG is caused by depolarization of the atria.
- The QRS complex is caused by depolarization of the ventricles. Widening of the QRS complex indicates slowed conduction through the ventricles.
- The T wave is caused by repolarization of the ventricles.
- The PR interval represents the time between onset of the P wave and onset of the QRS complex. PR prolongation indicates delayed AV conduction.
- The QT interval represents the time between onset of the QRS complex and completion of the T wave. QT prolongation indicates delayed ventricular repolarization.
- Dysrhythmias arise from disturbances of impulse formation (automaticity) or impulse conduction.
- Reentrant dysrhythmias result from a localized, self-sustaining circuit capable of repetitive cardiac stimulation.
- Tachydysrhythmias can be divided into two major groups: supraventricular tachydysrhythmias and ventricular tachydysrhythmias. In general, ventricular tachydysrhythmias disrupt cardiac pumping more than do supraventricular tachydysrhythmias.
- Treatment of supraventricular tachydysrhythmias is often directed at blocking impulse conduction through the AV node, rather than at eliminating the dysrhythmia.
- Treatment of ventricular dysrhythmias is usually directed at eliminating the dysrhythmia.
- All antidysrhythmic drugs are also prodysrhythmic (proarrhythmic). That is, they all can worsen existing dysrhythmias and generate new ones.
- Class I antidysrhythmic drugs block cardiac sodium channels, and thereby slow impulse conduction through the atria, ventricles, and His-Purkinje system.
- Slowing ventricular conduction widens the QRS complex.
- Quinidine (a class IA drug) blocks sodium channels and delays ventricular repolarization. Delaying ventricular repolarization prolongs the QT interval.
- Quinidine causes diarrhea and other GI symptoms in 33% of patients. These effects frequently force drug withdrawal.
- Quinidine can cause dysrhythmias. Widening of the QRS complex (by 50% or more) and excessive prolongation of the QT interval are warning signs.

- Quinidine can raise digoxin levels. If the drugs are used together, digoxin dosage must be reduced.
- Class IB agents differ from class IA agents in two ways: they accelerate repolarization and have little or no effect on the ECG.
- Lidocaine (a class IB agent) is used only for ventricular dysrhythmias. The drug is not active against supraventricular dysrhythmias.
- Lidocaine undergoes rapid inactivation by the liver. As a result, it must be administered by continuous IV infusion.
- Propranolol and other class II drugs block cardiac beta₁ receptors.
- By blocking cardiac beta₁ receptors, propranolol attenuates sympathetic stimulation of the heart, and thereby decreases SA nodal automaticity, AV conduction velocity, and myocardial contractility.
- By decreasing AV conduction velocity, propranolol prolongs the PR interval.
- The effects of propranolol on the heart result (ultimately) from suppressing calcium entry. Hence, the cardiac effects of propranolol and the effects of calcium channel blockers are nearly identical.
- Propranolol is especially useful for treating dysrhythmias caused by excessive sympathetic stimulation of the heart.
- In patients with supraventricular tachydysrhythmias, propranolol helps by (1) slowing discharge of the SA node and (2) decreasing impulse conduction through the AV node, which prevents the atria from driving the ventricles at an excessive rate.
- Class III antidysrhythmics block potassium channels, and thereby delay repolarization of fast potentials. As a result, they prolong the action potential duration and the effective refractory period. By delaying ventricular repolarization, they prolong the QT interval.
- Amiodarone (a class III agent) is highly effective against atrial and ventricular dysrhythmias, but can cause multiple serious adverse effects, including damage to the lungs, eyes, liver, and thyroid.
- Dronedaronone, a derivative of amiodarone, is somewhat less toxic than amiodarone, but also less effective. In patients with heart failure or permanent atrial fibrillation, dronedaronone doubles the risk of death.
- Verapamil and diltiazem (class IV antidysrhythmics) block cardiac calcium channels, and thereby reduce automaticity of the SA node, slow conduction through the AV node, and decrease myocardial contractility. These effects are identical to those of the beta blockers.
- By suppressing AV conduction, verapamil and diltiazem prolong the PR interval.
- Verapamil and diltiazem are used to slow ventricular rate in patients with atrial fibrillation or atrial flutter and to terminate SVT caused by an AV nodal reentrant circuit. In both cases, benefits derive from suppressing AV nodal conduction.
- Adenosine is a drug of choice for terminating paroxysmal SVT.
- Adenosine has a very short half-life (less than 10 seconds), and hence must be given by IV bolus.

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Summary of Major Nursing Implications*

Summaries are limited to the major antidysrhythmic drugs. Summaries for beta blockers (propranolol, acebutolol, and esmolol), phenytoin, calcium channel blockers (verapamil and diltiazem), and digoxin appear in Chapters 18, 24, 45, and 48, respectively.

QUINIDINE

Preadministration Assessment

Therapeutic Goal

The usual goal is long-term suppression of atrial and ventricular dysrhythmias.

Baseline Data

Obtain a baseline ECG and laboratory evaluation of liver function. Determine blood pressure.

Identifying High-Risk Patients

Quinidine is *contraindicated* for patients with a history of hypersensitivity to quinidine or other cinchona alkaloids and for patients with complete heart block, digoxin intoxication, or conduction disturbances associated with marked QRS widening and QT prolongation.

Exercise *caution* in patients with partial AV block, heart failure, hypotensive states, and hepatic dysfunction.

Implementation: Administration

Routes

Usual Route. Oral.

Rare Routes. IM and IV.

Administration

Before giving full therapeutic doses, assess for hypersensitivity by giving a small test dose (200 mg PO or IM).

Advise patients to take quinidine with meals. Warn them not to crush or chew sustained-release formulations.

Dosage size depends on the particular quinidine salt being used: 200 mg of quinidine sulfate is equivalent to 275 mg of quinidine gluconate.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor for beneficial changes in the ECG. Plasma drug levels should be kept between 2 and 5 mcg/mL.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Minimizing Adverse Effects

Diarrhea. Diarrhea and other GI disturbances occur in one-third of patients and frequently force drug withdrawal. **Inform patients that they can reduce GI effects by taking quinidine with meals.**

Cinchonism. Inform patients about symptoms of cinchonism (tinnitus, headache, nausea, vertigo, disturbed vision), and instruct them to notify the prescriber if these develop.

Cardiotoxicity. Monitor the ECG for signs of cardiotoxicity, especially widening of the QRS complex (by 50% or more) and excessive prolongation of the QT interval. Monitor pulses for significant changes in rate or regularity. If signs of cardiotoxicity develop, withhold quinidine and notify the prescriber.

Arterial Embolism. Embolism may occur during therapy of atrial fibrillation. Risk is reduced by treatment with an anticoagulant (eg, warfarin, dabigatran). Observe for signs of thromboembolism (eg, sudden chest pain, dyspnea) and report these immediately.

Minimizing Adverse Interactions

Digoxin. Quinidine can double digoxin levels. When these drugs are combined, digoxin dosage should be reduced. Monitor patients for digoxin toxicity (dysrhythmias).

PROCAINAMIDE

Preadministration Assessment

Therapeutic Goal

Procainamide is indicated for acute and long-term management of ventricular and supraventricular dysrhythmias. Because procainamide can be toxic with long-term use, quinidine is preferred to procainamide for chronic suppression.

Baseline Data

Obtain a baseline ECG, complete blood count, and laboratory evaluations of liver and kidney function. Determine blood pressure.

Identifying High-Risk Patients

Procainamide is *contraindicated* for patients with systemic lupus erythematosus (SLE), complete AV block, and second-degree or third-degree AV block in the absence of an electronic pacemaker.

Exercise *caution* in patients with hepatic or renal dysfunction or a history of procaine allergy.

Implementation: Administration

Routes

Oral, IM, IV.

Administration

Instruct patients to administer procainamide at evenly spaced intervals around-the-clock. Warn patients not to crush or chew sustained-release formulations.

When switching from IV procainamide to oral procainamide, allow 3 hours to elapse between stopping the infusion and giving the first oral dose.

Give IM injections deep into the gluteal muscle.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor the ECG for beneficial changes. Plasma drug levels should be kept between 3 and 10 mcg/mL.

Minimizing Adverse Effects

SLE-like Syndrome. Prolonged therapy can produce a syndrome resembling SLE. **Inform patients about manifestations of SLE (joint pain and inflammation; hepatomegaly; unexplained fever; soreness of the mouth, throat, or gums), and instruct them to notify the prescriber if these develop.** If SLE is diagnosed, procainamide should be discontinued. If discontinuation is impossible, signs and symptoms can be controlled with a nonsteroidal anti-inflammatory drug (eg, aspirin) or a glucocorticoid. The ANA titer should be measured periodically and, if it rises, procainamide withdrawal should be considered.

Blood Dyscrasias. Procainamide can cause agranulocytosis, thrombocytopenia, and neutropenia. Deaths have occurred. Obtain complete blood counts weekly during the first 3 months of treatment and periodically thereafter. **Instruct patients to inform the prescriber at the first sign of infection (fever, chills, sore throat), bruising, or bleeding.** If subsequent blood counts indicate hematologic disturbance, discontinue procainamide immediately.

Cardiotoxicity. Procainamide can cause dysrhythmias. Monitor pulses for changes in rate or regularity. Monitor the ECG for excessive QRS widening (greater than 50%) and for PR prolongation. If these occur, withhold procainamide and notify the prescriber.

Arterial Embolism. Embolism may occur during therapy of atrial fibrillation. Risk is reduced by treatment with an anticoagulant (eg, warfarin, dabigatran). Observe for signs of thromboembolism (eg, sudden chest pain, dyspnea) and report these immediately.

LIDOCAINE

Preadministration Assessment

Therapeutic Goal

Acute management of ventricular dysrhythmias.

Baseline Data

Obtain a baseline ECG and determine blood pressure.

Identifying High-Risk Patients

Lidocaine is *contraindicated* for patients with Stokes-Adams syndrome, Wolff-Parkinson-White syndrome, and severe degrees of SA, AV, or intraventricular block in the absence of electronic pacing.

Exercise *caution* in patients with hepatic dysfunction or impaired hepatic blood flow.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Implementation: Administration

Routes

Usual. IV.
Emergencies. IM.

Administration

Intravenous. Make certain the lidocaine preparation is labeled for IV use (ie, is devoid of preservatives and catecholamines). Dilute concentrated preparations with 5% dextrose in water.

The initial dose is 50 to 100 mg (1 mg/kg) infused at a rate of 25 to 50 mg/min. For maintenance, monitor the ECG and adjust the infusion rate on the basis of cardiac response. The usual rate is 1 to 4 mg/min.

Intramuscular. Reserve for emergencies. The usual dose is 300 mg injected into the deltoid muscle. Switch to IV lidocaine as soon as possible.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Continuous ECG monitoring is required. Plasma drug levels should be kept between 1.5 and 5 mcg/mL.

Minimizing Adverse Effects

Excessive doses can cause convulsions and respiratory arrest. Equipment for resuscitation should be available. Convulsions can be managed with diazepam or phenytoin.

AMIODARONE

Preadministration Assessment

Therapeutic Goal

Oral Therapy. Long-term treatment of (1) atrial fibrillation and (2) life-threatening recurrent ventricular fibrillation or recurrent hemodynamically unstable ventricular tachycardia in patients who have not responded to safer drugs.

Intravenous Therapy. Initial treatment of recurrent ventricular fibrillation, shock-resistant ventricular fibrillation, recurrent hemodynamically unstable ventricular tachycardia, atrial fibrillation, and AV nodal reentrant tachycardia.

Baseline Data

Obtain a baseline ECG, eye examination, and chest x-ray, along with potassium and magnesium levels, and tests for thyroid, pulmonary, and liver function.

Identifying High-Risk Patients

Amiodarone is *contraindicated* for patients with severe sinus node dysfunction or second- or third-degree AV block, and for women who are pregnant or breast-feeding.

Exercise *caution* in patients with thyroid disorders, hypokalemia, or hypomagnesemia.

Implementation: Administration

Routes

Oral. Used for maintenance therapy of atrial and ventricular dysrhythmias.

Intravenous. Used for acute therapy of atrial and ventricular dysrhythmias.

Administration and Dosage

Oral. Initiate treatment in a hospital. High doses are used initially (800 to 1600 mg/day for 1 to 3 weeks). The usual maintenance dosage is 100 to 400 mg/day.

Intravenous. Administer by continuous IV infusion, starting with a rapid infusion rate, and later reducing the rate for maintenance. Intravenous treatment may last from 2 days to 3 weeks.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor for beneficial changes in the ECG.

Minimizing Adverse Effects

Pulmonary Toxicity. Amiodarone can cause potentially fatal lung damage (hypersensitivity pneumonitis, interstitial/alveolar pneumonitis, and pulmonary fibrosis). Obtain a baseline chest x-ray and pulmonary function test, and monitor pulmonary function throughout treatment. **Inform patients about signs of lung injury (dyspnea, cough, chest pain) and instruct them to report these immediately.** Treatment consists of withdrawing amiodarone and supportive care, sometimes including glucocorticoids.

Cardiotoxicity. Amiodarone can cause heart failure and atrial and ventricular dysrhythmias. *Patients with pre-existing heart failure must not use the drug.* **Warn patients about signs of heart failure (eg, shortness of breath, reduced exercise tolerance, fatigue, tachycardia, weight gain) and instruct them to report these immediately.**

Liver Toxicity. Amiodarone can injure the liver. Obtain tests of liver function at baseline and periodically during treatment. If circulating liver enzymes exceed 3 times the normal level, amiodarone should be withdrawn. **Inform patients about signs and symptoms of liver injury (eg, anorexia, nausea, vomiting, malaise, fatigue, itching, jaundice, dark urine) and instruct them to report them immediately.**

Thyroid Toxicity. Amiodarone can cause hypothyroidism and hyperthyroidism. Obtain tests of thyroid function at baseline and periodically during treatment. Treat hypothyroidism with thyroid hormone supplements. Treat hyperthyroidism with an antithyroid drug (eg, methimazole) or thyroidectomy. Stopping amiodarone should be considered.

Toxicity in Pregnancy and Breast-feeding. Amiodarone can harm the developing fetus and breast-feeding infant. **Warn women to avoid pregnancy and breast-feeding while using amiodarone and for several months after stopping.**

Ophthalmic Effects. Amiodarone has been associated with optic neuropathy and optic neuritis, sometimes progressing to blindness. Obtain ophthalmic tests, including funduscopy and a slit-lamp examination, at baseline and periodically during treatment. **Advise patients to report reductions in visual acuity or peripheral vision.** If optic neuropathy or neuritis is diagnosed, discontinuing amiodarone should be considered.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Virtually all patients develop corneal microdeposits. In most cases, the deposits have no effect on vision, and hence only rarely lead to amiodarone cessation.

Dermatologic Effects. Photosensitivity reactions are common. **Advise patients to avoid sunlamps and to wear sunblock and protective clothing when outdoors.** With prolonged sun exposure, skin may develop a bluish-gray discoloration, which typically resolves a few months after amiodarone is stopped.

Minimizing Adverse Interactions

Amiodarone is subject to significant interactions with many drugs. Interactions of special concern are presented here.

Drugs Whose Levels Can Be Increased by Amiodarone. Amiodarone can increase levels of several drugs, including quinidine, procainamide, phenytoin, digoxin, diltiazem, warfarin, cyclosporine, and three statins: lovastatin, simvastatin, and atorvastatin. Dosages of these agents often require reduction.

Drugs That Can Reduce Amiodarone Levels. Amiodarone levels can be reduced by cholestyramine (which decreases amiodarone absorption) and by agents that induce CYP3A4 (eg, St. John's wort, rifampin). Monitor to ensure that amiodarone is still effective.

Drugs That Can Increase the Risk of Dysrhythmias. The risk of severe dysrhythmias is increased by diuretics (because they can reduce levels of potassium and magnesium) and by drugs that prolong the QT interval (see Chapter 7, Table 7-2).

Drugs That Can Cause Bradycardia. Combining amiodarone with a beta blocker, verapamil, or diltiazem can lead to excessive slowing of heart rate.

Grapefruit Juice. Grapefruit juice inhibits CYP3A4, and can thereby raise levels of amiodarone. Toxicity can result. **Advise patients to avoid grapefruit juice.**

*Patient education information is highlighted as **blue text**.

Prophylaxis of Coronary Heart Disease: Drugs That Help Normalize Cholesterol and Triglyceride Levels

Cholesterol

Plasma Lipoproteins

Structure and Function of Lipoproteins

Classes of Lipoproteins

LDL Cholesterol Versus HDL Cholesterol

Role of LDL Cholesterol in Atherosclerosis

Detection, Evaluation, and Treatment of High Cholesterol: Recommendations from ATP III

Cholesterol Screening

CHD Risk Assessment

Treatment of High LDL Cholesterol

Secondary Treatment Targets

Drugs and Other Products Used to Improve Plasma Lipid Levels

HMG-CoA Reductase Inhibitors (Statins)

Niacin (Nicotinic Acid)

Bile-Acid Sequestrants

Ezetimibe

Fibric Acid Derivatives (Fibrates)

Drug Combinations

Fish Oil

Plant Stanol and Sterol Esters

Estrogen

Cholestin

si Box 50-1. Inflammation, C-Reactive Protein, and Cardiovascular Risk

Our main topic for the chapter is drugs used to lower cholesterol. Drugs used to lower triglycerides are considered as well. Why focus on cholesterol? Because of its impact on *coronary artery atherosclerosis* (thickening of the coronary arteries), also known as coronary heart disease (CHD). Moderate CHD usually manifests first as anginal pain. Severe CHD sets the stage for acute coronary syndrome (ACS) and myocardial infarction (MI). In the United States, CHD is the leading killer of men and women, causing 406,000 deaths in 2007. According to the American Heart Association, about 16 million Americans have a history of coronary events (angina, MI,

or both). More than half of these people are women. Additional sobering statistics are presented in Table 50-1.

Until recently, atherosclerosis was largely a disease of older people. Not so any more. Why? Because lifestyles have changed. A generation ago, diets included generally healthy made-from-scratch “balanced” meals, and children were shooed out of the house to play. Nowadays, fast-food restaurants and heat-and-eat meals are the new tradition, even though (or because?) they may be loaded with all sorts of heart-unhealthy fats, along with the heart’s other big enemy: salt. And while many youngsters are shuttled off to school, then to soccer, then to baseball, track, or swimming, too many others seem to be in competition for Couch-Potato-of-the-Year, earning points on their video games or otherwise devoting much time to their smart phones or the Internet. So now, rather than developing CHD in their fourth or fifth decade, people are getting the disease sooner, as can be attested to by attending clinicians and the pathologists doing the autopsies.

How does atherosclerosis develop? Very briefly, it begins as a fatty streak in the arterial wall. This is followed by deposition of fibrous plaque. As atherosclerotic plaque grows, it impedes coronary blood flow, causing anginal pain. Worse yet, coronary atherosclerosis encourages formation of thrombi, which can block flow entirely, thereby causing MI.

It is important to appreciate that atherosclerosis is not limited to arteries of the heart: Atherosclerotic plaque can develop in any artery, and can thereby compromise circulation to any tissue. Furthermore, adverse effects can occur at sites distant from the original lesion: A ruptured lesion can produce a thrombus, which can travel downstream to block a new vessel. Blockage in the lungs and brain is of particular concern.

The risk of developing CHD is directly related to increased levels of blood cholesterol, in the form of low-density lipoproteins (LDLs). By reducing levels of LDL cholesterol, we can slow progression of atherosclerosis, reduce the risk of serious CHD and its potential consequences, and prolong life. The preferred method for lowering LDL cholesterol is modification of diet combined with exercise. Drugs are employed only when diet modification and exercise are insufficient.

We approach our primary topic—cholesterol and its impact on CHD—in three stages. First, we discuss cholesterol itself, plasma lipoproteins (structures that transport cholesterol in blood), and the process of atherogenesis. Second, we discuss guidelines for cholesterol screening and management of high cholesterol. Third,

TABLE 50-1 • Morbidity and Mortality from Cardiovascular Disease in General, and Coronary Heart Disease in Particular, United States

Cardiovascular Disease of All Types

- Cardiovascular disease took 813,804 lives in 2007—accounting for 34% of all deaths that year, regardless of cause. In 2007, the number of deaths from cardiovascular disease was about
 - 4 times the number of deaths from all cancers
 - 20 times the number of deaths caused by accidents
 - 48 times the number of deaths from HIV/AIDS

Coronary Heart Disease

- Coronary heart disease (CHD), characterized by buildup of atherosclerotic plaque in coronary arteries, is the major cause of angina pectoris, heart attacks, and death.
- In 2007, CHD caused 406,00 deaths, and it is the single leading cause of death in the United States today.
- In 2007, about 133,000 people died of heart attacks, either in an emergency department or without being hospitalized.
- 16 million people alive today have a history of heart attack, angina pectoris, or both—roughly 8.7 million males and 7.3 million females.
- Each year, about 1.2 million Americans will have a new or recurrent heart attack.

we discuss the pharmacology of the cholesterol-lowering drugs, as well as drugs used to lower triglycerides.

CHOLESTEROL

Cholesterol has several physiologic roles. Of greatest importance, cholesterol is a component of all cell membranes and membranes of intracellular organelles. In addition, cholesterol is required for synthesis of certain hormones (estrogen, progesterone, testosterone, adrenal corticosteroids) and for synthesis of bile salts, which are needed to absorb and digest dietary fats. Also, cholesterol is deposited in the stratum corneum of the skin, where it reduces evaporation of water and blocks transdermal absorption of water-soluble compounds.

Some of our cholesterol comes from dietary sources (exogenous cholesterol) and some is manufactured by cells (endogenous cholesterol), primarily in the liver. More cholesterol comes from endogenous production than from the diet. A critical step in hepatic cholesterol synthesis is catalyzed by an enzyme named *3-hydroxy-3-methylglutaryl coenzyme A reductase*, or simply *HMG-CoA reductase*. As discussed below, drugs that inhibit this enzyme—the statins—are our most effective and widely used cholesterol-lowering agents.

An increase in dietary cholesterol produces only a small increase in cholesterol in the blood, primarily because a rise in cholesterol intake inhibits endogenous cholesterol synthesis. Interestingly, an increase in dietary saturated fats produces a substantial (15% to 25%) increase in circulating cholesterol. Why? Because the liver uses saturated fats to make cholesterol. Accordingly, when we want to reduce cholesterol levels, it is more important to reduce intake of saturated fats than to reduce intake of cholesterol itself, although cholesterol intake should definitely be lowered.

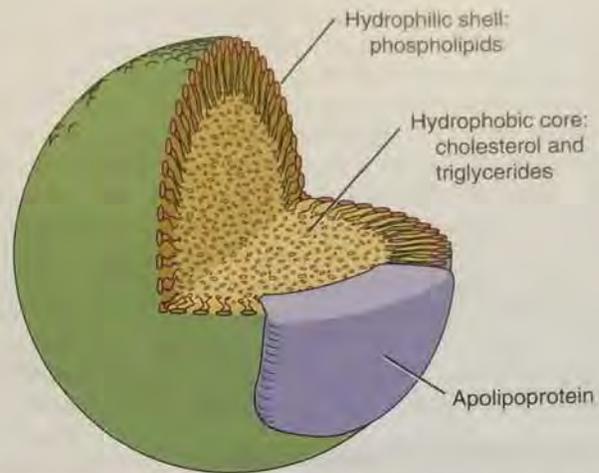


Figure 50-1 • Basic structure of plasma lipoproteins.

PLASMA LIPOPROTEINS

Structure and Function of Lipoproteins

Function. Lipoproteins serve as carriers for transporting lipids—cholesterol and triglycerides—in blood. Like all other nutrients and metabolites, lipids use the bloodstream to move throughout the body. However, being lipids, cholesterol and triglycerides are not water soluble, and hence cannot dissolve directly in plasma. Lipoproteins provide a means of solubilizing these lipids, thereby permitting transport.

Basic Structure. The basic structure of lipoproteins is depicted in Figure 50-1. As indicated, lipoproteins are tiny, spherical structures that consist of a *hydrophobic core*, composed of cholesterol and triglycerides, surrounded by a *hydrophilic shell*, composed primarily of phospholipids. Because the hydrophilic shell completely covers the lipid core, the entire structure is soluble in the aqueous environment of the plasma.

Apolipoproteins. All lipoproteins have one or more *apolipoprotein* molecules embedded in their shell (see Fig. 50-1). Apolipoproteins, which constitute the protein component of lipoproteins, have three functions:

- They serve as recognition sites for cell-surface receptors, and thereby allow cells to bind with and ingest lipoproteins.
- They activate enzymes that metabolize lipoproteins.
- They increase the structural stability of lipoproteins.

The apolipoproteins of greatest clinical interest are labeled A-I, A-II, and B-100. All lipoproteins that deliver cholesterol and triglycerides to nonhepatic tissues contain *apolipoprotein B-100*. Conversely, all lipoproteins that transport lipids from nonhepatic tissues back to the liver (ie, that remove lipids from tissues) contain *apolipoprotein A-I*.

Classes of Lipoproteins

There are six major classes of plasma lipoproteins. Distinctions among classes are based on size, density, apolipoprotein content, transport function, and primary core lipids (cholesterol or triglyceride). From a pharmacologic perspective, the features of greatest interest are *lipid content*, *apolipoprotein content*, and *transport function*.

For two reasons, the topic of lipoprotein *density* deserves comment. First, naming of lipoprotein types is based on their

density. Second, differences in density provide the basis for the physical isolation and subsequent measurement of plasma lipoproteins, as is done in research and clinical laboratories. The various classes of lipoproteins differ in density because they differ in their percent composition of lipid and protein. Because protein is more dense than lipid, lipoproteins that have a high percentage of protein (and a low percentage of lipid) have a relatively high density. Conversely, lipoproteins with a lower percentage of protein have a lower density.

Of the six major classes of lipoproteins, three are especially important in coronary atherosclerosis. These classes are named (1) very-low-density lipoproteins (VLDLs), (2) low-density lipoproteins (LDLs), and (3) high-density lipoproteins (HDLs). Properties of these classes are summarized in Table 50-2.

Very-Low-Density Lipoproteins

VLDLs contain mainly *triglycerides* (and some cholesterol), and they account for nearly all of the triglycerides in blood. The main physiologic role of VLDLs is to *deliver triglycerides* from the liver to adipose tissue and muscle, which can use the triglycerides as fuel. Each VLDL particle contains one molecule of *apolipoprotein B-100*, which allows VLDLs to bind with cell-surface receptors and thereby transfer their lipid content to cells.

The role of VLDLs in atherosclerosis is unclear. Although several studies suggest a link between elevated levels of VLDLs and development of atherosclerosis, this link has not been firmly established. However, we do know that elevation of triglyceride levels (above 500 mg/dL) increases the risk of *pancreatitis*.

Low-Density Lipoproteins

LDLs contain *cholesterol* as their primary core lipid, and they account for the majority (60% to 70%) of all cholesterol in blood. The physiologic role of LDLs is *delivery of cholesterol to nonhepatic tissues*. Each LDL particle contains one molecule of *apolipoprotein B-100*, which is needed for binding of LDL particles to LDL receptors on cells. LDLs can be viewed as by-products of VLDL metabolism, in that the lipids and apolipoproteins that compose LDLs are remnants of VLDL degradation.

Cells that require cholesterol meet their needs through endocytosis (engulfment) of LDLs from the blood. The process begins with binding of LDL particles to LDL receptors on the cell surface. When cellular demand for cholesterol increases, cells synthesize more LDL receptors and thereby increase their capacity for LDL uptake. Accordingly, cells that are unable to make more LDL receptors cannot increase cholesterol absorption. Increasing the number of LDL receptors on cells is an

important mechanism by which certain drugs increase LDL uptake, and thereby reduce LDL levels in blood.

Of all lipoproteins, LDLs make the greatest contribution to coronary atherosclerosis. The probability of developing CHD is directly related to the level of LDLs in blood. Conversely, by reducing LDL levels, we decrease the risk of CHD. Accordingly, *when cholesterol-lowering drugs are used, the main goal is to reduce elevated LDL levels.* Multiple studies have shown that, by reducing LDL levels, we can arrest or perhaps even reverse atherosclerosis, and can thereby reduce mortality from CHD. In fact, for each 1% reduction in the LDL level, there is about a 1% reduction in the risk of a major cardiovascular (CV) event.

High-Density Lipoproteins

Like LDLs, HDLs contain *cholesterol* as their primary core lipid, and account for 20% to 30% of all cholesterol in blood. In contrast to LDLs, whose function is delivery of cholesterol to peripheral tissues, HDLs carry cholesterol from peripheral tissues back to the liver. That is, *HDLs promote cholesterol removal.*

The influence of HDLs on CHD is dramatically different from that of LDLs. Whereas elevation of LDLs *increases* the risk of CHD, elevation of HDLs *reduces* the risk of CHD. That is, high HDL levels actively protect against CHD.

LDL Cholesterol Versus HDL Cholesterol

The discussion above shows that not all cholesterol in plasma has the same impact on CHD. As stated, a rise in cholesterol associated with LDLs increases the risk of CHD. In contrast, a rise in cholesterol associated with HDLs lowers the risk. Consequently, when speaking of plasma cholesterol levels, we need to distinguish between cholesterol that is associated with HDLs and cholesterol that is associated with LDLs. To make this distinction, we use the terms *HDL cholesterol* and *LDL cholesterol*. Because LDL cholesterol promotes atherosclerosis, it has been dubbed *bad cholesterol* or *lousy cholesterol*. Conversely, because HDL seems to protect against atherosclerosis, it is often called *good cholesterol* or *healthy cholesterol*.

ROLE OF LDL CHOLESTEROL IN ATHEROSCLEROSIS

LDLs initiate and fuel development of atherosclerosis. The process begins with transport of LDLs from the arterial lumen into endothelial cells that line the lumens of blood vessels.

TABLE 50-2 • Properties of the Plasma Lipoproteins That Affect Atherosclerosis

Lipoprotein Class*	Major Core Lipids	Apolipoproteins	Transport Function	Influence on Atherosclerosis
VLDL	Triglycerides	B-100, E, others	Delivery of triglycerides to nonhepatic tissues	Probably contribute to atherosclerosis
LDL	Cholesterol	B-100	Delivery of cholesterol to nonhepatic tissues	Definitely contribute to atherosclerosis
HDL	Cholesterol	A-I, A-II, A-IV	Transport of cholesterol from nonhepatic tissues back to the liver	Protect against atherosclerosis

*VLDL = very-low-density lipoprotein, LDL = low-density lipoprotein, HDL = high-density lipoprotein.

From there, they move into the space that underlies the arterial epithelium. Once in the subendothelial space, components of LDLs undergo *oxidation*. This step is critical in that oxidized LDLs

- Attract monocytes from the circulation into the subendothelial space, after which the monocytes are converted to macrophages (which are critical to atherogenesis)
- Inhibit macrophage mobility, thereby keeping macrophages at the site of atherogenesis
- Undergo uptake by macrophages (macrophages do not take up LDLs that have not been oxidized)
- Are cytotoxic, and hence can damage the vascular endothelium directly

As macrophages engulf more and more cholesterol, they become large and develop large vacuoles. When macrophages assume this form, they are referred to as *foam cells*. Foam cell accumulation beneath the arterial epithelium produces a *fatty streak*, which makes the surface of the arterial wall lumpy, causing blood flow to become turbulent. Continued accumulation of foam cells can eventually cause rupture of the endothelium, thereby exposing the underlying tissue to the blood. This results in platelet adhesion and formation of microthrombi. As the process continues, smooth muscle cells migrate to the site, synthesis of collagen increases, and there can be repeated rupturing and healing of the endothelium. The end result is a mature atherosclerotic lesion, characterized by a large lipid core and a tough *fibrous cap*. In less mature lesions, the fibrous cap is not strong, and hence the lesions are unstable and more likely to rupture. As a result, arterial pressure and shear forces (from turbulent blood flow) can cause the cap to rupture. Accumulation of platelets at the site of rupture can rapidly cause thrombosis, and can thereby cause infarction. Infarction is less likely at sites of mature atherosclerotic lesions. The atherosclerotic process is depicted in Figure 50-2.

It is important to appreciate that atherogenesis involves more than just deposition of lipids. In fact, atherogenesis is now considered primarily a chronic *inflammatory process*. When LDLs penetrate the arterial wall, they cause mild injury. The injury, in turn, triggers an inflammatory response that includes infiltration of macrophages, T lymphocytes, and other potentially noxious chemicals (eg, C-reactive protein [CRP]). In the late stage of the disease process, inflammation can weaken atherosclerotic plaque, leading to plaque rupture and subsequent thrombosis. The roles of inflammation and CRP in atherothrombosis are discussed further in Box 50-1.

DETECTION, EVALUATION, AND TREATMENT OF HIGH CHOLESTEROL: RECOMMENDATIONS FROM ATP III

It is well established that high levels of cholesterol (primarily LDL cholesterol) cause substantial morbidity and mortality, and that aggressive treatment can save lives. Accordingly, periodic cholesterol screening and risk assessment are recommended. If the assessment indicates CHD risk, lifestyle changes—especially diet and exercise—should be implemented. If CHD risk is high, LDL-lowering drugs should be added to the regimen.

In 1988, the National Cholesterol Education Program (NCEP) began issuing guidelines on cholesterol detection and

management. The most recent update was issued in 2001 and amended in 2004. A summary of the 2001 guidelines—*Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* (also known as Adult Treatment Panel III or simply ATP III)—was published in *JAMA* (Vol. 285, No. 19, 2486–2497, 2001) and is available online at www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf. The 2004 changes to the 2001 guidelines were published in *Circulation* (Vol. 110, 227–239, 2004) and are available online at www.nhlbi.nih.gov/guidelines/cholesterol/atp3upd04.pdf. Previous NCEP guidelines were issued in 1988 (ATP I) and 1993 (ATP II). The discussion below reflects recommendations in ATP III, including the 2004 updates.

Like earlier NCEP guidelines, ATP III focuses on the role of high cholesterol in CHD and stresses the importance of treatment. However, owing to revised risk assessment criteria, ATP III recommends drug therapy for many more Americans: about 50 million, compared with only 13 million under ATP II. In addition, ATP III addresses two new concerns: *elevated triglycerides* and *metabolic syndrome* (formerly known as syndrome X or insulin resistance syndrome).

Note: An update of ATP III—ATP IV—is long overdue. Publication was originally scheduled for 2010, but has been postponed until at least 2012. When ATP IV is finally released, we will revise the chapter and publish the revision on the Evolve site. Elsevier sales reps will inform faculty when the revised chapter is available.

Cholesterol Screening

Adults

Management of high LDL cholesterol begins with screening, generally done every 5 years for adults over the age of 20. The ATP III guidelines recommend a more thorough screen than before, consisting of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (TGs). Blood for these tests should be drawn after fasting. Classification of total cholesterol and LDL cholesterol levels in ATP III (Table 50-3) is nearly identical to the older ATP II classifications. (The only change is that optimal LDL cholesterol is now defined in ATP III as less than 100 mg/dL, compared with less than 130 mg/dL under ATP II. In addition, the cutoff for *low* HDL cholesterol is now less than 40 mg/dL, up from less than 35 mg/dL under ATP II.

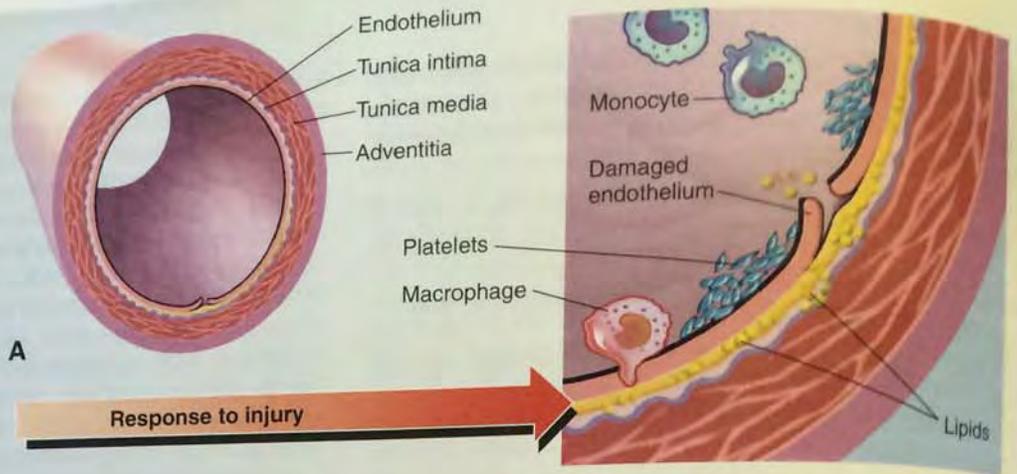
Children and Adolescents

Elevated cholesterol in pediatric patients is a growing concern, and is not addressed in ATP III. However, it is addressed in other guidelines, including one created in 2011 by an expert panel appointed by the National Heart, Lung, and Blood Institute, and endorsed by the American Academy of Pediatrics. This report—*Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents*—is available online at www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm#chap9.

When should testing be done? The guideline recommends lipid screening for *all* children between ages 9 and 11 years, followed by another screen between ages 18 and 21 years. For children with a family history of high cholesterol or heart disease, screening should start sooner: between ages 2 and

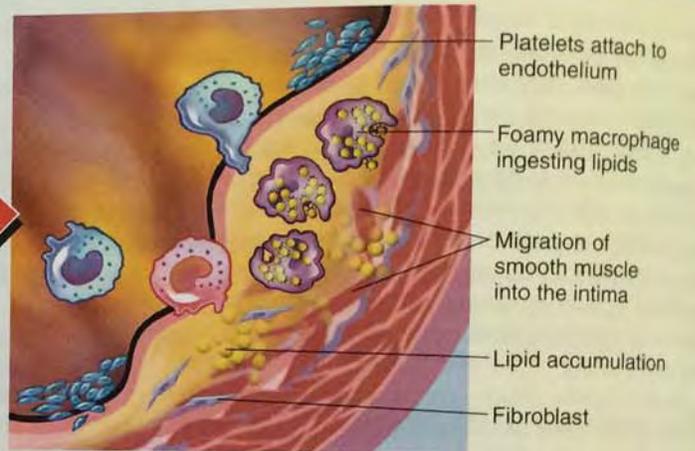
**Damaged endothelium:
Chronic endothelial injury**

- Hypertension
- Smoking
- Hyperlipidemia
- Hyperhomocystinemia
- Hemodynamic factors
- Toxins
- Viruses
- Immune reactions



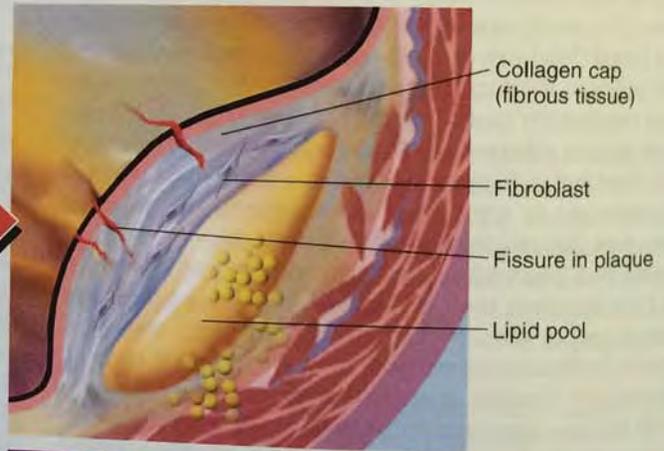
Fatty streak

B



Fibrous plaque

C



Complicated lesion

D

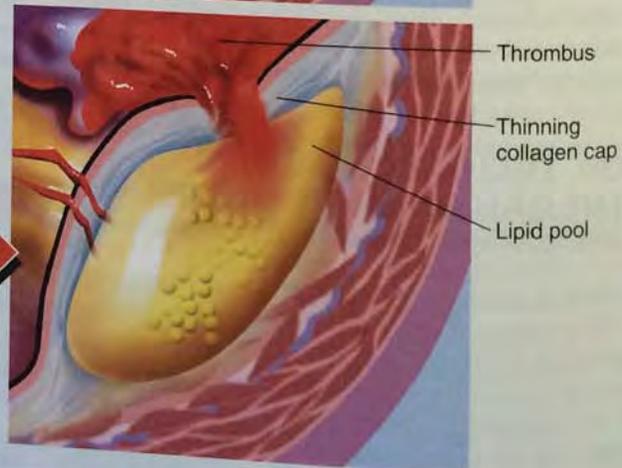


Figure 50-2 ■ Progression of atherosclerosis.

A, Damaged endothelium. **B**, Diagram of fatty streak and lipid core formation. **C**, Diagram of fibrous plaque. Raised plaques are visible: some are yellow and some are white. **D**, Diagram of a complicated lesion, showing a thrombus (in red) and collagen (in blue). (From McCance KL, Huether SE: Pathophysiology: The Biologic Basis for Disease in Adults and Children, 5th ed. St. Louis: Elsevier Mosby, 2006.)

TABLE 50-3 ■ Health Classification of Blood Cholesterol and Triglyceride Levels*

Cholesterol Type	Level (mg/dL)	Classification
LDL cholesterol	<100	Optimal
	100–129	Near/above optimal
	130–159	Borderline high
	160–189	High
	≥190	Very high
Total cholesterol	<200	Desirable
	200–239	Borderline high
	≥240	High
HDL cholesterol	<40	Low
	≥60	High
Triglycerides	<150	Normal
	150–199	Borderline high
	200–499	High
	≥500	Very high

*Cholesterol values are from the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001. Triglyceride values are from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

8 years. Cholesterol classification for children and adolescents is presented in Table 50-4.

If LDL cholesterol is high, what should be done? All patients and their families should receive nutritional counseling. In addition, patients should focus on weight reduction and increased activity, as indicated. Should children use cholesterol-lowering drugs? For two reasons, the answer is “Probably not.” First, these children are in no immediate danger: Their risk of developing clinically significant CHD in the next 20 years is close to zero. And second, we have no data from randomized, controlled trials showing that these drugs will improve outcomes when given to children.

CHD Risk Assessment

Under ATP III, CHD risk assessment is directed at determining the patient’s *absolute risk of developing clinical coronary disease over the next 10 years*. The LDL goal and the mode of intervention are determined by the individual’s degree of risk.

Factors in Risk Assessment

In order to assess the CHD risk for an individual, we need three kinds of information. Specifically, we need to (1) identify CHD risk factors, (2) calculate 10-year CHD risk, and (3) identify CHD risk equivalents.

Identifying CHD Risk Factors. Major risk factors that modify LDL treatment goals are summarized in Table 50-5. The table lists five positive risk factors (advancing age, family history of premature CHD, hypertension, cigarette smoking, and low HDL cholesterol) and one negative risk factor (high HDL cholesterol). (LDL itself is not listed because the reason for counting these risk factors is to modify treatment of high LDL.) For the purpose of CHD risk assessment, each positive factor counts as 1 point; if the patient has high HDL chole-

TABLE 50-4 ■ NCEP Classification of Cholesterol Levels for Children and Adolescents*

Category	Total Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)
Acceptable	<170	<110
Borderline	170–199	110–129
Elevated	≥200	≥130

*HDL levels should be greater than or equal to 35 mg/dL and triglycerides should be less than or equal to 150 mg/dL.

Data from National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 89(3 Pt 2):525–584, 1992.

TABLE 50-5 ■ Major Risk Factors (Other Than High LDL Cholesterol) That Modify LDL Treatment Goals

Positive Risk Factors

- *Age:*
 - Men 45 yr or older
 - Women 55 yr or older
- *Family history of premature CHD in a first-degree relative:*
 - Male first-degree relative less than 55 yr old *or*
 - Female first-degree relative less than 65 yr old
- *Hypertension:*
 - Blood pressure 140/90 mm Hg or higher *or*
 - Taking antihypertensive medication
- *Current cigarette smoking (smoked at least 1 in the last month)*
- *Low HDL cholesterol (below 40 mg/dL)*

Negative Risk Factor

- *High HDL cholesterol (60 mg/dL or higher)**

*High HDL cholesterol (60 mg/dL or higher) is protective, and hence counts as a “negative” risk factor; its presence removes one risk factor from the total count.

From the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001.

sterol (a negative risk factor), 1 point is subtracted. For example, if the subject were a 62-year-old female hypertensive smoker with an HDL level of 62 mg/dL, her point total score would be 2 (3 points for the three positive risk factors minus 1 point for the one negative risk factor).

It should be noted that diabetes carries more weight in risk assessment in ATP III than in ATP II. Why? Because we now know that diabetes is a very strong predictor of developing CHD. Accordingly, we no longer consider diabetes to be a risk factor (as it was in ATP II). Instead, for the purpose of risk assessment, diabetes is now considered a CHD risk *equivalent*. That is, having diabetes is considered equivalent to having CHD as a predictor of a major coronary event.

Box 50-1 discusses one additional factor—*C-reactive protein* (CRP)—that could aid with CHD risk prediction.

Calculating 10-Year CHD Risk. ATP III defines three 10-year risk categories: more than 20%, 10% to 20%, and less than 10%. Some people are automatically in the highest risk group—specifically, those with existing CHD (or other forms

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INFLAMMATION, C-REACTIVE PROTEIN, AND CARDIOVASCULAR RISK

Although we know about several risk factors for CHD—advancing age, obesity, hypertension, diabetes, smoking, high LDL cholesterol, and sedentary lifestyle—it is clear that other risk factors must exist. Why? Because many young, lean, active, normotensive, nondiabetic, nonsmokers with low cholesterol still manage to die from MI. Obviously, additional risk factors must be involved. The leading suspect is inflammation.

There is good evidence that inflammation plays a central role in atherosclerosis. Although inflammation normally protects tissues, it can also do harm. For example, inflammation in the lungs leads to bronchospasm in asthma, and inflammation of joints underlies tissue injury in arthritis. In arteries, inflammation appears to set the stage for atherogenesis. In addition, inflammation may weaken the surface of atherosclerotic plaques, thereby increasing the risk of plaque rupture. Factors that might evoke an inflammatory response include smoking, diabetes, and infection.

The strongest evidence implicating inflammation in CHD comes from measuring plasma levels of *C-reactive protein* (CRP), a compound that is produced when inflammation occurs. Large amounts are produced during major inflammatory disorders (eg, arthritis, infection), causing blood levels of CRP to climb very high. In contrast, relatively small amounts are produced by inflammation in arteries. Nonetheless, these amounts are still big enough to cause a measurable increase in blood levels, albeit much smaller than the increase seen in conditions like arthritis or infection. Please note that CRP itself is harmless: The compound is simply a *biomarker* for ongoing inflammatory processes; it does not cause injury by itself.

In clinical studies, elevation of CRP has been associated with increased CV risk. For example, in the *Physicians' Health Study*, high levels of CRP predicted danger 6 to 8 years in advance: Among people with no prior CV events, high levels of CRP were associated with a threefold increased risk of heart attacks and a twofold increased risk of stroke. In the *Women's Health Study*, similar results were obtained: Over an 8-year period, women with the highest levels of CRP experienced 4.5 times as many heart attacks or strokes as did women with the lowest levels. Furthermore, not only did elevated CRP predict CV risk, it did so for women whose LDL cholesterol was normal—not just those whose LDL cholesterol was high. This is important. Why? Because it means that elevated CRP is an *independent* risk factor for CV events; it's not simply a surrogate for LDL cholesterol. Hence, measuring CRP and LDL cholesterol might identify different risk groups.

Cardiovascular protection conferred by aspirin and statins may result in part from anti-inflammatory actions. It is well known that aspirin suppresses platelet aggregation, and thereby helps protect against MI. However, there is evidence that aspirin is most beneficial in patients with high levels of CRP, suggesting that aspirin's anti-inflammatory actions may also contribute to CV benefits. Likewise, it is well known that statins reduce LDL cholesterol levels, and thereby protect against CHD. However, in patients with *normal* cholesterol levels and high levels of CRP, pravastatin still offers protection. Specifically, the drug can lower CRP levels by 17% and reduce the risk

of recurrent MI—again suggesting that anti-inflammatory actions may partly explain clinical benefits.

Given that elevated CRP may predict CV events, should we screen people to see if their CRP is high? Yes, we should, according to a 2003 statement issued by an expert panel convened jointly by the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC). However, the AHA/CDC panel does not recommend screening for everyone. Rather, screening should be limited to patients deemed at *intermediate* CV risk (ie, having a 10% to 20% risk of developing CHD in the next 10 years) as indicated by their age, LDL cholesterol level, and other traditional risk criteria. The panel does not recommend screening for patients considered at high or low risk. Why? Because the test results are unlikely to reveal information that would alter treatment decisions: With people at high risk, we already have sufficient information to guide treatment; with people at low risk, CRP tests are unlikely to reveal a previously unknown risk that would indicate a need for treatment.

How should CRP be tested? The AHA/CDC panel recommends using a *high-sensitivity CRP* (hsCRP) test, rather than a conventional CRP test, even though both tests measure the same molecule (CRP). Why use the high-sensitivity test? Because it can accurately measure *low levels* of CRP (1 to 10 mg/L)—levels in the range affected by arterial inflammation. The conventional test cannot accurately measure levels this low. Because levels of hsCRP can vary over time, two tests should be done, about 2 weeks apart. The degree of CV risk associated with specific hsCRP levels is as follows:

- Less than 1 mg/L = low risk
- 1 to 3 mg/L = average risk
- More than 3 mg/L = high risk

People in the high-risk group have a twofold greater risk of an adverse CV event compared with people in the low-risk group.

If the hsCRP level indicates high risk, what should be done? Recall that hsCRP testing is recommended only for patients already classified as having intermediate risk, as determined by traditional risk criteria. For these people, a high level of hsCRP would signal a need for more intensive intervention.

It is important to note that hsCRP should not be tested in the presence of trauma, infection, or systemic inflammatory disorders. Why? Because these conditions can raise hsCRP levels substantially, up to 50 mg/L or even higher. Hence, if hsCRP test results were high, we couldn't tell if these conditions or vascular inflammation were the cause.

Does lowering CRP reduce CV risk? Yes! This was shown for the first time in two sister studies: the *Pravastatin or Atorvastatin Evaluation and Infection Therapy* (PROVE-IT) trial and the *Reversing Atherosclerosis with Aggressive Lipid Lowering* (REVERSAL) trial. In both studies, patients with existing CHD were randomized to receive either standard doses of pravastatin [Pravachol] or high doses of atorvastatin [Lipitor]. The results? In PROVE-IT, patients on the high-dose regimen experienced greater reductions in LDL and CRP levels than did patients on the standard regimen, and they also experienced fewer CV

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INFLAMMATION, C-REACTIVE PROTEIN, AND CARDIOVASCULAR RISK—cont'd

events. Furthermore, whether LDL levels were low or high, reducing CRP levels improved outcomes. The REVERSAL trial, which monitored progression of coronary atherosclerosis, produced parallel results. That is, reductions in LDL and CRP were independently associated with slowed progression of atheroma volume. In fact, among patients with the greatest reductions in LDL and CRP, atheroma volume actually declined.

The results of PROVE-IT and REVERSAL were reinforced and extended by a major new trial—*Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin* (JUPITER)—designed to see if statins can reduce CV events in people with elevated CRP, but with *healthy* levels of LDL cholesterol. The study enrolled nearly 18,000 healthy men and women with LDL cholesterol levels below 130 mg/dL, and with CRP levels of 2 mg/L or higher (ie, levels associated with increased cardiovascular risk). Half the participants received rosuvastatin (20 mg/day) and the other half received a daily placebo. JUPITER was supposed to last 4 years, but was stopped after just 1.9 years. Why? Because early results showed “unequivocal evidence” that rosuvastatin reduced cardiovascular morbidity and mortality: Compared with controls, the rosuvastatin group had a 55% relative reduction in nonfatal MI, a 48% reduction in nonfatal stroke, and a 47% reduction in “hard cardiac events,” defined as the combination of MI

(fatal or not), stroke (fatal or not), the need for coronary vessel revascularization (eg, by angioplasty and placement of a stent), and overall death from cardiovascular causes. What was the effect on LDL cholesterol and CRP? Rosuvastatin reduced LDL cholesterol by 50% and CRP by 37%. By comparison, LDL cholesterol and CRP were largely unchanged in the control group. Some experts reviewing these results were underawed. Why? Because, although treatment produced a notable reduction in the *relative* risk, the reduction in *absolute* risk was less impressive. As one authority calculated, we would have to treat 120 patients for nearly 2 years to prevent just one death from cardiovascular causes. Nonetheless, when we consider that millions of patients are at risk, this treatment could easily save tens of thousands of lives.

Taken together, the PROVE-IT, REVERSAL, and JUPITER studies indicate that reducing CRP levels with statins provides protection against CV events independent of the protection ascribable to reducing LDL.

Since we know that reducing CRP is beneficial, how can we do it? Interestingly, the same measures that reduce LDL cholesterol—healthy diet, exercise, weight loss, smoking cessation, and statin therapy—also reduce levels of CRP. Drugs designed specifically to reduce CRP are in development.

of atherosclerotic disease) and those with diabetes. For all other people, 10-year risk must be calculated. The instrument employed most often is the Framingham Risk Prediction Score, which takes five factors into account: age, total cholesterol, HDL cholesterol, smoking status, and systolic blood pressure. These are similar to risk factors noted above. Framingham scores can be determined using either (1) the tables for men and women shown in Figure 50–3 or (2) a web-based risk calculator, such as the one provided by the NCEP at [hp2010.nhlbi.nih.net/atpiii/calculator.asp](http://2010.nhlbi.nih.net/atpiii/calculator.asp).

Identifying CHD Risk Equivalents. A CHD risk equivalent is a condition that poses the same risk of a major coronary event as does established CHD (ie, more than 20% risk of a major event within 10 years). There are three basic CHD risk equivalents:

- Diabetes
- Atherosclerotic disease other than CHD (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)
- The presence of multiple risk factors that confer a Framingham Risk Prediction Score greater than 20%

Identifying an Individual's CHD Risk Category

Under ATP III, there are four categories of CHD risk, labeled I, II, III, and IV (Table 50–6). People in category I are at highest risk: Their risk of a major coronary event within 10 years is over 20%. In comparison, the 10-year risk for people in category IV is low—less than 10%.

Category assignment is based on (1) the presence or absence of CHD (or a CHD risk equivalent, such as diabetes), (2) the number of risk factors the individual has (other than high LDL cholesterol), and (3) the individual's 10-year Fra-

mingham Risk Prediction Score. Although this assessment sounds complicated, it's not. Let's consider the hypothetical case of Ralph J.—and follow along by looking at Figure 50–3. Mr. J. is 62 years old, hypertensive, and smokes—but, remarkably, his HDL cholesterol is high (above 60 mg/dL). He has no family history of premature CHD, does not have CHD himself, and does not have diabetes. His 10-year Framingham Risk Prediction Score is 11%. What CHD risk category does he belong in? Well, his age, blood pressure, and smoking status represent three major risk factors, but his high (healthy) HDL cholesterol allows subtraction of one risk factor, leaving a net of two risk factors. The presence of two major risk factors plus the 11% Framingham score place Mr. J. in CHD risk category II (the next to highest risk group). Pretty easy, huh? And even easier if you use an online computational tool, such as the ones available at www.framinghamheartstudy.org/risk/index.html.

Risk category IV deserves comment. People assigned to this group have either no CHD risk factors or just one, and do not have CHD. As a rule, their 10-year CHD risk is not calculated. Why? Because there's no need: With so few risk factors, their 10-year risk is almost always below 10%.

Final Note: Each Type of Dyslipidemia a Patient Has Contributes Independently to CHD Risk

Patients are likely to have more than one type of dyslipidemia—for example, high LDL cholesterol combined with low HDL cholesterol and high triglycerides—and each of these disorders contributes *independently* to cardiovascular risk. This means that fixing just one of these problems will not eliminate the risk posed by the others. Accordingly, to get maximal risk reduction, we must correct all lipid abnormalities that are present.

Estimate of 10-year risk for MEN

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Estimate of 10-year risk for WOMEN

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mm Hg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Systolic BP (mm Hg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥30

10-Year Risk _____ %

Point Total	10-Year Risk %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	2
16	3
17	4
18	5
19	6
20	8
21	11
22	14
23	17
24	22
25	27
≥25	≥30

10-Year Risk _____ %

Figure 50-3 ■ Tables for calculating Framingham Risk Prediction Scores.

To determine an individual's 10-year risk of developing clinical coronary disease, simply circle the appropriate points for each of the five risk factors considered (age, total cholesterol, smoking status, HDL cholesterol, and systolic blood pressure) and then add up the points. The point total indicates the 10-year risk. For example, a total of 13 points indicates a 10-year risk of 12% for men. (Framingham scores can also be determined using a web-based calculator, such as the one provided by the NCEP at <http://hp2010.nhlbi.nih.net/atpiii/calculator.asp>.)

TABLE 50-6 ■ LDL Cholesterol Goals and Therapeutic Interventions for People in Specific CHD Risk Categories

CHD Risk Category	LDL Goal	LDL Level at Which to Initiate TLCs*	LDL Level at Which to Consider Drug Therapy
I <i>High Risk:</i> Has CHD or a CHD risk equivalent† (10-year risk is >20%)	<100 mg/dL (with an optional goal of <70 mg/dL)‡	Any level	≥100 mg/dL (at <100 mg/dL, LDL-lowering drugs are optional)§
II <i>Moderately High Risk:</i> Has 2 or more risk factors, but not CHD, and 10-year risk is 10–20%	<130 mg/dL (with an optional goal of <100 mg/dL)	Any level	≥130 mg/dL (between 100 and 129 mg/dL, LDL-lowering drugs are optional)§
III <i>Moderate Risk:</i> Has 2 or more risk factors, but not CHD, and 10-year risk is <10%	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
IV <i>Low to Moderate Risk:</i> Has 0–1 risk factor, but not CHD (10-year risk is probably <10%)¶	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (between 160 and 189 mg/dL, LDL-lowering drugs are optional)

*TLCs = therapeutic lifestyle changes.

†CHD risk equivalents include diabetes, forms of atherosclerosis other than CHD (eg, peripheral arterial disease, symptomatic coronary artery disease), and any combination of risk factors that creates a 10-year Framingham Risk Prediction Score of greater than 20%.

‡For patients at very high risk (eg, those with a recent heart attack or those with CV disease combined with diabetes), the LDL goal may be set at less than 70 mg/dL, rather than 100 mg/dL.

§When LDL-lowering drugs are used in patients at high risk or moderately high risk, treatment should be sufficient to decrease the LDL level by 30% to 40%.

¶Almost all people with 0 to 1 risk factor and no CHD have a 10-year risk below 10%, and hence formal evaluation of 10-year risk is not needed.

Modified from the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001; as updated in Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 110:227–239, 2004.

Treatment of High LDL Cholesterol

Treatment of high LDL cholesterol is based on the individual's CHD risk category: The greater the 10-year risk, the more aggressive the treatment. As CHD risk increases, the target LDL goal gets lower, as does the LDL level at which treatment should commence. For example, among individuals in risk category I, the LDL goal is quite low (below 100 mg/dL—or below 70 in people at highest risk), compared with the higher goal (below 160 mg/dL) for people in category IV. Similarly, for individuals in category I, drugs are recommended if the LDL level is 100 mg/dL or above, compared with a much higher value (190 mg/dL or above) for those in category IV. Table 50-6 summarizes the LDL goal and the LDL levels at which to initiate treatment for people in all four CHD risk categories.

To reduce LDL levels, ATP III recommends two forms of intervention: (1) therapeutic lifestyle changes (TLCs) and (2) drug therapy. For some people, cholesterol can be reduced adequately with TLCs alone. Others require TLCs *plus* cholesterol-lowering drugs. Please note: Drugs should be used only as an *adjunct* to TLCs—not as a *substitute*.

Therapeutic Lifestyle Changes

Therapeutic lifestyle changes are nondrug measures used to lower LDL cholesterol. TLCs focus on four main issues: diet, exercise, weight control, and smoking cessation. These measures are first-line treatment for LDL reduction, and should be implemented before trying drugs. Unfortunately, TLCs can be a challenge simply because some people just won't eat healthier diets, nor will they exercise. Furthermore, arthritis and other physical conditions can limit attempts at exercise.

The TLC Diet. This diet has two objectives: (1) reducing LDL cholesterol and (2) establishing and maintaining a healthy weight. The central feature of the diet is reduced intake of cholesterol and saturated fats: Individuals should limit intake of cholesterol to 200 mg/day or less and intake of saturated fat to 7% or less of total calories. Intake of *trans fats*—found primarily in crackers, commercial baked goods, and French fries—should be minimized. (Many food manufacturers are adding “no trans fat” labels to their product labels, making shopping somewhat easier.) ATP III recommendations for cholesterol, fats, and other nutrients are summarized in Table 50-7. A list of specific foods to choose, eat in moderation, or avoid, appears in Table 50-8.

If the basic TLC diet fails to lower LDL cholesterol adequately, ATP III recommends two additional measures: increased intake of soluble fiber (10 to 25 gm/day; oatmeal is a good source) and increased intake of plant stanols and sterols (2 gm/day). Plant stanols and sterols are cholesterol-lowering chemicals found (albeit in very small amounts) in certain vegetable oils (eg, canola), nuts (walnuts are a good source), certain fruits, and most beans and many other vegetables. They are also found in some of the cholesterol-lowering margarines, commonly advertised as “buttery spreads” (see below under *Plant Stanol and Sterol Esters*).

Weight Control. Being overweight or obese is a major risk factor for CHD. Conversely, weight loss can reduce both LDL cholesterol and CHD risk. Weight loss is especially important for people with metabolic syndrome (see below). In ATP III, achieving a healthy weight is encouraged for all people.

TABLE 50-7 • Nutrient Composition of the TLC Diet Described in ATP III

Nutrient	Recommended Intake
Cholesterol	Less than 200 mg/day
Saturated fat*	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25%–35% of total calories
Carbohydrates†	50%–60% of total calories
Protein	About 15% of total calories
Fiber	20–30 gm/day
Total calories	Balance energy intake and expenditure‡ to maintain a desirable body weight or prevent weight gain

TLC = therapeutic lifestyle changes.

**Trans*-fatty acids should be kept to a minimum.

†Carbohydrates should be derived mainly from foods rich in complex carbohydrates, such as fruits, vegetables, and grains (especially whole grains).

‡Daily energy expenditure should include at least moderate physical activity (contributing about 200 kcal/day).

From the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001.

Exercise. A sedentary lifestyle carries an increased risk of CHD. Conversely, performing regular exercise lowers CHD risk. Running and swimming, for example, can decrease LDL cholesterol and elevate HDL cholesterol, thereby reducing risk. In addition, exercise can reduce blood pressure, improve overall CV performance, and decrease insulin resistance (important because many people with high cholesterol also have diabetes). Accordingly, ATP III encourages regular physical activity (defined as 30 to 60 minutes of activity on most days). Improvements in the plasma lipid profile depend more on the total time spent exercising than on the intensity of exercise or improvements in fitness.

Smoking Cessation. Smoking cigarettes raises LDL cholesterol and lowers HDL cholesterol, thereby increasing the risk of CHD. Smokers should be strongly encouraged to quit—and nonsmokers should be urged not to start. Drugs to aid smoking cessation are discussed in Chapter 39.

Drug Therapy

Drugs are not the first-line therapy for lowering LDL cholesterol. Rather, drugs should be employed only if TLCs fail to reduce LDL cholesterol to an acceptable level—and then only if the combination of elevated LDL cholesterol and the patient's CHD risk category justify drug use (see Table 50-6). When drugs are used, it is essential that lifestyle modification continues. Why? Because the beneficial effects of diet and drugs are additive; drugs alone may be unable to achieve the LDL goal. (Unfortunately, many people would rather rely on drugs alone, rather than continuing with TLCs.) It is important to note that the principal benefit of drug therapy is *primary prevention*: Drugs are much better at preventing or retarding CHD than at promoting regression of established

coronary atherosclerosis. Furthermore, because LDL cholesterol levels will return to pretreatment values if drugs are withdrawn, *treatment must continue lifelong*. Patients should be made aware of this requirement.

Table 50-9 summarizes properties of the drug families used to lower LDL cholesterol. The most effective agents are the *HMG-CoA reductase inhibitors* (eg, atorvastatin [Lipitor]), usually referred to simply as *statins*. Lesser used alternatives are *bile-acid sequestrants* (eg, cholestyramine) and *niacin* (nicotinic acid). Although *fibrates* are listed in Table 50-9, these drugs are used primarily to reduce levels of TGs—not LDLs. Treatment is initiated with a single drug, almost always a statin. If the statin is ineffective, a bile-acid sequestrant or niacin can be added to the regimen.

In addition to lowering LDL cholesterol, drugs may be used to raise HDL cholesterol. The most effective agents are niacin and the fibrates. However, as indicated in Table 50-9, virtually all of the drugs that we use to lower LDL cholesterol have the added benefit of increasing HDL cholesterol, at least to some degree. This rise of HDL, therefore, can be considered a beneficial “side effect.”

Secondary Treatment Targets

Metabolic Syndrome

The term *metabolic syndrome* (also known as *syndrome X*) refers to a group of metabolic abnormalities associated with an increased risk of CHD and type 2 diabetes. The metabolic abnormalities involved are high blood glucose, high triglycerides, high apolipoprotein B, low HDL, small LDL particles, a prothrombotic state, and a proinflammatory state. Hypertension is both common and important.

How is metabolic syndrome diagnosed? According to a joint scientific statement—issued in 2009 by the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity—the metabolic syndrome is diagnosed when three or more of the following are present:

- **Abdominal obesity**—waist circumference 40 inches or more for most men or 35 inches or more for most women (these limits can vary depending on ethnicity, country, or geographic region within a country)
- **High TG levels**—150 mg/dL or higher (or undergoing drug therapy for high TGs)
- **Low HDL cholesterol**—below 40 mg/dL for men or below 50 mg/dL for women (or undergoing drug therapy for reduced HDL)
- **Hyperglycemia**—fasting blood glucose 100 mg/dL or higher (or undergoing drug therapy for hyperglycemia/diabetes mellitus)
- **High blood pressure**—systolic 130 mm Hg or higher and/or diastolic 85 mm Hg or higher (or undergoing drug therapy for hypertension)

Treatment has two primary goals: reducing the risk of atherosclerotic disease and reducing the risk of type 2 diabetes. According to ATP III, basic therapy consists of weight reduction and increased physical activity, which, together, can reduce all symptoms of the metabolic syndrome. In addition, specific treatment should be directed at lowering blood pres-

TABLE 50-8 ■ Recommended Dietary Modifications to Lower Serum Cholesterol

Food Type	Recommendation	
	Choose	Decrease
Fish, chicken, turkey, and lean meats	Fish; poultry without skin; lean cuts of beef, lamb, pork, or veal; shellfish	Fatty cuts of beef, lamb, or pork; spareribs; organ meats; regular cold cuts; sausage; hot dogs
Milk, cheese, yogurt, and other dairy products	Skim and 1% fat milk (liquid, powdered, evaporated), buttermilk Nonfat (%) or low-fat yogurt Low-fat cottage cheese (1% or 2% fat) Low-fat cheeses, farmer or pot cheeses (all of these cheeses should have no more than 2-6 gm of fat per ounce)	4% fat milk (regular, evaporated, condensed), 2% fat milk, cream, half-and-half, imitation milk products, most nondairy creamers, whipped toppings Whole-milk yogurt Whole-milk cottage cheese (4%) All natural cheeses (eg, blue, Roquefort, Camembert, cheddar, Swiss) Cream cheese (including low-fat and "light" types), sour cream (including low-fat and "light" types)
Eggs	Sherbet, sorbet Egg whites (2 whites = 1 whole egg in recipes), cholesterol-free egg substitutes	Ice cream Egg yolks*
Fruits and vegetables	Fresh, frozen, canned, and dried fruits and vegetables	Vegetables prepared in butter, cream, and other sauces
Breads and cereals	Homemade baked goods using unsaturated oils sparingly, angel food cake, low-fat crackers, low-fat cookies Rice, pasta Whole-grain breads and cereals (oatmeal, whole wheat, rye, bran, multigrain, etc.)	Commercial baked goods: pies, cakes, muffins, doughnuts, croissants, biscuits, high-fat crackers, high-fat cookies Egg noodles Breads in which eggs are a major ingredient
Fats and oils	Unsaturated vegetable oils: corn, olive, canola (rapeseed), safflower, sesame, soybean, sunflower oils Margarine (regular or diet), [†] shortening made from one of the unsaturated oils listed above Mayonnaise, salad dressings made with one of the unsaturated oils listed above; low-fat or (preferred) fat-free dressings Seeds and nuts (especially walnuts) Baking cocoa	Butter, the so-called "tropical oils" (coconut oil, palm oil, palm kernel oil), lard, bacon fat Dressings made with egg yolk Coconut Chocolate

*Author's note: Consuming up to 1 egg/day is not associated with an increased risk of fatal or nonfatal MI or ischemic or hemorrhagic stroke, except possibly in people with diabetes.

†Author's note: Since the publication of this table in 1988, new evidence indicates that *stick* margarine (but probably not newer low-fat spreads), which contains 17% trans fat, raises LDL cholesterol and lowers HDL cholesterol, and hence should not be recommended.

From the National Cholesterol Education Program Adult Treatment Panel report. Arch Intern Med 148:36, 1988.

sure and TG levels. Patients should take low-dose aspirin to reduce the risk of thrombosis, unless they are at high risk of intracranial bleeds (hemorrhagic stroke).

Although the term *metabolic syndrome* is widely used, there is debate about its clinical relevance. In the cardiovascular community, most clinicians believe the term has great utility. By contrast, in the diabetes community, many clinicians feel the term is misleading, in that it implies the existence of a specific disease entity, even though it is defined only by a cluster of risk factors that may or may not have a common underlying cause. Furthermore, they point out that the risk associated with a diagnosis of metabolic syndrome is no greater than the sum of the risks of its components. Accordingly, until there is more proof that the metabolic

syndrome actually exists, they believe the term serves no clinical purpose and hence should be avoided. This position was voiced in a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. The American Heart Association and the National Heart, Lung, and Blood Institute countered with a joint statement of their own, reasserting their belief that the metabolic syndrome is an important clinical entity. Although the two camps disagree about whether the metabolic syndrome is an actual disease, both sides strongly agree that the risk factors that define the syndrome should be identified and treated.

One final point: Whether or not you think *metabolic syndrome* is a useful term, you will still see lots of patients who

TABLE 50-9 ■ Drugs Used to Improve Plasma Levels of LDL, HDL, and Triglycerides

Drug Class	Effect on LDL, HDL, and TGs	Common or Serious Adverse Effects	Contraindications	Clinical Trial Results
HMG-CoA reductase inhibitors (statins)	LDL ↓ 21%–63% HDL ↑ 5%–22% TG ↓ 6%–43%	<ul style="list-style-type: none"> • Myopathy • Hepatotoxicity 	<p><i>Absolute:</i></p> <ul style="list-style-type: none"> • Active or chronic liver disease • Pregnancy <p><i>Relative:</i></p> <ul style="list-style-type: none"> • Concurrent use of certain drugs* 	Reduced major coronary events, stroke, CHD deaths, need for coronary procedures, and total mortality
Bile-acid sequestrants	LDL ↓ 15%–30% HDL ↑ 3%–5% TG ↓/no change	<ul style="list-style-type: none"> • GI distress • Constipation • Reduced drug absorption 	<p><i>Absolute:</i></p> <ul style="list-style-type: none"> • Dysbetalipoproteinemia • TG above 400 mg/dL <p><i>Relative:</i></p> <ul style="list-style-type: none"> • TG above 200 mg/dL 	Reduced major coronary events and CHD deaths
Niacin (nicotinic acid)	LDL ↓ 14%–17% HDL ↑ 22%–26% TG ↓ 28%–35%	<ul style="list-style-type: none"> • Flushing • Hyperglycemia • Hyperuricemia • Upper GI distress • Hepatotoxicity 	<p><i>Absolute:</i></p> <ul style="list-style-type: none"> • Chronic liver disease • Gout <p><i>Relative:</i></p> <ul style="list-style-type: none"> • Diabetes • Hyperuricemia • Peptic ulcer disease 	Reduced major coronary events and, possibly, reduced mortality
Fibrates	LDL ↓ 6%–10%, but may increase if TGs are high HDL ↑ 10%–20% TG ↓ 20%–50%	<ul style="list-style-type: none"> • Dyspepsia • Gallstones • Myopathy 	<p><i>Absolute:</i></p> <ul style="list-style-type: none"> • Severe renal disease • Severe liver disease 	Reduced major coronary events
Ezetimibe	LDL ↓ 19% HDL ↑ 1%–4% TG ↓ 5%–10%	<ul style="list-style-type: none"> • Headache • Myalgia, arthralgia, possible myopathy • Abdominal pain, diarrhea 	<p><i>Absolute:</i></p> <ul style="list-style-type: none"> • Moderate to severe liver injury, especially in patients taking a statin 	Impact on coronary events and mortality has not been established

↑ = increase, ↓ = decrease.

*Use caution in patients taking niacin, fibrates, and agents that inhibit CYP3A4 (the 3A4 isozyme of P450), including cyclosporine, macrolide antibiotics (eg, erythromycin), azole antifungal drugs (eg, ketoconazole), and HIV protease inhibitors (eg, ritonavir).

Modified from the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001. Data on ezetimibe are from other sources.

meet the criteria. Fact is, patients with several of these risk factors are much more common than patients with just one.

High Triglycerides

High TG levels (above 200 mg/dL) may be an independent risk factor for CHD. In clinical practice, high TGs are seen most often in patients with metabolic syndrome. However, high levels may also be associated with obesity, sedentary lifestyle, cigarette smoking, excessive alcohol intake, type 2 diabetes, certain genetic disorders, and high carbohydrate intake (when carbohydrates account for more than 60% of total caloric intake). In most patients with high TG levels, the first treatment goal is to achieve the original LDL goal. Dietary modification is always recommended. Statins being taken to lower cholesterol may help lower TGs as well, perhaps to a satisfactory level. However, if triglyceride levels remain unacceptably high, medications specific to TGs—niacin and fibrates—may be needed. Unfortunately, when these drugs are combined with cholesterol-lowering drugs (as they often are), the adverse effects of cholesterol-lowering agents may be intensified.

DRUGS AND OTHER PRODUCTS USED TO IMPROVE PLASMA LIPID LEVELS

As discussed above, the lipid abnormality that contributes most to cardiovascular disease is high LDL cholesterol. Accordingly, we will focus primarily on drugs for this disorder. Nonetheless, we also need to consider other lipid abnormalities, especially (1) high total cholesterol,* (2) low HDL cholesterol, and (3) high TGs.

Some drugs for dyslipidemias are more selective than others. That is, whereas some drugs may improve just one dyslipidemia (eg, high TGs), others may improve two or more dyslipidemias. The highly selective agents can be useful as add-ons, to “target” a particular lipid abnormality when other medications prove inadequate.

Drugs that lower *LDL cholesterol* levels include HMG-CoA reductase inhibitors (statins), bile-acid sequestrants, ni-

*Note that total cholesterol is slightly different from the simple sum of LDL cholesterol (LDL-C) plus HDL cholesterol (HDL-C), triglycerides (TG) also contribute to the value, as in the following equation: total cholesterol = HDL-C + LDL-C + (TG/5) (provided TG levels are below 400 mg/dL.)

TABLE 50-10 ■ HMG-CoA Reductase Inhibitors: Selected Aspects of Clinical Pharmacology

Drug	% Change in Serum Lipids*			Liver Function Test (LFT) Monitoring†	Effect of CYP3A4 Inhibitors on Statin Levels‡	Effect of Renal or Hepatic Impairment on Statin Levels
	LDL-C	HDL-C	TGs			
Atorvastatin [Lipitor]	↓ 25-60	↑ 5-15	↓ 15-50	At 12 wk and then every 6 months	Moderate ↑	No change with renal disease; significant ↑ with hepatic impairment
Fluvastatin [Lescol, Lescol XL]	↓ 20-40	↑ 2-11	↓ 10-25	At 12 wk and then every 6 months	None	No change with renal disease; possible ↑ with hepatic impairment
Lovastatin [Altoprev, Mevacor]	↓ 20-40	↑ 5-10	↓ 5-25	At 6 and 12 wk and then every 6 months	Significant ↑	↑ with significant renal impairment; no change with hepatic impairment
Pitavastatin [Livalo]	↓ 40-45	↑ 6-8	↓ 15-30	At 12 wk and then every 12 months	Little or none	↑ with significant renal impairment; little or no change with hepatic impairment
Pravastatin [Pravachol]	↓ 20-40	↑ 1-15	↓ 10-25	At 12 wk and then every 6 months	None	Potential ↑ with either renal or hepatic impairment
Rosuvastatin [Crestor]	↓ 30-60	↑ 3-20	↓ 10-40	At 12 wk and then every 6 months	None	↑ levels with severe renal impairment or hepatic dysfunction
Simvastatin [Zocor]	↓ 25-50	↑ 7-15	↓ 8-40	At 6 and 12 months (and also at 3 months if 80 mg/day is used)	Significant ↑	Potential ↑ with severe renal or hepatic impairment

↑ = increase, ↓ = decrease.

*LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TGs = triglycerides. The values were obtained from a variety of studies, and do not reflect dose dependency of drug responses.

†LFTs should be performed at baseline and at the indicated times after the first dose and after any change in dosage.

‡Inhibitors of CYP3A4 (the 3A4 isozyme of P450) include itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, cyclosporine, nefazodone, and substances in grapefruit juice.

cin, and ezetimibe. All are effective to varying degrees. The HMG-CoA reductase inhibitors—the statins—are more effective than the others, cause fewer adverse effects, are better tolerated, and are more likely to improve clinical outcomes.

As we consider the drugs for lipid disorders, you should be aware of the following: Although all of these drugs can improve lipid profiles, not all of them improve clinical outcomes (reduced morbidity and mortality). This leads us to question whether some of the lipid abnormalities are a true cause of pathophysiology and ultimate death, or whether they are simply “associated markers” of some other pathophysiology that we don’t yet understand.

HMG-CoA Reductase Inhibitors (Statins)

HMG-CoA reductase inhibitors, commonly called *statins* (because their generic names all end in *statin*), are the most effective drugs for lowering LDL and total cholesterol. In addition, they can raise HDL cholesterol and lower TGs in some patients. Most important, these drugs have been shown to improve clinical outcomes, including lowering the risk of heart failure, MI, and sudden death. Because of these benefits, and because so many people have CHD risks associated with dyslipidemias, statins are among our most widely prescribed drugs—and have earned tens of billions for their makers.

Beneficial Actions

The statins have several actions that can benefit patients with (or at risk of) atherosclerosis. The most obvious and important are reductions of LDL cholesterol.

Reduction of LDL Cholesterol. Statins have a profound effect on LDL cholesterol. Low doses decrease LDL cholesterol by about 25%, and larger doses decrease levels by as much as 63% (Table 50-10). Reductions are significant within 2 weeks and maximal within 4 to 6 weeks. Because cholesterol synthesis normally increases during the night, statins are most effective when given in the evening. If statin therapy is stopped, serum cholesterol will return to pretreatment levels within weeks to months. Hence, treatment should continue lifelong, unless serious adverse effects or specific contraindications (especially pregnancy or muscle damage) arise. The mechanism by which statins reduce cholesterol levels is discussed below.

Elevation of HDL Cholesterol. Statins can increase levels of HDL cholesterol. Recall that low levels of HDL cholesterol (below 40 mg/dL) are an independent risk factor for CHD. Hence, by raising HDL cholesterol, statins may help reduce the risk of CV events in yet another way. The objective is to raise levels to 50 mg/dL or more.

Reduction of Triglyceride Levels. Although statins mainly affect cholesterol synthesis, and thereby lower LDL cholesterol levels, these drugs may also lower TGs. Just why these “anti-cholesterol” drugs lower TGs is unknown, but the

response has been amply documented. Please note that, although statins may reduce TG levels, they are not actually prescribed for this action. Hence TG reduction is usually a beneficial side effect in patients taking statins to lower their LDL cholesterol. Of note, the ability to lower TGs seems to be short lived, and hence a drug designed to lower TGs (eg, niacin) eventually may need to be added.

Nonlipid Beneficial Cardiovascular Actions. There is increasing evidence that statins do more than just alter lipid levels. Specifically, they can promote atherosclerotic plaque stability (by decreasing plaque cholesterol content), reduce inflammation at the plaque site, slow progression of coronary artery calcification, improve abnormal endothelial function, enhance the ability of blood vessels to dilate, reduce the risk of atrial fibrillation, and reduce the risk of thrombosis by (1) inhibiting platelet deposition and aggregation and (2) suppressing production of thrombin, a key factor in clot formation. All of these actions help reduce the risk of CV events.

Increased Bone Formation. There is evidence that statins can promote bone formation, and may thereby reduce the risk of osteoporosis and related fractures. This has been shown in several case-control studies in humans. However, other case-control studies have failed to demonstrate a protective effect. The reason for this discrepancy could lie with the inherent weaknesses of case-control studies. Hence, the issue is likely to remain unresolved until data from randomized controlled trials are available. In the meantime, osteoporosis should be managed with bisphosphonates and/or other drugs with proven efficacy (see Chapter 75, Drugs Affecting Calcium Levels and Bone Mineralization).

Mechanism of Cholesterol Reduction

The mechanism by which statins decrease LDL cholesterol levels is complex, and depends ultimately on *increasing the number of LDL receptors on hepatocytes* (liver cells). The process begins with inhibition of hepatic HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. In response to decreased cholesterol production, hepatocytes synthesize more HMG-CoA reductase. As a result, cholesterol synthesis is largely restored to pretreatment levels. However—and for reasons that are not fully understood—inhibition of cholesterol synthesis causes hepatocytes to synthesize more LDL receptors. As a result, hepatocytes are better able to remove more LDLs from the blood. In patients who are genetically unable to synthesize LDL receptors, statins fail to reduce LDL levels, indicating that (1) inhibition of cholesterol synthesis, by itself, is not sufficient to explain cholesterol-lowering effects; and (2) in order for statins to be effective, synthesis of LDL receptors must increase.

In addition to inhibiting HMG-CoA reductase, statins decrease production of apolipoprotein B-100. As a result, hepatocytes decrease production of VLDLs. This lowers VLDL levels, and triglyceride levels too, since they're the main lipid in VLDLs. Also, statins also raise HDL levels by 5% to 22%.

Clinical Trials

Statins slow progression of CHD and decrease the risk of stroke, hospitalization, cardiac events, peripheral vascular disease, and death. Benefits are seen in men and women, and in apparently healthy people as well as those with a history of CV events. Hence, the statins are useful for both primary and secondary prevention. Furthermore, these drugs can even help people with *normal* LDL levels, in addition to those whose LDL is high. Statins may also have some added protective effects in people with diabetes.

Secondary Prevention Studies. In patients with evidence of existing CHD (angina pectoris or previous MI), statins reduce the risk of death from cardiac causes. This was first demonstrated conclusively in the landmark *Scandinavian Simvastatin Survival Study* (4S). After 4.9 to 6.3 years of follow-up, the death rate was 12% among patients taking placebo and 8% among those taking simvastatin—a 30% decrease in overall mortality. Benefits were due to a decrease in cardiac-related mortality; deaths from noncardiac causes were the same in both groups.

The *Cholesterol and Recurrent Events* (CARE) trial demonstrated the ability of statins to reduce the risk of stroke in addition to coronary events. In this study, 4159 people with a history of MI were given pravastatin (40 mg daily) or placebo. After 5 years, the incidence of MI (fatal or nonfatal) was 13.2% in those taking placebo and 10.2% in those taking the drug. Pravastatin also produced a 26% decrease in the risk of stroke.

The *Pravastatin or Atorvastatin Evaluation and Infection Therapy* (PROVE-IT) trial was the first to show that *intensive* reductions in LDL with statin therapy provide more CV protection than moderate reductions. In PROVE-IT, 4162 patients with acute coronary syndromes were randomized to either a moderate statin regimen (pravastatin, 40 mg daily) or an intensive statin regimen (atorvastatin, 80 mg daily). The result? LDL levels in the moderate group dropped to 62 mg/dL, compared with 95 mg/dL in the intensive group. Furthermore, not only did intensive therapy produce a greater decrease in LDL cholesterol, it produced a greater reduction in adverse outcomes: After 24 months, the incidence of CV events (death, MI, unstable angina, or revascularization) was only 22.4% in the intensive group compared with 26.3% in the moderate group. These results led the ATP III panel to recommend lower target LDL levels in patients at very high CV risk.

Primary Prevention Studies. Two major studies have demonstrated the ability of statins to reduce mortality in people with no previous history of coronary events. In the first trial—the *West of Scotland Coronary Prevention Study* (WOSCOPS)—6595 men with high cholesterol were given either pravastatin (40 mg/day) or placebo. During an average follow-up of 4.9 years, 4.1% of those taking placebo died, compared with only 3.2% of those taking the statin. The second trial—the *Air Force/Texas Coronary Atherosclerosis Prevention Study* (AFCAPS/TexCAPS)—enrolled 6605 low-risk patients: men and women with average cholesterol levels (221 mg/dL) and no history of CV events. The subjects were randomly assigned to receive lovastatin (20 to 40 mg/day) or placebo. After an average follow-up of 5.5 years, the incidence of first major coronary events was 5.5% for those taking placebo and 3.5% for those taking the drug—representing a 36% decrease in risk.

Primary Prevention in Patients with Normal Cholesterol Levels. The landmark *Heart Protection Study*, published in 2002, was the first major trial to demonstrate that statins can reduce the risk of major coronary events in people who have normal levels of cholesterol. This double-blind, placebo-controlled trial enrolled 20,536 high-risk British patients: men and women with diabetes, prior MI, stroke, or prior angioplasty. Some had high levels of LDL and total cholesterol; others had normal levels. Subjects were randomly assigned to receive either simvastatin (40 mg/day) or placebo. After 5 years, the incidence of death was 12.9% in the treatment group, compared with 14.7% in the placebo group. Death from CHD was reduced by 18%. In addition, simvastatin reduced the risk of nonfatal MI by 38% and of stroke by 25%, and reduced the need for coronary revascularization (eg, angioplasty) by 30%. Most strikingly, benefits were seen in patients whose LDL cholesterol was *normal or low*, as well as in those whose levels were high. These data suggest a radical shift in practice. Specifically, they suggest *we should treat people at high CHD risk—not simply those with high cholesterol levels*. Obviously, doing so would greatly expand the number of patients receiving statin therapy.

A more recent trial—*Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin* (JUPITER)—reinforced the results of the Heart Protection Study. The new study, discussed in Box 50-1, demonstrated that rosuvastatin can reduce the risk of coronary events in people with normal LDL levels, but with high levels of C-reactive protein and other risk factors for CHD.

Prevention in Patients with Diabetes. Results of the *Collaborative Atorvastatin Diabetes Study* (CARDS) indicate that statin therapy can reduce the risk of CV events in diabetes patients, even if LDL levels are normal. This randomized trial, conducted in Britain and Ireland, enrolled 2838 patients with type 2 diabetes who had no history of CV disease. Half received 10 mg of atorvastatin [Lipitor] daily and half received a placebo. After a mean of 4 years, the combined incidence of acute coronary events, coronary revascularization, and stroke was only 5.8% in the atorvastatin group, compared with 9% in the placebo group, representing a 36% reduction in risk. These results suggest that statin therapy could benefit most patients with diabetes, regardless of their LDL level.

TABLE 50-11 ■ HMG-CoA Reductase Inhibitors: FDA-Approved Indications

Indication	Atorvastatin [Lipitor]	Fluvastatin [Lescol, Lescol XL]	Lovastatin [Altoprev, Mevacor]	Pitavastatin [Livalo]	Pravastatin [Pravachol]	Rosuvastatin [Crestor]	Simvastatin [Zocor]
Primary hypercholesterolemia	✓	✓	✓	✓	✓	✓	✓
Homozygous familial hyperlipidemia	✓					✓	✓
Heterozygous familial hypercholesterolemia in adolescents	✓	✓	✓		✓		✓
Mixed dyslipidemia	✓	✓	✓	✓	✓	✓	✓
Primary dysbetalipoproteinemia	✓				✓	✓	✓
Hypertriglyceridemia*	✓				✓	✓	✓
Primary prevention of coronary events	✓		✓		✓	✓	✓
Secondary prevention of cardiovascular events	✓	✓	✓		✓		✓
Increasing HDL cholesterol in primary hypercholesterolemia	✓	✓	✓		✓	✓	✓
Prevention of MI and stroke in type 2 diabetes	✓						
Slowing progression of coronary atherosclerosis		✓				✓	

*Statins are not indicated in patients who have hypertriglyceridemia but also have low or normal LDL-C, even if total cholesterol levels are elevated. Rosuvastatin is approved for primary prevention in patients who have *normal* LDL cholesterol and no clinical evidence of CHD, but who do have high levels of C-reactive protein combined with other risk factors for CV disease.

Therapeutic Uses

When the statins were introduced, they were approved only for hypercholesterolemia (elevated LDL cholesterol levels) in adults. As understanding of their benefits grew, so has the list of indications. Today the statins have nearly a dozen Food and Drug Administration (FDA)-approved indications, and can be prescribed for young patients as well as adults. Indications for individual statins are summarized in Table 50-11. Major indications are discussed below.

Hypercholesterolemia. Statins are the most effective drugs we have for lowering LDL cholesterol. In sufficient dosage, statins can decrease LDL cholesterol by more than 60%. For many patients, the treatment goal is to drop LDL cholesterol to below 100 mg/dL. For patients at very high CV risk, a target of 70 mg/dL may be appropriate.

Primary and Secondary Prevention of CV Events. As discussed, statins can reduce the risk of CV events (eg, MI, angina, stroke) in patients who have never had one (primary prevention) and they can reduce the risk of a subsequent event after one has occurred (secondary prevention). Risk reduction is related to the reduction in LDL: the greater the LDL reduction, the greater the reduction in risk.

Primary Prevention in People with Normal LDL Levels. One agent—*rosuvastatin* [Crestor]—is now approved for reducing the risk of CV events in people with *normal* levels of LDL and no clinically evident CHD, but who do have an increased risk based on advancing age, high levels of *high-sensitivity C-reactive protein* (see Box 50-1), and at least one other risk factor for CV disease (eg, hypertension, low HDL, smoking). Approval for this use was based in large part on results of the JUPITER trial, discussed in Box 50-1.

Post-MI Therapy. Patients who have survived an MI, and who were not on statin therapy at the time of the event, are routinely started on a statin, the rationale being “better late than never.” How soon should statin therapy start? The current trend is to begin statins as soon as the patient is stabilized and able to take oral drugs. Other drugs for MI are discussed in Chapter 53.

Diabetes. Cardiovascular disease is the primary cause of death in people with diabetes. Hence, to reduce mortality, controlling CV risk factors—especially hypertension and high cholesterol—is as important as controlling high blood glucose. The American Diabetes Association recommends a statin for all patients over the age of 40 whose *total* cholesterol is 135 mg/dL or higher—regardless of LDL cholesterol level. The American College of Physicians recommends a statin for (1) all patients with type 2 diabetes plus diagnosed CHD—even if they don't have *high cholesterol*; and (2) all adults with type 2 diabetes plus one additional risk factor (eg, hypertension, smoking, age over 55)—even if they don't have *high cholesterol*. Taken together, these guidelines suggest that most patients with diabetes should receive a statin.

Potential Uses. Potential uses of statins extend well beyond diabetes and cardiovascular disorders. Judging from preliminary evidence, these drugs may eventually be used to prevent and/or treat a variety of conditions, including Parkinson's disease, Alzheimer's disease, kidney disease, multiple sclerosis, macular degeneration, glaucoma, rheumatoid arthritis, weak or brittle bones, and even certain cancers.

Pharmacokinetics

Statins are administered orally. The amount absorbed ranges between 30% and 90%, depending on the drug. Regardless of

how much is absorbed, most of an absorbed dose is extracted from the blood on its first pass through the liver, the principal site at which statins act. Only a small fraction of each dose reaches the systemic circulation. Statins undergo rapid hepatic metabolism followed by excretion primarily in the bile. Only four agents—*lovastatin*, *pitavastatin*, *pravastatin*, and *simvastatin*—undergo clinically significant (10% to 20%) excretion in the urine.

Three statins—*atorvastatin*, *lovastatin*, and *simvastatin*—are metabolized by CYP3A4 (the 3A4 isozyme of cytochrome P450). As a result, levels of these drugs can be lowered by agents that induce CYP3A4 synthesis and speed up the metabolic inactivation of the statin. More importantly, statin levels can be increased—sometimes dramatically—by agents that inhibit CYP3A4 (see below).

One agent—*rosuvastatin*—reaches abnormally high levels in people of Asian heritage. At usual therapeutic doses, *rosuvastatin* levels in these people are about twice those in whites. Accordingly, if *rosuvastatin* is used by Asians, dosage should be reduced.

Adverse Effects

Statins are generally well tolerated. Side effects are uncommon. Some patients develop headache, rash, or GI disturbances (dyspepsia, cramps, flatulence, constipation, abdominal pain). However, these effects are usually mild and transient. Serious adverse effects—*hepatotoxicity* and *myopathy*—are relatively rare. Some statins pose a greater risk than others, as noted below.

Myopathy/Rhabdomyolysis. Statins can injure muscle tissue. *Mild injury* occurs in 5% to 10% of patients. Characteristic symptoms are muscle aches, tenderness, or weakness that may be localized to certain muscle groups or diffuse. Rarely, mild injury progresses to *myositis*, defined as muscle inflammation associated with moderate elevation of creatine kinase (CK), an enzyme released from injured muscle. Release of potassium from muscle may cause blood potassium concentrations to rise. Rarely, *myositis* progresses to potentially fatal *rhabdomyolysis*, defined as muscle disintegration or dissolution. Release of muscle components leads to marked elevations of blood CK (greater than 10 times the upper limit of normal [ULN]) and elevations of free myoglobin. High levels of CK, in turn, may cause *renal impairment*. How? When present in high amounts, CK can plug up the glomeruli, thereby preventing normal filtration.

Fortunately, fatal rhabdomyolysis is extremely rare; the overall incidence is less than 0.15 case per 1 million prescriptions. Nonetheless, patients should be informed about the risk of myopathy and instructed to notify the prescriber if unexplained muscle pain or tenderness occurs. How statins cause myopathy is unknown.

Several factors increase the risk of myopathy. Among these are advanced age, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency, especially associated with diabetes), use of statins in high doses, concurrent use of fibrates (which can cause myopathy too), and use of drugs that can raise statin levels (see below). In addition, hypothyroidism increases risk. Accordingly, if muscle pain develops, thyroid function should be assessed.

Measurement of CK levels can facilitate diagnosis. Levels should be determined at baseline, and again if symptoms of myopathy appear. If the CK level is more than 10 times the ULN, the statin should be discontinued. If the level is less than

10 times the ULN, the statin can be continued, provided myopathy symptoms and the CK level are followed weekly. However, given that weekly blood tests are expensive and inconvenient, it may be best to stop the statin and re-evaluate therapy, even when CK levels are less than 10 times the ULN. Routine monitoring of CK in asymptomatic patients is unnecessary.

What is the rhabdomyolysis risk with individual statins? Of the seven statins in current use, *rosuvastatin* [Crestor] poses the highest risk of rhabdomyolysis. But even with this drug, the absolute number of cases is extremely low. With the other statins, the risk is even lower. Another statin—*cerivastatin* [Baycol]—was withdrawn in 2001 because the risk was 16 to 80 times higher than with other statins.

Should concerns about myopathy discourage statin use? Definitely not! Remember: The risk of serious myopathy is extremely low, whereas the risk of untreated LDL cholesterol is very high. Accordingly, when statins are used to lower cholesterol, the benefits of therapy (reduction of cardiovascular events) far outweigh the small risk of myopathy.

Hepatotoxicity. Liver injury, as evidenced by elevations in serum transaminase levels, develops in 0.5% to 2% of patients treated 1 year or longer. However, jaundice and other clinical signs are rare. Progression to outright liver failure occurs very rarely. Because of the risk of liver injury, product labeling recommends that liver function tests (LFTs) be done before treatment and every 6 to 12 months thereafter (see Table 50–10). However, there is evidence that routine monitoring may not really be needed. If serum transaminase levels rise to 3 times the ULN and remain there, statins should be discontinued. Transaminase levels decline to pretreatment levels following drug withdrawal.

Should statins be used by patients with active liver disease? The answer depends on the disease. In patients with viral or alcoholic hepatitis, statins should be avoided. However, in patients with the most common cause of hepatitis—nonalcoholic fatty liver disease—statins are acceptable therapy. In fact, in these patients, not only can statins reduce cholesterol levels, they may also decrease liver inflammation, improve LFTs, and reduce steatosis (fatty infiltration in the liver). Should LFTs be monitored? Yes—at baseline and every 3 months thereafter. If LFTs climb to 3 times the ULN, statin use should stop.

Drug Interactions

With Other Lipid-Lowering Drugs. Combining a statin with most other lipid-lowering drugs (except probably the bile-acid sequestrants) can increase the incidence and severity of the most serious statin-related adverse events: muscle injury, liver injury, and kidney damage. Increased risk occurs primarily with fibrates (gemfibrozil, fenofibrate), which are commonly combined with statins. The bottom line: When statins are combined with other lipid-lowering agents, use extra caution and monitor for adverse effects more frequently.

With Drugs That Inhibit CYP3A4. Drugs that inhibit CYP3A4 can raise levels of *lovastatin* and *simvastatin* substantially, and can raise levels of *atorvastatin* moderately. How? By slowing their inactivation. Important inhibitors of CYP3A4 include macrolide antibiotics (eg, erythromycin), azole antifungal drugs (eg, ketoconazole, itraconazole), HIV protease inhibitors (eg, ritonavir), amiodarone (an antiarrhythmic drug), and cyclosporine (an immunosuppressant). If these drugs are combined with a statin, increased caution is

Price. Three statins—lovastatin, pravastatin, and simvastatin—are now available as generic products, and hence are cheaper than all other statins.

Niacin (Nicotinic Acid)

Niacin [Niacor, Niaspan] reduces LDL and TG levels—and it increases HDL levels better than any other drug. However, despite these favorable effects on lipid levels, niacin does little to improve outcomes, as shown by the AIM-HIGH trial in 2011. Principal adverse effects are intense flushing, GI upset, and liver injury. Niacin is available in three formulations, which differ with respect to onset, duration, and the incidence and severity of side effects. In 2010, sales of one product—Niaspan—were nearly \$1 billion. However, since release of the AIM-HIGH data, sales of Niaspan have begun to drop. **Effect on Plasma Lipoproteins.** Niacin reduces LDL cholesterol by 14% to 17% and TGs by 28% to 35%. In addition, it raises HDL cholesterol by 28% to 35%. Triglyceride levels begin to fall within the first 4 days of therapy. LDL levels decline more slowly, taking 3 to 5 weeks for maximum reductions. Combining niacin with lovastatin can reduce LDL cholesterol by 45% and can raise HDL cholesterol by 41%. Triple therapy (niacin plus a statin plus a bile-acid sequestrant) can decrease LDL cholesterol by 70% or more.

Mechanism of Action. The mechanism underlying effects on plasma lipids is not completely understood. We do know that niacin acts in the liver and adipose tissue to inhibit synthesis of triglycerides, and thereby decreases production of VLDLs. Since LDLs are by-products of VLDL degradation, the fall in VLDL levels causes LDL levels to fall too. How niacin raises levels of HDL is unclear.

The AIM-HIGH Trial. This trial, sponsored by the U.S. National Heart, Lung, and Blood Institute, was designed to answer an important question: Does raising HDL cholesterol with niacin reduce the risk of CV events? The study enrolled 3414 patients with low HDL cholesterol, high TGs, and a history of CV disease. Half received simvastatin plus a placebo, and half received simvastatin plus Niaspan (extended-release niacin tablets). The result? After 32 months, Niaspan significantly reduced CV risk factors: Compared with patients who took simvastatin alone, patients who took simvastatin plus niacin had higher levels of HDL cholesterol and lower levels of TGs. However, despite these favorable effects on lipid levels, clinical outcomes were not changed: patients who received simvastatin plus niacin had the same incidence of CV events—stroke, fatal or nonfatal MI, hospitalization for acute coronary syndrome, revascularization of coronary arteries—as did those who took simvastatin alone. Clearly, the reduction in risk factors with niacin did not reduce actual risk. At this time, we don't know if these unexpected results apply to all drugs that raise HDL levels, or if they apply only to niacin. **Therapeutic Use.** Niacin is a drug of choice for lowering TG levels in patients at risk of pancreatitis. Additional uses include mixed elevation of LDLs and TGs, and elevation of TGs in combination with low levels of HDLs. One formulation—sold as Niaspan—is approved for raising HDL cholesterol. Niacin also has a role as a vitamin. The doses employed to correct niacin deficiency are much lower than those employed to reduce lipoprotein levels (about 25 mg/day rather than 1 to 3 gm/day). The role of niacin as a vitamin is discussed in Chapter 81.

advised. Some authorities recommend an automatic reduction in statin dosage if these inhibitors are used. As discussed in Chapter 6, chemicals in grapefruit and grapefruit juice can inhibit CYP3A4. Furthermore, the inhibition may persist for 3 days or more after eating the fruit or drinking its juice. Accordingly, statin users should avoid grapefruits and their juice.

Use in Pregnancy

Stains are classified in Food and Drug Administration Pregnancy Risk Category X: The risks to the fetus outweigh any potential benefits of treatment. Some statins have caused fetal malformation in animal models—but only at doses far higher than those used in humans. To date, teratogenic effects in humans have not been reported. Nonetheless, because statins inhibit synthesis of cholesterol, and since cholesterol is required for synthesis of cell membranes as well as several fetal hormones, concern regarding human fetal injury remains. Moreover, there is no compelling reason to continue lipid-lowering drugs during pregnancy: Stopping the statin for 9 months is not going to cause a sudden, dangerous rise in cholesterol levels or risk of CHD. Women of child-bearing age should be informed about the potential for fetal harm and warned against becoming pregnant. If pregnancy occurs, statins should be discontinued.

Preparations, Dosage, and Administration

Statins are available alone and in fixed-dose combinations. The single-ingredient products are discussed later in the chapter under the heading *Drug Combinations*. Seven statins are available for use alone: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Information on preparations, dosage, and administration is summarized in Table 50-12. Dosing is done once daily, preferably in the evening either with the evening meal or at bedtime. Why take these drugs late in the day? Because endogenous cholesterol synthesis increases during the night. As a result, statins have the greatest impact when given in the evening.

Drug Selection

Several factors bear on statin selection, including the LDL goal, drug interactions, kidney function, safety in Asians, and price. **LDL Goal.** If a 30% to 40% reduction in LDL is deemed sufficient, any statin will do. However, if LDL must be lowered by more than 40%, then atorvastatin or simvastatin may be preferred. Furthermore, not only are these two drugs highly effective, clinical experience with them is extensive.

Drug Interactions. Drugs that inhibit CYP3A4 can raise levels of atorvastatin, lovastatin, and simvastatin, thereby increasing the risk of toxicity, especially myopathy and liver injury. Accordingly, in patients taking a CYP3A4 inhibitor, other statins may be preferred.

Kidney Function. For patients with normal renal function, any statin is acceptable. However, for patients with significant renal impairment, atorvastatin and fluvastatin are preferred (because no dosage adjustment is needed). **Safety in Asians.** The same dose of rosuvastatin, when given to Asian and Caucasian subjects, may produce twofold higher blood levels in the Asians. Accordingly, when rosuvastatin is used in Asians, start with the lowest available dosage and monitor diligently.

TABLE 50-12 ■ HMG-CoA Reductase Inhibitors: Preparations, Dosage, and Administration

Drug	Dosage	Administration with Regard to Meals	Dosage Changes in Special Populations	Preparations
Atorvastatin [Lipitor]	<i>Initial:</i> 10 mg at bedtime <i>Maximum:</i> 80 mg at bedtime	Take without regard to meals	No changes needed	<i>Lipitor (tablets):</i> 10, 20, 40, 80 mg
Fluvastatin [Lescol, Lescol XL]	<i>Initial:</i> 20 mg at bedtime <i>Maximum, Lescol:</i> 40 mg twice a day <i>Maximum, Lescol XL:</i> 80 mg at bedtime	Take without regard to meals	No changes needed	<i>Lescol (capsules):</i> 20, 40 mg <i>Lescol XL (extended-release tablets):</i> 80 mg
Lovastatin [Altoprev, Mevacor; generics]	<i>Initial:</i> 20 mg with the evening meal <i>Maximum:</i> 40 mg twice daily or 80 mg at bedtime	Take with evening meal to increase absorption	Reduce dosage for severe renal impairment	<i>Altoprev (extended-release tablets):</i> 10, 20, 40, 60 mg <i>Mevacor and generics (tablets):</i> 10, 20, 40 mg
Pitavastatin [Livalo]	<i>Initial:</i> 2 mg once daily at any time of day <i>Maximum:</i> 4 mg once daily	Take without regard to meals	Reduce dosage for moderate to severe renal impairment	<i>Livalo (tablets):</i> 1, 2, 4 mg
Pravastatin [Pravachol; generics]	<i>Initial:</i> 20 mg at bedtime <i>Maximum:</i> 40 mg at bedtime	Take without regard to meals	Reduce dosage for moderate to severe renal or hepatic impairment	<i>Pravachol and generics (tablets):</i> 10, 20, 40, 80 mg
Rosuvastatin [Crestor]	<i>Initial:</i> 20 mg at bedtime <i>Maximum:</i> 80 mg at bedtime	Take without regard to meals	Reduce dosage for severe renal impairment Reduce dosage in Asian patients	<i>Crestor (tablets):</i> 5, 10, 20, 40 mg
Simvastatin [Zocor; generics]	<i>Initial:</i> 20 mg at bedtime <i>Maximum:</i> 40 mg/day (Prior to 2011, the maximum recommended dosage was higher: 80 mg/day)	Take without regard to meals	Reduce dosage for severe renal impairment	<i>Zocor and generics (tablets):</i> 5, 10, 20, 40, 80 mg <i>Generic (tablets, rapidly disintegrating):</i> 10, 20, 40, 80 mg

Adverse Effects. The most frequent adverse reactions involve the skin (flushing, itching) and GI tract (gastric upset, nausea, vomiting, diarrhea). *Intense flushing* of the face, neck, and ears occurs in practically all patients receiving niacin in pharmacologic doses. This reaction diminishes in several weeks, and can be attenuated by taking 325 mg of aspirin 30 minutes before each dose. (Aspirin reduces flushing by preventing synthesis of prostaglandins, which mediate the flushing response.) Flushing can also be reduced by using extended-release niacin (eg, Niaspan) rather than immediate-release niacin (eg, Niacor).

Niacin is *hepatotoxic*. Severe liver damage has occurred. Liver injury is least likely with Niaspan, the extended-release formulation noted above. Other long-acting products—sustained-release, controlled-release, or timed-release (eg, Slo-Niacin)—should be avoided, owing to increased risk of hepatotoxicity. Because of possible hepatotoxicity, liver function should be assessed before treatment and periodically thereafter.

Niacin can elevate blood levels of uric acid. Exercise caution in patients with gout, and even in patients who have hyperuricemia but no symptoms of gout.

Additional adverse effects are *hyperglycemia* and *gouty arthritis*.

Preparations, Dosage, and Administration. Niacin (niacin) is marketed generically and under several trade names. The drug is available in tablets (immediate-release [IR], timed-release, controlled-release, sustained-

release, extended-release) or capsules (timed-release, extended-release, sustained-release).

With IR formulations (prescription Niacor and over-the-counter products), blood levels of niacin climb rapidly. As a result, these products are associated with the highest incidence and severity of facial and upper body flushing, at least for the first few weeks. Thereafter, the intensity of these responses tends to fade. To manage flushing, patients using IR niacin often take prophylactic aspirin. (The need for aspirin is much lower with the long-acting products.) With IR niacin, blood levels of niacin can fall relatively soon. Therefore, to maintain steady blood levels, the total daily dose should be given as two or three divided doses (1 to 3 gm each), rather than as one large dose.

The most popular niacin formulation is *Niaspan*, an extended-release formulation. Following oral dosing, the tablet slowly dissolves, causing blood levels to rise slowly and remain relatively steady. As a result, flushing is minimized, and once-daily dosing (usually 1 to 3 gm) is adequate. The major drawback to *Niaspan* is that it costs more than other niacin products.

Long-acting niacin [Slo-Niacin] has a longer half-life than other formulations. While this may seem like a therapeutic advantage (longer lasting high levels of drug), there is an increased risk of hepatotoxicity, and hence this product should be avoided.

In addition to being available alone, niacin is available in two fixed-dose combinations: niacin/lovastatin [Advicor] and niacin/simvastatin [Simcor]. These are discussed separately below.

Bile-Acid Sequestrants

Bile-acid sequestrants reduce LDL cholesterol levels. In the past, these drugs were a mainstay of lipid-lowering therapy. Today, they are used primarily as adjuncts to statins. Three agents are available: colestevlam, cholestyramine, and

colestipol. Colesevelam is newer than the other two, and better tolerated.

Colesevelam

Colesevelam [Welchol], approved for hyperlipidemia in 2000, is the drug of choice when a bile-acid sequestrant is indicated. Like the older sequestrants, colesevelam is a nonabsorbable resin that binds (sequesters) bile acids and other substances in the GI tract, and thereby prevents their absorption and promotes their excretion. Colesevelam is preferred to the older sequestrants for three reasons: (1) the drug is better tolerated (less constipation, flatulence, bloating, and cramping); (2) it does not reduce absorption of fat-soluble vitamins (A, D, E, and K); and (3) it does not significantly reduce the absorption of statins, digoxin, warfarin, and most other drugs studied.

In addition to its beneficial effects on plasma lipids, colesevelam can help control hyperglycemia in patients with type 2 diabetes. The drug was approved for adjunctive therapy of diabetes in 2008. Diabetes and its management are the subject of Chapter 57.

Effect on Plasma Lipoproteins. The main response to bile-acid sequestrants is a reduction in LDL cholesterol. LDL decline begins during the first week of therapy, and becomes maximal (about a 20% drop) within about a month. When these drugs are discontinued, LDL cholesterol returns to pretreatment levels in 3 to 4 weeks.

Bile-acid sequestrants may increase VLDL levels in some patients. In most cases, the elevation is transient and mild. However, if VLDL levels are elevated prior to treatment, the increase induced by the bile-acid sequestrants may be sustained and substantial. Accordingly, bile-acid sequestrants are not drugs of choice for lowering LDL cholesterol in patients with high VLDL levels.

Pharmacokinetics. Bile-acid sequestrants are biologically inert. Also, they are insoluble in water, cannot be absorbed from the GI tract, and are not attacked by digestive enzymes. Following oral administration, they simply pass through the intestine and become excreted in the feces.

Mechanism of Action. The bile-acid sequestrants lower LDL cholesterol through a mechanism that ultimately depends on increasing LDL receptors on hepatocytes. As background, you need to know that bile acids secreted into the intestine are normally reabsorbed and reused. Bile-acid sequestrants prevent this reabsorption. Here's what happens. Following oral dosing, these drugs form an insoluble complex with bile acids in the intestine; this complex prevents the reabsorption of bile acids, and thereby accelerates their excretion. Because bile acids are normally reabsorbed, the increase in excretion creates a demand for increased synthesis, which takes place in the liver. Since bile acids are made from cholesterol, liver cells require an increased cholesterol supply in order to increase bile acid production. The required cholesterol is provided by LDL. To avail themselves of more LDL cholesterol, liver cells increase their number of LDL receptors, thereby increasing their capacity for LDL uptake. The result is an increase in LDL uptake from plasma, which decreases circulating LDL levels. Individuals who are genetically incapable of increasing LDL receptor synthesis are unable to benefit from these drugs.

Therapeutic Use. Colesevelam is indicated as adjunctive therapy to diet and exercise for reducing LDL cholesterol in patients with primary hypercholesterolemia. The drug may be used alone, but usually is combined with a statin. On average,

colesevelam alone can lower LDL cholesterol by about 20% (the typical range is between 15% and 30%). In contrast, combined therapy with a statin can reduce LDL cholesterol by up to 50%. Similar results can be obtained by combining a sequestrant with niacin.

Adverse Effects. The bile-acid sequestrants are not absorbed from the GI tract, and hence are devoid of systemic effects. Accordingly, they are safer than all other lipid-lowering drugs.

Adverse effects are limited to the GI tract. *Constipation* is the main complaint. This can be minimized by increasing dietary fiber and fluids. If necessary, a mild laxative may be used. Other GI effects include *bloating, indigestion, and nausea*. The older agents—cholestyramine and colestipol—can decrease fat absorption, and may thereby *decrease uptake of fat-soluble vitamins*. However, this does not seem to be a problem with colesevelam.

Drug Interactions. The bile-acid sequestrants can form insoluble complexes with other drugs. Medications that undergo binding cannot be absorbed, and hence are not available for systemic effects. Drugs known to form complexes with the sequestrants include thiazide diuretics, digoxin, warfarin, and some antibiotics. To reduce formation of sequestrant-drug complexes, oral medications that are known to interact should be administered either 1 hour before the sequestrant or 4 hours after.

Preparations, Dosage, and Administration. Colesevelam [Welchol] is supplied in tablets (625 mg) and a powder (1.875 and 3.75 g) for making an oral suspension. With the tablets, the initial adult dosage is 3 tablets (1.9 gm) twice daily or 6 tablets (3.8 gm) once daily. With the oral suspension, the initial adult dosage is 1.875 gm twice daily or 3.75 gm once daily. All doses are taken with food and water. Of note, the dosage for colesevelam is much smaller than that of cholestyramine (8 to 24 gm/day) or colestipol (5 to 30 gm/day).

Older Agents: Cholestyramine and Colestipol

Cholestyramine and colestipol have been available for decades, but have been largely replaced by colesevelam. Why? Because colesevelam is better tolerated, does not impede absorption of fat-soluble vitamins, and has minimal effects on other drugs. Although cholestyramine and colestipol are very safe, they frequently cause constipation, abdominal discomfort, and bloating.

Cholestyramine [Questran, Questran Light, Prevalite] is supplied in powdered form. Instruct patients to mix the powder with fluid, because swallowing it dry can cause esophageal irritation and impaction. Appropriate liquids for mixing include water, fruit juices, and soups. Pulp fruits with a high fluid content (eg, applesauce, crushed pineapple) may also be used. The dosage range is 4 to 16 gm/day.

Colestipol hydrochloride [Colestid] is supplied in granular form (5 gm) and in 1-gm tablets. The dosage for the *granules* is 5 to 30 gm/day administered in one or more doses. Instruct patients to mix the granules with fluids or pulp fruits before ingestion. The dosage for the *tablets* is 2 to 16 gm/day administered in one or more doses. Tablets should be swallowed whole and taken with fluid.

Ezetimibe

Ezetimibe [Zetia, Ezetrol[®]], approved in 2002, is a unique drug for reducing plasma cholesterol. Benefits derive from blocking cholesterol absorption.

Mechanism of Action and Effect on Plasma Lipoproteins. Ezetimibe acts on cells of the brush border of the small intestine to inhibit dietary cholesterol absorption. The drug also inhibits reabsorption of cholesterol secreted in the bile. Treatment reduces plasma levels of total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B. In addition, ezetimibe can produce a small *increase* in HDL cholesterol.

Therapeutic Use. Ezetimibe is indicated as an adjunct to diet modification for reducing total cholesterol, LDL chole-

terol, and apolipoprotein B in patients with primary hypercholesteremia. The drug is approved for monotherapy and for combined use with a statin. In clinical trials, ezetimibe alone reduced LDL cholesterol by about 19%, increased HDL cholesterol by 1% to 4%, and decreased TGs by 5% to 10%. When ezetimibe was combined with a statin, the reduction in LDL cholesterol was about 25% greater than with the statin alone. Despite these desirable effects on blood lipids, there is no evidence that ezetimibe reduces atherosclerosis or improves clinical outcomes.

Pharmacokinetics. Ezetimibe is administered orally, and absorption is not affected by food. In the intestinal wall and liver, ezetimibe undergoes extensive conversion to ezetimibe glucuronide, an active metabolite. Both compounds—ezetimibe itself and its main metabolite—are eliminated primarily in the bile. The elimination half-life is about 22 hours.

Adverse Effects. Ezetimibe is generally well tolerated. During clinical trials, the incidence of significant side effects was nearly identical to that seen with placebo. However, during postmarketing surveillance, there have been reports of myopathy, rhabdomyolysis, hepatitis, pancreatitis, and thrombocytopenia. In contrast to the bile-acid sequestrants, ezetimibe does not cause constipation and other adverse GI effects.

Drug Interactions. Statins. In patients taking a statin, adding ezetimibe slightly increases the risk of liver damage (as indicated by elevated transaminase levels). If the drugs are combined, transaminase levels should be carefully monitored. Combining ezetimibe with a statin may also increase the risk of myopathy.

Fibrates. Both ezetimibe and fibrates (gemfibrozil and fenofibrate) can increase the cholesterol content of bile, and can thereby increase the risk of gallstones. Both also increase the risk of myopathy. Accordingly, combined use is not recommended.

Bile-Acid Sequestrants. Cholestyramine (and possibly colestipol) can significantly decrease the absorption of ezetimibe. To minimize effects on absorption, ezetimibe should be administered at least 2 hours before a sequestrant or more than 4 hours after.

Cyclosporine. Cyclosporine may greatly increase levels of ezetimibe. If the drugs are combined, careful monitoring is needed.

Caution. In patients with hepatic impairment, bioavailability of ezetimibe is significantly increased. At this time, we do not know if increased availability is harmful. Until more is known, patients with moderate or severe hepatic insufficiency should not be given the drug.

Preparations, Dosage, and Administration. Ezetimibe [Zetia, Ezetrol] is available in 10-mg tablets. The recommended dosage is 10 mg once a day, taken with or without food. If ezetimibe is combined with a statin, both drugs can be taken at the same time. If ezetimibe is combined with a bile-acid sequestrant, ezetimibe should be taken 2 hours before the sequestrant or 4 hours after.

Fibric Acid Derivatives (Fibrates)

The fibric acid derivatives, also known as fibrates, are the most effective drugs we have for lowering triglyceride levels. In addition, these drugs can raise HDL cholesterol, but have little or no effect on LDL cholesterol. Furthermore, there is no proof that fibrates reduce mortality from CHD. Fibrates can increase the risk of bleeding in patients taking warfarin (an anticoagulant) and the risk of rhabdomyolysis in patients taking statins.

Because of these and other undesired effects, and because mortality is not reduced, fibrates are considered third-line drugs for managing lipid disorders. In the United States, three preparations are available: gemfibrozil [Lopid], fenofibrate [Tricor, others], and fenofibric acid [TriLipix], a delayed-release preparation noteworthy for being the first and only fibrate approved for use with a statin.

Gemfibrozil

Gemfibrozil [Lopid] decreases triglyceride (VLDL) levels and raises HDL cholesterol levels. The drug does not reduce LDL cholesterol to a significant degree. Its principal indication is hypertriglyceridemia.

Effect on Plasma Lipoproteins. Gemfibrozil decreases plasma TG content by lowering VLDL levels. Maximum reductions in VLDLs range from 40% to 55%, and are achieved within 3 to 4 weeks of treatment. Gemfibrozil can raise HDL cholesterol by 6% to 10%. In patients with normal TG levels, the drug can produce a small reduction in LDL levels. However, if TG levels are high, gemfibrozil may actually increase LDL levels.

Mechanism of Action. Gemfibrozil and other fibrates appear to work by interacting with a specific receptor subtype—known as peroxisome proliferator-activated receptor alpha (PPAR alpha)—present in the liver and brown adipose tissue. Activation of PPAR alpha leads to (1) increased synthesis of lipoprotein lipase (LPL) and (2) reduced production of apolipoprotein C-III (an inhibitor of LPL). Both actions accelerate the clearance of VLDLs, and thereby reduce levels of TGs. How do fibrates elevate HDL levels? By activating PPAR alpha, fibrates increase production of apolipoproteins A-I and A-II, which in turn facilitates HDL formation.

Therapeutic Use. Gemfibrozil is used primarily to reduce high levels of plasma triglycerides (VLDLs). Treatment is limited to patients who have not responded adequately to weight loss and diet modification. Gemfibrozil can also reduce LDL cholesterol slightly. However, other drugs (statins, cholestyramine, colestipol) are much more effective.

Gemfibrozil can be used to raise HDL cholesterol, although it is not approved for this application. When tested in patients with normal LDL cholesterol and low HDL cholesterol, gemfibrozil reduced the risk of major CV events—but did not reduce mortality from CHD. Because LDL cholesterol was normal, it appears that benefits were due primarily to elevation of HDL cholesterol, along with reduction of plasma triglycerides.

Adverse Effects. Gemfibrozil is generally well tolerated. The most common reactions are rash and GI disturbances (nausea, abdominal pain, diarrhea).

Gallstones. Gemfibrozil increases biliary cholesterol saturation, thereby increasing the risk of gallstones. Patients should be informed about manifestations of gallbladder disease (eg, upper abdominal discomfort, intolerance of fried foods, bloating) and instructed to notify the prescriber at once if these develop. Patients with pre-existing gallbladder disease should not take the drug.

Myopathy. Like the statins, gemfibrozil and other fibrates can cause myopathy. Warn patients to report any signs of muscle injury, such as tenderness, weakness, or unusual muscle pain.

Liver Injury. Gemfibrozil is hepatotoxic. The drug can disrupt liver function and may also pose a risk of liver cancer. Periodic tests of liver function are required.

Drug Interactions. Gemfibrozil displaces warfarin from plasma albumin, thereby increasing anticoagulant effects. Prothrombin time (international normalized ratio) should be

measured frequently to assess coagulation status. Warfarin dosage may need to be reduced.

As noted, gemfibrozil increases the risk of *statin-induced myopathy*. Accordingly, the combination of a statin with gemfibrozil should be used with great caution, if at all.

Preparations, Dosage, and Administration. Gemfibrozil [Lopid] is available in 600-mg tablets. The adult dosage is 600 mg twice a day. Dosing is done 30 minutes before the morning and evening meals.

Fenofibrate

Actions and Uses. Fenofibrate [Tricor, Antara, Lofibra, Triglide, Lipidil[®]] is indicated for hypertriglyceridemia in patients who have not responded to dietary measures. The drug lowers triglycerides by decreasing levels of VLDLs.

Pharmacokinetics. Fenofibrate is well absorbed from the GI tract, especially in the presence of food. Once absorbed, the drug is rapidly converted to fenofibric acid, its active form. In the blood, the drug is 98% protein bound. Elimination is the result of hepatic metabolism followed by renal excretion. The plasma half-life is about 20 hours.

Adverse Effects and Drug Interactions. The most common adverse effects are rash and GI disturbances. Like gemfibrozil, fenofibrate can cause gallstones and liver injury. In animal models, doses 1 to 6 times the maximum human dose caused cancers of the pancreas and liver. Like gemfibrozil, fenofibrate can increase the risk of bleeding with warfarin and the risk of myopathy with statins.

Preparations, Dosage, and Administration. Fenofibrate is available in several formulations that differ with respect to dosage and the impact of food on absorption. Four products are discussed below.

Tricor tablets (48 and 145 mg) are made using NanoCrystal technology to enhance absorption. As a result, dosing can be done with or without food. The dosage range is 48 to 145 mg/day.

Triglide tablets (50 and 160 mg), like *Tricor* tablets, may be administered with or without food. The dosage range is 50 to 160 mg/day.

Antara capsules (43 and 130 mg), which contain micronized particles, must be administered with food to maximize absorption. The dosage range is 43 to 130 mg/day.

Lofibra capsules (67, 134, and 200 mg) contain micronized particles. Like *Antara*, *Lofibra* must be administered with food to maximize absorption. The dosage range is 67 to 200 mg/day.

Fenofibric Acid

Fenofibric acid [TriLipix], approved in December 2008, is the active metabolite of fenofibrate. Accordingly, the pharmacology of the drug is much like that of the parent compound. Fenofibric acid stands out from other fibrates for being the only group member *approved* for use with a statin. However, there is no proof that combining the drug with a statin reduces the risk of a major CV event. Furthermore, just like other fibrates, fenofibric acid can cause myopathy, and hence combined use with a statin still poses significant myopathy risk. Therefore, the combination must be employed with great care. Fenofibric acid is available in delayed-release capsules (45 and 135 mg). Daily dosages for hypertriglyceridemia range from 45 mg to 135 mg. In patients with renal impairment, a low dosage (45 mg/day) should be used. When combined with a statin for patients with mixed dyslipidemias, fenofibric acid should be dosed at 135 mg/day.

Drug Combinations

Lovastatin/Niacin [Advicor]

Actions and Uses. Lovastatin (immediate-release) and niacin (extended-release) are available in fixed-dose combinations sold as *Advicor*. Lovastatin serves primarily to lower LDL cholesterol; niacin raises HDL cholesterol and lowers TGs. In one clinical trial, using the combination for 12 months lowered LDL cholesterol by 45%, raised HDL cholesterol by 41%, and lowered TGs by 42%. The product has two indications: primary hypercholesterolemia and mixed dyslipidemia. However, it should not be used for initial therapy of either condition. Rather, it should be reserved for patients who have not responded adequately to lovastatin or niacin alone.

Adverse Effects. The principal concerns are *flushing* (from the niacin) and *hepatotoxicity* (from both drugs). Flushing can be reduced by taking aspirin or ibuprofen 30 minutes before dosing. To monitor liver injury, LFTs should be obtained at baseline, every 6 to 12 weeks for the first 6 months of treatment, and every 6 months thereafter.

Lovastatin poses a very small risk of *myopathy*. Nonetheless, advise patients to report any muscle pain or weakness. Adding a fibrate to the regimen

increases the risk of myopathy (because, like the statins, fibrates can promote muscle injury).

Preparations, Dosage, and Administration. *Advicor* is available in three lovastatin/niacin strengths: 20/500 mg, 20/750 mg, and 20/1000 mg. The recommended initial dosage is 20/500 mg once a day at bedtime. At 4-week intervals, the niacin dosage can be increased by 500 mg/day. The maximum dosage is 40/2000 mg. All doses should be taken with a low-fat snack, which can enhance absorption and reduce GI distress.

Simvastatin/Niacin [Simcor]

Actions and Uses. Simvastatin and extended-release niacin are available in a fixed-dose combination sold as *Simcor*. The product is indicated for hypercholesterolemia and hypertriglyceridemia. Benefits derive from the actions described above for these drugs individually. Most studies show that simvastatin/niacin is no better than simvastatin alone for lowering LDL cholesterol, although the combination is better than simvastatin alone for raising HDL cholesterol and lowering TGs. However, despite these beneficial effects on blood lipids, the combination is no better than simvastatin alone at improving CV outcomes (eg, MI, stroke), as shown in the AIM-HIGH trial discussed above.

Adverse Effects. The most common side effects of *Simcor*, regardless of the dose, are flushing, pruritus, and headache. These are the classic and most common side effects of niacin.

Preparations, Dosage, and Administration. *Simcor* tablets are available in three simvastatin/niacin strengths: 20/500 mg, 20/750 mg, and 20/1000 mg. Therapy usually starts with the 20/500-mg product, taken once daily at bedtime. Dosing with a low-fat snack is recommended to reduce the incidence and severity of niacin-related stomach upset. If needed and tolerated, the daily niacin dose can be gradually increased to 2000 mg (with 40 mg of simvastatin).

Simvastatin/Ezetimibe [Vytorin]

Actions and Uses. Simvastatin and ezetimibe are available in fixed-dose combination tablets sold as *Vytorin*. Following its approval in 2004, the product quickly became one of our "top 10" most-prescribed drugs. *Vytorin* has only one indication: hypercholesterolemia. Because ezetimibe has a different mechanism of action than simvastatin, the combination can lower cholesterol more effectively than simvastatin alone.

With this combination, the dose of simvastatin required to effectively lower cholesterol may be lower than the dose required when simvastatin is used alone. As a result, the risk of statin-related adverse effects can be reduced. Additional benefits of the combination are convenience (take just one pill instead of two) and reduced cost (the combination costs less than both drugs purchased separately).

Despite the advantages of *Vytorin*, some authorities are concerned that the combination may be less beneficial than simvastatin alone. This concern is based on four facts:

- We have proof that simvastatin *alone* can decrease adverse outcomes (ie, MI and other CV events).
- We have no proof that the combination can decrease adverse outcomes of elevated cholesterol (even though it *can* reduce levels of cholesterol).
- In addition to lowering cholesterol, statins have other beneficial actions (eg, they often lower elevated TGs).
- When ezetimibe and simvastatin are combined, cholesterol goals can be met using simvastatin in reduced dosage (which is a problem for reasons discussed immediately below).

Because the combination permits a reduction in simvastatin dosage, there is concern that, although the target cholesterol goal may be reached, the reduction in adverse outcomes may be smaller than when cholesterol is lowered using simvastatin alone. Until data on adverse outcomes with the combination are available, this concern will remain unresolved.

Adverse Effects and Drug Interactions. *Vytorin* is generally well tolerated. However, myopathy is a concern (because both drugs can cause muscle injury). Concurrent use of a fibrate, which can also cause myopathy, increases risk. The risk of myopathy and other adverse effects is also increased by inhibitors of CYP3A4, the enzyme that inactivates simvastatin. Because *Vytorin* contains a statin, the product is contraindicated for women who are pregnant and for patients with liver disease.

Preparations, Dosage, and Administration. *Vytorin* tablets contain 10 mg of ezetimibe plus either 10, 20, 40, or 80 mg of simvastatin. The usual starting dosage is 10 mg ezetimibe/20 mg simvastatin each day. Dosing is done once daily, preferably in the evening. The simvastatin dosage can be increased as needed and tolerated.

Pravastatin/Aspirin [Pravigard PAC]

Pravastatin tablets and aspirin tablets are available co-packaged under the brand name *Pravigard PAC*. The product is approved for preventing MI, stroke, and

death in patients with evidence of cardiovascular or cerebrovascular disease. Pravastatin improves lipid profiles, and aspirin suppresses platelet aggregation.

Potential side effects include myopathy (from the statin), and bleeding and GI mucosal damage (from the aspirin). Pravigard PAC should not be used by patients under 18 years old, by women who are pregnant, by anyone with severe hepatic or renal impairment, or by any patient for whom aspirin alone is contraindicated.

Each Pravigard PAC package contains 30 pravastatin tablets and 30 buffered aspirin tablets. Six pravastatin/aspirin combinations are available: 20/81 mg, 20/325 mg, 40/81 mg, 40/325 mg, 80/81 mg, and 80/325 mg. The usual dosage is 40/81 mg or 40/325 mg. Dosing is done once daily with a full glass of water, with or without food. Although this package may be convenient, please note that we can achieve the same benefits—at much lower cost—by purchasing generic simvastatin and the cheapest buffered aspirin available. The pharmacology of aspirin is discussed in Chapter 71.

Atorvastatin/Amlodipine [Caduet]

Atorvastatin and amlodipine (a calcium channel blocker) are available in fixed-dose combination tablets under the trade name *Caduet*. This is the first single product indicated for dyslipidemia combined with hypertension and/or angina. The combination has two advantages over taking each drug separately: fewer pills to swallow and slightly lower cost. Eleven amlodipine/atorvastatin combinations are available; 2.5 mg amlodipine with either 10, 20, or 40 mg atorvastatin; 5 mg amlodipine with either 10, 20, 40, or 80 mg atorvastatin; and 10 mg amlodipine with either 10, 20, 40, or 80 mg atorvastatin. Dosage is individualized on the basis of therapeutic response and tolerance of adverse effects. The pharmacology of amlodipine and other calcium channel blockers is discussed in Chapter 45.

Simvastatin/Sitagliptin [Juvissync]

Simvastatin and sitagliptin (a drug for reducing blood glucose) are available in a fixed-dose combination sold as *Juvissync*. This is the first single product indicated for dyslipidemia combined with diabetes. Why do we have such a combination? Because many patients with hypercholesterolemia also have type 2 diabetes, both of which are major risk factors for cardiovascular disease. Hence, by giving *Juvissync*, we can reduce both risk factors with a single pill. Major adverse effects of simvastatin are rhabdomyolysis and liver injury. Major adverse effects of sitagliptin are pancreatitis and hypersensitivity reactions. *Juvissync* tablets contain 100 mg of sitagliptin plus either 10, 20, or 40 mg of simvastatin. Dosing is done once daily in the evening. The pharmacology of sitagliptin is discussed in Chapter 57.

Fish Oil

Consuming fatty fish or fish-oil supplements is associated with a decreased risk of CHD and CHD-related death. Fish oil may also decrease the risk of thrombotic stroke.

Why is fish oil beneficial? Because it contains two “heart healthy” compounds: *eicosapentaenoic acid* (EPA) and *docosahexaenoic acid* (DHA). Structures are shown in Figure 50-4. Both compounds are long-chain, omega-3 polyunsaturated fatty acids, with a methyl group at one end and a carboxyl group at the other. They are called *omega-3 fatty acids* because they have a double bond located three carbons in from the methyl terminus.

How do omega-3 fatty acids help us? The answer is unclear. We know that high doses (1 to 4 gm) can lower TG levels. Benefits of lower doses (850 mg to 1 gm) may result from reducing platelet aggregation; reducing thrombosis (by effects on platelets and the vascular endothelium); reducing inflammation (which may help stabilize atherosclerotic plaques); and reducing blood pressure and cardiac dysrhythmias.

To reduce the risk of CV events, the American Heart Association recommends eating at least two servings of fish a week. Fish with high concentrations of EPA and DHA are preferred. Among these are mackerel, halibut, herring, salmon, albacore tuna, and trout. The goal is to take in, on average, about 1 gm of fish oil a day.

Because fish concentrate certain environmental contaminants—especially methylmercury, dioxins, and polychlorinated biphenyls (PCBs)—eating fish carries some risk. Methylmercury can cause heart disease as well as neurologic damage, manifesting as tremor, numbness, tingling, altered vision, and impaired concentration. Exposure *in utero* or during early childhood can lead to mental retardation, blindness, and seizures. With dioxin and PCBs, carcinogenesis is the major concern. Does this mean we should avoid eating fish? No. For postmenopausal women, and for men who are middle-aged or older, the benefits of fish outweigh the risks. For women who are pregnant or breastfeeding, fish consumption should be limited to 12 ounces a week, and certain species—swordfish, king mackerel, shark, and golden snapper, all of which may have high levels of methylmercury—should be avoided entirely. Young



Eicosapentaenoic acid (EPA)



Docosahexaenoic acid (DHA)

Figure 50-4 ■ Structures of omega-3 fatty acids in fish oil.

children should limit fish consumption too. For people who like salmon, dioxin exposure can be reduced by eating wild salmon, which contains much less dioxin than farm-raised salmon. Exposure to all contaminants can be reduced by using fish-oil supplements, which have much less contamination than fish themselves.

Lovaza. Lovaza is the trade name for the first preparation of omega-3-acid ethyl esters approved by the FDA. The product, available only by prescription, contains a combination of EPA and DHA. Lovaza is approved as an adjunct to dietary measures to reduce very high levels of TGs (500 mg/dL or greater). When used alone, Lovaza can reduce TG levels by 20% to 50%. Combining it with simvastatin produces a further decrease. Because large doses of omega-3 fatty acids can impair platelet function, leading to prolonged bleeding time, the product should be used with care in patients taking anticoagulants or antiplatelet drugs, including aspirin. Lovaza is supplied in 1-gm, liquid-filled, soft-gelatin capsules that contain approximately 465 mg of EPA and approximately 375 mg of DHA. The recommended dosage is 4 gm/day, taken either all at once (4 capsules) or in two doses (2 capsules twice a day).

Plant Stanol and Sterol Esters

Stanol esters and sterol esters, which are analogs of cholesterol, can reduce intestinal absorption of cholesterol (by 10%), and can thereby reduce levels of LDL cholesterol (by 14%). These compounds do not affect HDL levels or TG levels. ATP III recommends adding plant stanols or sterols to the diet if the basic TLC diet fails to reduce LDL cholesterol to the target level. Where can you get plant stanols and sterols? Two good sources are the *Benecol* brand of margarine, and soft spreads sold under the trade name *Promise*.

Estrogen

In postmenopausal women, estrogen therapy (0.625 mg/day) reduces LDL cholesterol by 15% to 25% and increases HDL cholesterol by 10% to 15%. However, despite these beneficial effects on blood lipids, estrogen therapy does little to reduce CV morbidity or mortality in older women. In fact, when estrogen is combined with a progestin for postmenopausal therapy, the risk of MI and other CV events actually goes up. Accordingly, estrogen therapy is no longer recommended for CV protection in postmenopausal women. The risks and benefits of estrogen therapy are discussed at length in Chapter 6 (Estrogens and Progestins).

Cholestin

Cholestin is the trade name for a dietary supplement that can lower cholesterol levels. The product is made from rice fermented with red yeast. Its principal active ingredient—*lovastatin*—is identical to the active ingredient in Mevacor, a brand-name, cholesterol-lowering drug. In addition to lovastatin, *Cholestin* contains at least seven other HMG-CoA reductase inhibitors (statins).

Several clinical trials have demonstrated that *Cholestin* can lower cholesterol levels, although none has studied its effects on CV events. In a trial conducted at Tufts University School of Medicine, *Cholestin* reduced total cholesterol by 11.4% and LDL cholesterol by 21%, and increased HDL cho-

lesterol by 14.6%. Similarly, in a study conducted at the University of California at Los Angeles Medical School, Cholestin reduced total cholesterol by 16% and LDL cholesterol by 22%. Whether Cholestin also reduces the incidence of CHD is unknown.

Information on Cholestin is lacking in four important areas: clinical benefits, adverse effects, drug interactions, and precise mechanism of action. As noted, there are no data on the ability of Cholestin to reduce the risk of MI, stroke, or any other CV event. In contrast, the clinical benefits of prescription statins (lovastatin and all the others) are fully documented. There is little or no information on the adverse effects or drug interactions of Cholestin. In contrast, the safety (and hazards) of prescription statins, as well as their drug interactions, have been studied extensively.

The mechanism by which Cholestin lowers cholesterol levels is only partly understood. The recommended daily dose of Cholestin contains only 5 mg of lovastatin and varying doses of other HMG-CoA reductase inhibitors, compared with 10 mg for the lowest recommended dose of Mevacor. Hence, it seems unlikely that the statins in Cholestin can fully account for the supplement's ability to reduce cholesterol levels. This implies that Cholestin has one or more active ingredients that have not yet been identified. What they are and how they may work is a mystery.

What's the bottom line? Until more is known about Cholestin, stick with statins—medications of proven safety and efficacy. Furthermore, for people with health insurance, using statins is cheaper: Most insurers will cover the cost of statins, but will not pay for Cholestin.

KEY POINTS

- Lipoproteins are structures that transport lipids (cholesterol and triglycerides [TGs]) in blood.
- Lipoproteins consist of a hydrophobic core, a hydrophilic shell, plus at least one apolipoprotein, which serves as a recognition site for receptors on cells.
- Lipoproteins that contain apolipoprotein B-100 transport cholesterol and/or TGs from the liver to peripheral tissues.
- Lipoproteins that contain apolipoproteins A-I or A-II transport cholesterol from peripheral tissues back to the liver.
- There are three major types of lipoproteins: VLDLs (very-low-density lipoproteins), LDLs (low-density lipoproteins), and HDLs (high-density lipoproteins).
- VLDLs transport TGs to peripheral tissues.
- The contribution of VLDLs to CHD is unclear.
- LDLs transport cholesterol to peripheral tissues.
- Elevation of LDL cholesterol greatly increases the risk of CHD.
- By reducing LDL cholesterol levels, we can arrest or reverse atherosclerosis, and can thereby reduce morbidity and mortality from CHD.
- HDLs transport cholesterol back to the liver.
- HDLs protect against CHD.
- Atherogenesis is a chronic inflammatory process that begins with accumulation of LDLs beneath the arterial endothelium, followed by oxidation of LDLs.
- Under ATP III, all adults over the age of 20 should be screened every 5 years for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs.
- Under ATP III, treatment of high LDL cholesterol is based on the individual's 10-year risk of having a major coronary event.
- Individuals with established CHD or a CHD risk equivalent (eg, diabetes) are in the highest 10-year risk group.
- The higher the 10-year risk, the lower the LDL goal and the LDL levels at which therapeutic lifestyle changes (TLCs) and drug therapy should be implemented.
- Diet modification along with exercise is the primary method for reducing LDL cholesterol. Drugs are employed only if diet modification and exercise fail to reduce LDL cholesterol to the target level.
- Therapy with cholesterol-lowering drugs must continue lifelong. If these drugs are withdrawn, cholesterol levels will return to pretreatment values.
- Statins (HMG-CoA reductase inhibitors) are the most effective drugs for lowering LDL cholesterol, and they cause few adverse effects.
- Statins can slow progression of CHD, decrease the number of adverse cardiac events, and reduce mortality.
- Statins reduce LDL cholesterol levels by increasing the number of LDL receptors on hepatocytes, thereby enabling hepatocytes to remove more LDLs from the blood. The process by which LDL receptor number is increased begins with inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis.
- Four statins—atorvastatin, fluvastatin, lovastatin, and simvastatin—are metabolized by CYP3A4, and hence their levels can be increased by CYP3A4 inhibitors (eg, cyclosporine, erythromycin, ketoconazole, ritonavir).
- Statins cause liver damage. Tests of liver function should be done at baseline and every 6 to 12 months thereafter.
- Statins cause myopathy. Patients who experience unusual muscle pain, soreness, tenderness, and/or weakness should inform their provider. A marker for muscle injury—creatine kinase (CK)—should be measured at baseline, before starting the drug; periodically thereafter; and whenever signs or symptoms that could be due to myositis or myopathy develop.
- Statins should not be used during pregnancy.
- Niacin reduces LDL and TG levels and raises HDL levels—and causes adverse effects in nearly all patients.
- In patients with a history of CV disease who are taking a statin (simvastatin), adding niacin can reduce CV risk factors (ie, it can elevate HDL cholesterol and lower TGs), but it does *not* reduce the risk of CV events.
- Immediate-release formulations of niacin cause intense flushing of the face, neck, and ears in most patients. Flushing can be reduced by taking aspirin or ibuprofen 30 minutes before dosing, by dividing the total daily dose into smaller doses taken more often, or by using an extended-release product (eg, Niaspan).
- Niacin can cause liver injury. The risk is highest with older sustained-release formulations, and lowest with extended-release niacin tablets [Niaspan].
- Bile-acid sequestrants (eg, colestevlam) reduce LDL cholesterol levels by increasing the number of LDL receptors on hepatocytes. The mechanism is complex and begins with preventing reabsorption of bile acids in the intestine.

- Bile-acid sequestrants are not absorbed from the GI tract, and hence do not cause systemic adverse effects. However, they can cause constipation and other GI effects. (GI effects with one agent—colesevelam—are minimal.)
- Older bile-acid sequestrants form complexes with other drugs, and thereby prevent their absorption. Accordingly, oral medications should be administered 1 hour before the sequestrant or 4 hours after. With a newer sequestrant—colesevelam—these interactions are minimal.

- Ezetimibe lowers LDL cholesterol by reducing cholesterol absorption in the small intestine.
- Like the statins, ezetimibe can cause muscle injury.
- Gemfibrozil and other fibrates are the most effective drugs for lowering TG levels.
- Like the statins, the fibrates can cause muscle injury.

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Summary of Major Nursing Implications*

IMPLICATIONS THAT APPLY TO ALL DRUGS THAT LOWER LDL CHOLESTEROL

Preadministration Assessment

Baseline Data

Obtain laboratory values for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs).

Identifying CHD Risk Factors

The patient history and physical examination should identify CHD risk factors. These include smoking, obesity, advancing age (men over 45 years, women over 55 years), family history of premature CHD, a personal history of cerebrovascular or peripheral vascular disease, reduced levels of HDL cholesterol (below 40 mg/dL), and hypertension.

In the past, diabetes was considered a CHD risk factor. However, because the association between diabetes and CHD is so strong, diabetes is now considered a CHD risk equivalent (ie, it poses the same 10-year risk of a major coronary event as CHD itself).

Measures to Enhance Therapeutic Effects

Diet Modification

Diet modification should precede and accompany drug therapy for elevated LDL cholesterol. **Inform patients about the importance of diet in controlling cholesterol levels and arrange for dietary counseling.** Advise patients to limit consumption of cholesterol (to below 200 mg/day) and saturated fat (to below 7% of caloric intake) and to follow the other dietary recommendations listed in Tables 50-7 and 50-8. If these measures fail to reduce LDL cholesterol to the target level, advise patients to add soluble fiber and plant stanols or sterols to the regimen.

Exercise

Regular exercise can reduce LDL cholesterol and elevate HDL cholesterol, thereby reducing the risk of CHD. **Help the patient establish an appropriate exercise program.**

Reduction of CHD Risk Factors

Correctable CHD risk factors should be addressed. **Encourage smokers to quit. Encourage obese patients to lose weight.** Disease states that promote CHD—diabetes mellitus and hypertension—must be treated.

Promoting Compliance

Drug therapy for elevated LDL cholesterol must continue lifelong; if drugs are withdrawn, cholesterol levels will return to pretreatment values. **Inform patients about the need for continuous therapy, and encourage them to adhere to the prescribed regimen.**

HMG-COA REDUCTASE INHIBITORS (STATINS)

Atorvastatin
Fluvastatin
Lovastatin
Pitavastatin
Pravastatin
Rosuvastatin
Simvastatin

In addition to the implications discussed below, *see above* for implications that apply to all drugs that lower LDL cholesterol.

Preadministration Assessment

Therapeutic Goal

Statins, in combination with diet modification and exercise, are used primarily to lower levels of LDL cholesterol. Additional indications are shown in Table 50-11.

Baseline Data

Obtain a baseline lipid profile, consisting of total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs). Also, obtain baseline LFTs and a CK level.

Identifying High-Risk Patients

Statins are *contraindicated* for patients with viral or alcoholic hepatitis and for women who are pregnant.

Exercise *caution* in patients with nonalcoholic fatty liver disease, in those who consume alcohol to excess, and in those taking fibrates or ezetimibe, or agents that inhibit CYP3A4 (eg, cyclosporine, erythromycin, ketoconazole, ritonavir). Use *rosuvastatin* with *caution* in Asian patients.

Implementation: Administration

Route

Oral.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Administration

Instruct patients to take lovastatin with the evening meal; all other statins can be administered without regard to meals. Advise patients that dosing in the evening is preferred for all statins.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Cholesterol levels should be monitored monthly early in treatment and at longer intervals thereafter.

Minimizing Adverse Effects

Statins are very well tolerated. Side effects are uncommon, and serious adverse effects—hepatotoxicity and myopathy—are relatively rare.

Hepatotoxicity. Statins can injure the liver, but jaundice and other clinical signs are rare. Liver function should be assessed before treatment and every 6 to 12 months thereafter (see Table 50-10). If serum transaminase becomes persistently excessive (more than 3 times the ULN), statins should be discontinued. Statins should be avoided in patients with alcoholic or viral hepatitis, but may be used in patients with nonalcoholic fatty liver disease.

Myopathy. Statins can cause muscle injury. If statins are not withdrawn, injury may progress to severe myositis or potentially fatal rhabdomyolysis. **Inform patients about the risk of myopathy, and instruct them to notify the prescriber if unexplained muscle pain or tenderness develops.** If muscle pain does develop, the CK level should be measured, and, if it is more than 10 times the ULN, the statin should be withdrawn.

Minimizing Adverse Interactions

The risk of myopathy is increased by (1) gemfibrozil, fenofibrate, and ezetimibe, which promote myopathy themselves; and by (2) inhibitors of CYP3A4—such as cyclosporine, macrolide antibiotics (eg, erythromycin), azole antifungal drugs (eg, ketoconazole), and HIV protease inhibitors (eg, ritonavir)—which can cause statin levels to rise. The combination of a statin with any of these drugs should be used with caution.

Use in Pregnancy

Statins are contraindicated during pregnancy. **Inform women of child-bearing age about the potential for fetal harm and warn them against becoming pregnant.** If pregnancy occurs, statins should be withdrawn.

NIACIN (NICOTINIC ACID)

In addition to the implications discussed below, *see above* for implications that apply to all drugs that lower LDL cholesterol.

Preadministration Assessment

Therapeutic Goal

Niacin, in conjunction with diet modification and exercise, is used to reduce levels of LDL cholesterol, VLDLs, and TGs. It is also used to raise HDL cholesterol.

Baseline Data

Obtain laboratory values for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs). Obtain a baseline test of liver function.

Identifying High-Risk Patients

Niacin is *contraindicated* for patients with active liver disease or severe or recurrent gout.

Exercise *caution* in patients with diabetes mellitus, asymptomatic hyperuricemia, mild gout, and peptic ulcer disease.

Implementation: Administration

Formulations

Advise patients to use an immediate-release formulation (eg, Niacor) or an extended-release formulation (eg, Niaspan), but not a long-acting formulation (eg, Slo-Niacin).

Route

Oral.

Administration

Instruct patients to take niacin with meals to reduce GI upset.

Measures to Enhance Therapeutic Effects

Dietary Therapy

Diet modification should precede and accompany drug therapy for elevated TGs and VLDLs. **Inform patients about the importance of diet in controlling lipid levels and arrange for dietary counseling.** In addition to following the guidelines presented above for all drugs that reduce LDL cholesterol, patients with hypertriglyceridemia should restrict consumption of alcohol and other sources of triglycerides.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Blood lipid levels should be monitored monthly early in treatment and at longer (3- to 6-month) intervals thereafter.

Minimizing Adverse Effects

Flushing. Niacin causes flushing of the face, neck, and ears in most patients. **Advise patients that flushing can be reduced by taking 325 mg of aspirin 30 minutes before each dose, or by using an extended-release product (eg, Niaspan).**

Hepatotoxicity. Niacin may injure the liver, causing jaundice or other symptoms. Liver function should be assessed before treatment and periodically thereafter. Liver injury is least likely with Niaspan, an extended-release formulation. Other long-acting products—sustained-release, controlled-release, or timed-release (eg, Slo-Niacin)—should be avoided, owing to increased risk of liver damage. Use with any statin also increases the risks.

Hyperglycemia. Niacin may cause hyperglycemia and reduced glucose tolerance. Blood glucose should be monitored frequently. Exercise caution in patients with diabetes.

Hyperuricemia. Niacin can elevate blood levels of uric acid. Exercise caution in patients with gout, and even in patients who have hyperuricemia but no symptoms of gout.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

BILE-ACID SEQUESTRANTS

Cholestyramine
 Colesevelam
 Colestipol

In addition to the implications discussed below, *see above* for implications that apply to all drugs that lower LDL cholesterol.

Preadministration Assessment

Therapeutic Goal

Bile-acid sequestrants, in conjunction with diet modification and exercise (and a statin if necessary), are used to reduce elevated levels of LDL cholesterol.

Baseline Data

Obtain laboratory values for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs).

Implementation: Administration

Route

Oral.

Administration

Instruct patients to mix cholestyramine powder and colestipol granules with water, fruit juice, soup, or pulpy fruit (eg, applesauce, crushed pineapple) to reduce the risk of esophageal irritation and impaction. Inform patients that the sequestrants are not water soluble, and hence the mixtures will be cloudy suspensions, not clear solutions.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Cholesterol levels should be monitored monthly early in treatment and at longer intervals thereafter.

Minimizing Adverse Effects

Constipation. *Cholestyramine* and *colestipol*—but not *colesevelam*—can cause constipation. Inform patients that constipation can be minimized by increasing dietary fiber and fluids. A mild laxative may be used if needed. Instruct patients taking *cholestyramine* or *colestipol* to notify the prescriber if constipation becomes bothersome, in which case a switch to *colesevelam* should be considered.

Vitamin Deficiency. *Cholestyramine* and *colestipol*—but not *colesevelam*—can impair absorption of fat-soluble vitamins (A, D, E, and K). Vitamin supplements may be required. *Colesevelam* does not reduce vitamin absorption.

Minimizing Adverse Interactions. *Cholestyramine* and *colestipol*—but not *colesevelam*—can bind with other drugs and prevent their absorption. Advise patients to administer other medications 1 hour before these sequestrants or 4 hours after.

GEMFIBROZIL

Preadministration Assessment

Therapeutic Goal

Gemfibrozil, in conjunction with diet modification, is used to reduce elevated levels of TGs (VLDLs). The drug is not very effective at lowering LDL cholesterol. It may also be used to raise low levels of HDL cholesterol.

Baseline Data

Obtain laboratory values for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs).

Identifying High-Risk Patients

Gemfibrozil is *contraindicated* for patients with liver disease, severe renal dysfunction, and gallbladder disease.

Use with *caution* in patients taking statins or warfarin.

Implementation: Administration

Route

Oral.

Administration

Instruct patients to administer gemfibrozil 30 minutes before the morning and evening meals.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Obtain periodic tests of blood lipids.

Minimizing Adverse Effects

Gallstones. Gemfibrozil increases gallstone development. Inform patients about symptoms of gallbladder disease (eg, upper abdominal discomfort, intolerance of fried foods, bloating), and instruct them to notify the prescriber if these develop.

Myopathy. Gemfibrozil can cause muscle damage. Warn patients to report any signs of muscle injury, such as tenderness, weakness, or unusual muscle pain.

Liver Disease. Gemfibrozil may disrupt liver function. Cancer of the liver may also be a risk. Obtain periodic tests of liver function.

Minimizing Adverse Interactions

Warfarin. Gemfibrozil enhances the effects of warfarin, thereby increasing the risk of bleeding. Obtain more frequent measurements of prothrombin time and assess the patient for signs of bleeding. Reduction of warfarin dosage may be required, and reassessment and readjustment of the warfarin dosage may be needed if the fibrates are stopped.

Statins. Gemfibrozil and statins both cause muscle injury. Risks rise when both are used. Use the combination with caution.

*Patient education information is highlighted as blue text.

Drugs for Angina Pectoris

Determinants of Cardiac Oxygen Demand and Oxygen Supply

Angina Pectoris: Pathophysiology and Treatment Strategy

Chronic Stable Angina (Exertional Angina)

Variant Angina (Prinzmetal's Angina, Vasospastic Angina)

Unstable Angina

Organic Nitrates

Nitroglycerin

Isosorbide Mononitrate and Isosorbide Dinitrate

Amyl Nitrite

Beta Blockers

Calcium Channel Blockers

Ranolazine

Revascularization Therapy: CABG and PCI

Summary of Treatment Measures

Guidelines for Management of Chronic Stable Angina

Management of Variant Angina

Angina pectoris is defined as sudden pain beneath the sternum, often radiating to the left shoulder, left arm, and jaw. Anginal pain is precipitated when the oxygen supply to the heart is insufficient to meet oxygen demand. Most often, angina occurs secondary to atherosclerosis of the coronary arteries. Hence, angina should be seen as a symptom of a disease and not as a disease in its own right. In the United States, over 7 million people have chronic stable angina; about 350,000 new cases develop annually.

Drug therapy of angina has two goals: (1) prevention of myocardial infarction (MI) and death and (2) prevention of myocardial ischemia and anginal pain. Two types of drugs are employed to decrease the risk of MI and death: cholesterol-lowering drugs and antiplatelet drugs. These agents are discussed in Chapters 50 and 52, respectively.

In this chapter, we focus on antianginal drugs (ie, drugs that prevent myocardial ischemia and anginal pain). There are three main families of antianginal agents: *organic nitrates* (eg, nitroglycerin), *beta blockers* (eg, propranolol), and *calcium channel blockers* (eg, verapamil). In addition, a fourth agent—*ranolazine*—can be combined with these drugs to supplement their effects. Most of the chapter focuses on the organic nitrates. Beta blockers and calcium channel blockers are discussed at length in previous chapters, and hence consideration here is limited to their use in angina.

DETERMINANTS OF CARDIAC OXYGEN DEMAND AND OXYGEN SUPPLY

Before discussing angina pectoris, we need to review the major factors that determine cardiac oxygen demand and supply.

Oxygen Demand. The principal determinants of cardiac oxygen demand are heart rate, myocardial contractility, and, most importantly, intramyocardial wall tension. Wall tension is determined by two factors: cardiac preload and cardiac afterload. (Preload and afterload are defined in Chapter 43.) In summary, cardiac oxygen demand is determined by (1) heart rate, (2) contractility, (3) preload, and (4) afterload. Drugs that reduce these factors reduce oxygen demand.

Oxygen Supply. Cardiac oxygen supply is determined by myocardial blood flow. Under resting conditions, the heart extracts nearly all of the oxygen delivered to it by the coronary vessels. Hence, the only way to accommodate an increase in oxygen demand is to increase blood flow. When oxygen demand increases, coronary arterioles dilate; the resultant decrease in vascular resistance allows blood flow to increase. During exertion, coronary blood flow increases four- to fivefold. It is important to note that myocardial perfusion takes place only during diastole (ie, when the heart relaxes). Perfusion does not take place during systole. Why? Because the vessels that supply the myocardium are squeezed shut when the myocardium contracts.

ANGINA PECTORIS: PATHOPHYSIOLOGY AND TREATMENT STRATEGY

Angina pectoris has three forms: (1) *chronic stable angina* (exertional angina), (2) *variant angina* (Prinzmetal's or vasospastic angina), and (3) *unstable angina*. Our focus is on stable angina and variant angina. Consideration of unstable angina is brief.

Chronic Stable Angina (Exertional Angina)

Pathophysiology. Stable angina is triggered most often by an increase in physical activity. Emotional excitement, large meals, and cold exposure may also precipitate an attack. Because stable angina usually occurs in response to strain, this condition is also known as *exertional angina* or *angina of effort*.

The underlying cause of exertional angina is coronary artery disease (CAD), a condition characterized by deposition of fatty plaque in the arterial wall. If an artery is only partially blocked by plaque, blood flow will be reduced and angina pectoris will result. However, if complete vessel blockage occurs, blood flow will stop and MI (heart attack) will result.

The impact of CAD on the balance between myocardial oxygen demand and oxygen supply is illustrated in Figure 51-1. As depicted, in both the healthy heart and the heart with CAD, oxygen supply and oxygen demand are in balance during rest. (In the presence of CAD, resting oxygen demand is met through dilation of arterioles distal to the partial occlusion. This dilation reduces resistance to blood flow and thereby compensates for the increase in resistance created by plaque.)

The picture is very different during exertion. In the healthy heart, as cardiac oxygen demand rises, coronary arterioles dilate, causing blood flow to increase. The increase keeps oxygen supply in balance with oxygen demand. By contrast, in people with CAD, arterioles in the affected region are already fully dilated during rest. Hence, when exertion occurs, there is no way to increase blood flow to compensate for the increase in oxygen demand. The resultant imbalance between oxygen supply and oxygen demand causes anginal pain.

Treatment Strategy. The goal of antianginal therapy is to reduce the intensity and frequency of anginal attacks. Because anginal pain results from an imbalance between oxygen supply and oxygen demand, logic dictates two possible remedies: (1) increase cardiac oxygen supply or (2) decrease oxy-

gen demand. Since the underlying cause of stable angina is occlusion of the coronary arteries, there is little we can do to increase cardiac oxygen supply. Hence, the first remedy is not a real option. Consequently, all we really can do is *decrease cardiac oxygen demand*. As discussed above, oxygen demand can be reduced with drugs that decrease heart rate, contractility, afterload, and preload.

Overview of Therapeutic Agents. Stable angina can be treated with three main types of drugs: *organic nitrates*, *beta blockers*, and *calcium channel blockers*. As noted above, *nifedipine* can be combined with these drugs for additional benefit. All four groups relieve the pain of stable angina primarily by decreasing cardiac oxygen demand (Table 51-1). Please note that drugs only provide symptomatic relief; they do not affect the underlying pathology. To reduce the risk of MI, all patients should receive an antiplatelet drug (eg, aspirin) unless it is contraindicated. Other measures to reduce the risk of infarction are discussed later under *Drugs Used to Prevent Myocardial Infarction and Death*.

Non-drug Therapy. Patients should attempt to avoid factors that can precipitate angina. These include overexertion, heavy meals, emotional stress, and exposure to cold.

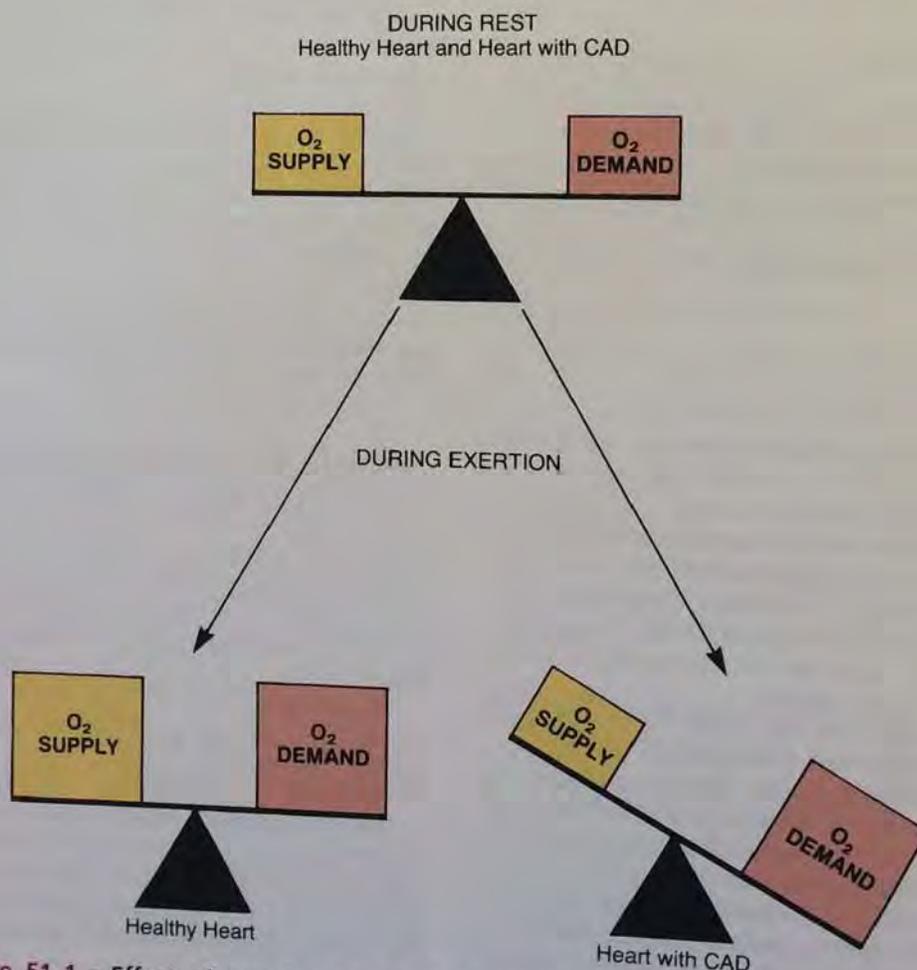


Figure 51-1 = Effect of exertion on the balance between oxygen supply and oxygen demand in the healthy heart and the heart with CAD. In the healthy heart, O₂ supply and O₂ demand are always in balance; during exertion, coronary arteries dilate, producing an increase in blood flow to meet the increase in O₂ demand. In the heart with CAD, O₂ supply and O₂ demand are in balance only during rest. During exertion, dilation of coronary arteries cannot compensate for the increase in O₂ demand, and an imbalance results.

TABLE 51-1 ■ Mechanisms of Antianginal Action

Drug Class	Mechanism of Pain Relief	
	Stable Angina	Variant Angina
Nitrates	Decrease oxygen demand by dilating veins, which decreases preload	Increase oxygen supply by relaxing coronary vasospasm
Beta Blockers	Decrease oxygen demand by decreasing heart rate and contractility	Not used
Calcium Channel Blockers	Decrease oxygen demand by dilating arterioles, which decreases afterload (all calcium blockers), and by decreasing heart rate and contractility (verapamil and diltiazem)	Increase oxygen supply by relaxing coronary vasospasm
Ranolazine	Appears to decrease oxygen demand, possibly by helping the myocardium generate energy more efficiently	Not used

Risk factors for stable angina should be corrected. Important among these are smoking, obesity, hypertension, hyperlipidemia, and a sedentary lifestyle. Patients should be strongly encouraged to quit smoking. Overweight patients should be given a restricted-calorie diet; the diet should be low in saturated fats (less than 7% of total caloric intake), and total fat content should not exceed 30% of caloric intake. The target weight is 110% of ideal or less. Patients with a sedentary lifestyle should be encouraged to establish a regular program of aerobic exercise (eg, walking, jogging, swimming, biking). Hypertension and hyperlipidemia are major risk factors and should be treated. These disorders are discussed in Chapters 47 and 50, respectively.

Variant Angina (Prinzmetal's Angina, Vasospastic Angina)

Pathophysiology. Variant angina is caused by *coronary artery spasm*, which restricts blood flow to the myocardium. Hence, as in stable angina, pain is secondary to insufficient oxygenation of the heart. In contrast to stable angina, whose symptoms occur primarily at times of exertion, variant angina can produce pain at any time, even during rest and sleep. Frequently, variant angina occurs in conjunction with stable angina. Alternative names for variant angina are *vasospastic angina* and *Prinzmetal's angina*.

Treatment Strategy. The goal is to reduce the incidence and severity of attacks. In contrast to stable angina, which is treated primarily by reducing oxygen demand, variant angina is treated by *increasing cardiac oxygen supply*. This makes sense in that the pain is caused by a reduction in oxygen supply, rather than by an increase in demand. Oxygen supply is increased with vasodilators, which prevent or relieve coronary artery spasm.

Overview of Therapeutic Agents. Vasospastic angina is treated with two groups of drugs: *calcium channel blockers* and *organic nitrates*. Both relax coronary artery spasm. Beta blockers and ranolazine, which are effective in stable angina, are not effective in variant angina. As with stable angina, therapy is symptomatic only; drugs do not alter the underlying pathology.

Unstable Angina

Pathophysiology. Unstable angina is a medical emergency. Symptoms result from severe CAD complicated by vasospasm, platelet aggregation, and transient coronary thrombi or emboli. The patient may present with either symptoms of angina at rest, new-onset exertional angina, or intensification of existing angina. Unstable angina poses a much greater risk of death than stable angina, but a smaller risk of death than MI. The risk of dying is greatest initially and then declines to baseline in about 2 months.

Treatment. In March of 2002, the American College of Cardiology (ACC) and the American Heart Association (AHA) issued updated guidelines for the diagnosis and management of unstable angina. The document—*ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction*—is available free online at www.acc.org and www.americanheart.org. According to the guideline, the treatment strategy is to *maintain oxygen supply and decrease oxygen demand*. The goal is to reduce pain and prevent progression to MI or death. All patients should be hospitalized. Acute management consists of anti-ischemic therapy combined with antiplatelet and anticoagulation therapy.

Anti-ischemic therapy consists of

- Nitroglycerin—give the first dose sublingually (tablet or spray) and follow with IV therapy.
- A beta blocker—give the first dose IV if chest pain is ongoing. If beta blockers are contraindicated, substitute a nondihydropyridine calcium channel blocker (verapamil or diltiazem).
- Supplemental oxygen—for patients with cyanosis or respiratory distress.
- IV morphine sulfate—if pain is not relieved immediately by nitroglycerin, or if pulmonary congestion or severe agitation is present.
- An angiotensin-converting enzyme inhibitor—but only for patients with persistent hypertension, and only if they have left ventricular dysfunction or congestive heart failure.

Antiplatelet therapy, which should be started promptly, consists of

- Aspirin—continue indefinitely.
- Clopidogrel [Plavix]—continue for at least 1 month.
- Abciximab [ReoPro], a glycoprotein IIb/IIIa inhibitor—but only if angioplasty is planned.
- Eptifibatid [Integrilin] or tirofiban [Aggrastat] (both are glycoprotein IIb/IIIa inhibitors)—but only in high-risk patients with continuing ischemia, and only if angioplasty is *not* planned.

Anticoagulant therapy consists of subcutaneous low-molecular-weight heparin (eg, dalteparin [Fragmin]) or intravenous unfractionated heparin.

ORGANIC NITRATES

The organic nitrates are the oldest and most frequently used antianginal drugs. These agents relieve angina by causing vasodilation. Nitroglycerin, the most familiar organic nitrate, will serve as our prototype.

Nitroglycerin

Nitroglycerin has been used to treat angina since 1879. The drug is effective, fast acting, and inexpensive. Despite availability of newer antianginal agents, nitroglycerin remains the drug of choice for relieving an acute anginal attack.

Vasodilator Actions

Nitroglycerin acts directly on vascular smooth muscle (VSM) to promote vasodilation. At usual therapeutic doses, the drug acts primarily on *veins*. Dilation of arterioles is only modest.

The biochemical events that lead to vasodilation are outlined in Figure 51-2. The process begins with uptake of nitrate by VSM, followed by conversion of nitrate to its active form: *nitric oxide*. As indicated, conversion requires the presence of *sulfhydryl groups*. Nitric oxide then activates guanylyl cyclase, an enzyme that catalyzes the formation of cyclic GMP (cGMP). Through a series of reactions, elevation of cGMP leads to dephosphorylation of light-chain myosin in VSM. (Recall that, in all muscles, phosphorylated myosin interacts with actin to produce contraction.) As a result of dephosphorylation, myosin is unable to interact with actin, and hence VSM relaxes, causing vasodilation. For our purposes, the most important aspect of this sequence is the conversion of nitrate to its active form—nitric oxide—in the presence of a sulfhydryl source.

Mechanism of Antianginal Effects

Stable Angina. Nitroglycerin decreases the pain of exertional angina primarily by *decreasing cardiac oxygen demand*. Oxygen demand is decreased as follows: By dilating veins, nitroglycerin decreases venous return to the heart, and thereby decreases ventricular filling; the resultant decrease in wall tension (preload) decreases oxygen demand.

In patients with stable angina, nitroglycerin does not appear to increase blood flow to ischemic areas of the heart. This statement is based on two observations. First, nitroglycerin does not dilate atherosclerotic coronary arteries. Second, when nitroglycerin is injected directly into coronary arteries during an anginal attack, it does not relieve pain. Both observations suggest that pain relief results from effects of nitroglycerin on peripheral blood vessels—not from effects on coronary blood flow.

Variant Angina. In patients with variant angina, nitroglycerin acts by relaxing or preventing spasm in coronary arteries. Hence, the drug *increases oxygen supply*. It does not reduce oxygen demand.

Pharmacokinetics

Absorption. Nitroglycerin is *highly lipid soluble* and crosses membranes with ease. Because of this property, nitroglycerin can be administered by uncommon routes (sublingual, buccal, transdermal) as well as by more conventional routes (oral, intravenous).

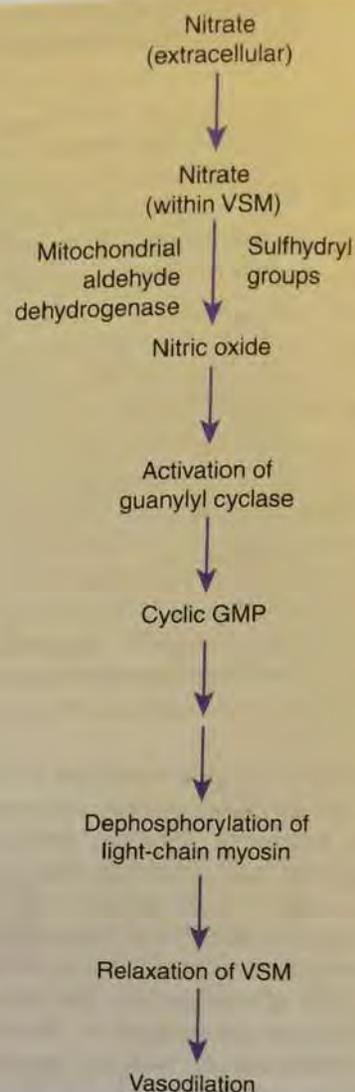


Figure 51-2 • Biochemistry of nitrate-induced vasodilation. Note that sulfhydryl groups are needed to catalyze the conversion of nitrate to its active form, nitric oxide. If sulfhydryl groups are depleted from VSM, tolerance to nitrates will occur.

Metabolism. Nitroglycerin undergoes *rapid inactivation* by hepatic enzymes (organic nitrate reductases). As a result, the drug has a plasma half-life of only 5 to 7 minutes. When nitroglycerin is administered orally, most of each dose is destroyed on its first pass through the liver.

Adverse Effects

Nitroglycerin is generally well tolerated. Principal adverse effects—headache, hypotension, and tachycardia—occur secondary to vasodilation.

Headache. Initial therapy can produce severe headache. This response diminishes over the first few weeks of treatment. In the meantime, headache can be reduced with aspirin, acetaminophen, or some other mild analgesic.

Orthostatic Hypotension. Relaxation of VSM causes blood to pool in veins when the patient assumes an erect posture. Pooling decreases venous return to the heart, which reduces cardiac output, causing blood pressure to fall. Symptoms of orthostatic hypotension include lightheadedness and dizziness. Patients should be instructed to sit or lie down if

these occur. Lying with the feet elevated promotes venous return, and can thereby help restore blood pressure.

Reflex Tachycardia. Nitroglycerin lowers blood pressure—primarily by decreasing venous return, and partly by dilating arterioles. By lowering blood pressure, the drug can activate the baroreceptor reflex, thereby causing sympathetic stimulation of the heart. The resultant increase in both heart rate and contractile force increases cardiac oxygen demand, which negates the benefits of therapy. Pretreatment with a beta blocker or verapamil (a calcium channel blocker that directly suppresses the heart) can prevent sympathetic cardiac stimulation.

Drug Interactions

Hypotensive Drugs. Nitroglycerin can intensify the effects of other hypotensive agents. Consequently, care should be exercised when nitroglycerin is used concurrently with beta blockers, calcium channel blockers, diuretics, and all other drugs that can lower blood pressure, including inhibitors of phosphodiesterase type 5 (PDE5). Also, patients should be advised to avoid alcohol.

Phosphodiesterase Type 5 Inhibitors. As discussed in Chapter 66, PDE5 inhibitors—sildenafil [Viagra], tadalafil [Cialis], and vardenafil [Levitra]—are used for erectile dysfunction. All three drugs can greatly intensify nitroglycerin-induced vasodilation. Life-threatening hypotension can result. Accordingly, concurrent use of PDE5 inhibitors with nitroglycerin is *absolutely contraindicated*.

What's the mechanism of the interaction? Nitroglycerin and the PDE5 inhibitors both increase cGMP (nitrates increase cGMP formation and PDE5 inhibitors decrease cGMP breakdown). Hence, if these drugs are combined, levels of cGMP can rise dangerously high, thereby causing excessive vasodilation and a precipitous drop in blood pressure.

Beta Blockers, Verapamil, and Diltiazem. These drugs can suppress nitroglycerin-induced tachycardia. Beta blockers do so by preventing sympathetic activation of beta₁-adrenergic receptors on the heart. Verapamil and diltiazem prevent tachycardia through direct suppression of pacemaker activity in the sinoatrial node.

Tolerance

Tolerance to nitroglycerin-induced vasodilation can develop rapidly (over the course of a single day). One possible mechanism is depletion of sulfhydryl groups in VSM: In the absence of sulfhydryl groups, nitroglycerin cannot be converted to nitric oxide, its active form. Another possible mechanism is reversible oxidative injury to mitochondrial aldehyde dehydrogenase, an enzyme needed to convert nitroglycerin into nitric oxide. Patients who develop tolerance to nitroglycerin display cross-tolerance to all other nitrates and vice versa. Development of tolerance is most likely with high-dose therapy and uninterrupted therapy. To prevent tolerance, nitroglycerin and other nitrates should be used in the lowest effective dosages; long-acting formulations (eg, patches, sustained-release preparations) should be used on an intermittent schedule that allows at least 8 drug-free hours every day, usually during the night. If pain occurs during the nitrate-free interval, it can be managed with sparing use of a short-acting nitrate (eg, sublingual nitroglycerin) or by adding a beta blocker or calcium channel blocker to the regimen. Tolerance can be reversed by withholding nitrates for a short time.

TABLE 51-2 ■ Organic Nitrates: Time Course of Action

Drug and Dosage Form	Onset*	Duration†
Nitroglycerin		
Sublingual tablets	Rapid (1–3 min)	Brief (30–60 min)
Translingual spray	Rapid (2–3 min)	Brief (30–60 min)
Oral capsules, SR	Slow (20–45 min)	Long (3–8 hr)
Transdermal patches	Slow (30–60 min)	Long (24 hr) [‡]
Topical ointment	Slow (20–60 min)	Long (2–12 hr)
Isosorbide Mononitrate		
Oral tablets, IR	Slow (30–60 min)	Long (6–10 hr)
Oral tablets, SR	Slow (30–60 min)	Long (7–12 hr)
Isosorbide Dinitrate		
Sublingual tablets	Rapid (2–5 min)	Long (1–3 hr)
Oral tablets, IR	Slow (20–40 min)	Long (4–6 hr)
Oral tablets, SR	Slow (30 min)	Long (6–8 hr)
Oral capsules, SR	Slow (30 min)	Long (6–8 hr)

IR = immediate release, SR = sustained release.

*Nitrates with a *rapid* onset have two uses: (1) termination of an ongoing anginal attack and (2) short-term prophylaxis prior to anticipated exertion. Of the rapid-acting nitrates, nitroglycerin (sublingual tablet or translingual spray) is preferred to the others for terminating an ongoing attack.

†*Long-acting* nitrates are used for sustained prophylaxis (prevention) of anginal attacks. All cause tolerance if used without interruption.

‡Although patches can release nitroglycerin for up to 24 hours, they should be removed after 12 to 14 hours to avoid tolerance.

Preparations and Routes of Administration

Nitroglycerin is available in several formulations for administration by several routes. This proliferation of dosage forms reflects efforts to delay hepatic metabolism, and thereby prolong therapeutic effects.

All nitroglycerin preparations produce qualitatively similar responses; differences relate only to onset and duration of action (Table 51-2). With two preparations, effects begin rapidly (in 1 to 5 minutes) and then fade in less than 1 hour. With three others, effects begin slowly but last several hours. Only one preparation—sublingual tablets—has both a rapid onset and long duration.

Applications of specific preparations are based on their time course. Preparations with a *rapid onset* are employed to *terminate an ongoing anginal attack*. When used for this purpose, rapid-acting preparations are administered as soon as pain begins. Rapid-acting preparations can also be used for *acute prophylaxis of angina*. For this purpose, they are taken just prior to anticipated exertion. *Long-acting preparations* are used to provide *sustained protection* against anginal attacks. To provide protection, they are administered on a fixed schedule (but one that permits at least 8 drug-free hours each day).

Trade names and dosages for nitroglycerin preparations are summarized in Table 51-3.

Sublingual Tablets. When administered sublingually (beneath the tongue), nitroglycerin is absorbed directly through the oral mucosa and into the bloodstream. Hence, unlike orally administered drugs, which must pass through the

TABLE 51-3 • Organic Nitrates: Trade Names and Dosages

Drug and Formulation	Trade Name	Usual Dosage
Nitroglycerin		
Sublingual tablets	Nitrostat	0.3–0.6 mg as needed
Translingual spray	Nitrolingual Pumpspray, NitroMist	1–2 sprays (up to 3 sprays in a 15-min period)
Oral capsules, SR	Nitro-Time	2.5–6.5 mg 3 or 4 times daily; to avoid tolerance, administer only once or twice daily; do not crush or chew
Transdermal patches	Minitran, Nitro-Dur, Transderm Nitro♦, Trinipatch♦	1 patch a day; to avoid tolerance, remove after 12–14 hr, allowing 10–12 patch-free hours each day. Patches come in sizes that release 0.1–0.8 mg/hr
Topical ointment	Nitro-Bid	1–2 inches (7.5–40 mg) every 4–8 hr
Intravenous	Generic only	5 mcg/min initially, then increased gradually as needed (max 200 mcg/min); tolerance develops with prolonged continuous infusion
Isosorbide Mononitrate		
Oral tablets, IR	ISMO, Monoket	20 mg twice daily; to avoid tolerance, take the first dose upon awakening and the second dose 7 hr later
Oral tablets, SR	Imdur	60–240 mg once a day; do not crush or chew
Isosorbide Dinitrate		
Sublingual tablets	Generic only	2.5–15 mg every 4–6 hr; do not crush or chew
Oral tablets, IR	Isordil Titradoso	5–80 mg every 6 hr; to avoid tolerance, take only 2 or 3 times daily, with the last dose no later than 7:00 PM
Oral tablets, SR	Generic only	40 mg every 6–12 hr; to avoid tolerance, take only once or twice daily (at 8:00 AM and 2:00 PM)
Oral capsules, SR	Dilatrate-SR	40 mg every 6–12 hr; to avoid tolerance, take only once or twice daily (at 8:00 AM and 2:00 PM)
Amyl Nitrite		
Inhalant	Generic only	0.18 or 0.3 mL

IR = immediate release, SR = sustained release.

liver on their way to the systemic circulation, sublingual nitroglycerin bypasses the liver, and thereby temporarily avoids inactivation. Because the liver is bypassed, sublingual doses can be low (between 0.3 and 0.6 mg). These doses are about 10 times lower than those required when nitroglycerin is dosed orally.

Effects of sublingual nitroglycerin begin rapidly—in 1 to 3 minutes—and persist up to 1 hour. Because sublingual administration works fast, this route is ideal for (1) terminating an ongoing attack and (2) short-term prophylaxis when exertion is anticipated.

To terminate an acute anginal attack, sublingual nitroglycerin should be administered as soon as pain begins. Administration should not be delayed until the pain has become severe. According to current guidelines, if pain is not relieved in 5 minutes, the patient should call 911 or report to an emergency department, since anginal pain that does not respond to nitroglycerin may indicate MI. While awaiting emergency care, the patient can take 1 more tablet, and then a third tablet 5 minutes later.

Sublingual administration is unfamiliar to most patients. Accordingly, education is needed. The patient should be instructed to place the tablet under the tongue and leave it there while it dissolves. Nitroglycerin tablets formulated for sublingual use are ineffective if swallowed.

Nitroglycerin tablets available today have good chemical stability. When stored properly, they should remain effective until the expiration date on the container. To ensure good

stability, the tablets should be stored moisture free at room temperature in their original container, which should be closed tightly after each use.

Sustained-Release Oral Capsules. Sustained-release oral capsules are intended for long-term prophylaxis only; these formulations cannot act fast enough to terminate an ongoing anginal attack. Sustained-release capsules contain a large dose of nitroglycerin that is slowly absorbed across the GI wall. In theory, doses are large enough so that amounts of nitroglycerin sufficient to produce a therapeutic response will survive passage through the liver. Because they produce sustained blood levels of nitroglycerin, these formulations can cause tolerance. To reduce the risk of tolerance, these products should be taken only once or twice daily. Patients should be instructed to swallow sustained-release capsules intact.

Transdermal Delivery Systems. Nitroglycerin patches, which look like Band-Aids, contain a reservoir from which nitroglycerin is slowly released. Following release, the drug is absorbed through the skin and then into the blood. The rate of release is constant for any particular transdermal patch and, depending upon the patch used, can range from 0.1 to 0.8 mg/hr. Effects begin within 30 to 60 minutes and persist as long as the patch remains in place (up to 14 hours). Patches are applied once daily to a hairless area of skin. The site should be rotated to avoid local irritation.

Tolerance develops if patches are used continuously (24 hours a day every day). Accordingly, a daily “patch-free” interval of 10 to 12 hours is recommended. This can be ac-

complished by applying a new patch each morning, leaving it in place for 12 to 14 hours, and then removing it in the evening.

Because of their long duration, patches are well suited for sustained prophylaxis. Since patches have a delayed onset, they cannot be used to abort an ongoing attack.

Translingual Spray. Nitroglycerin can be delivered to the oral mucosa using a metered-dose spray device. Each activation delivers a 0.4-mg dose. Indications for nitroglycerin spray are the same as for sublingual tablets: suppression of an acute anginal attack and prophylaxis of angina when exertion is anticipated. As with sublingual tablets, no more than three doses should be administered within a 15-minute interval. *Instruct patients not to inhale the spray.*

Topical Ointment. Topical nitroglycerin ointment is used for sustained protection against anginal attacks. The ointment is applied to the skin of the chest, back, abdomen, or anterior thigh. (Since nitroglycerin acts primarily by dilating peripheral veins, there is no mechanistic advantage to applying topical nitroglycerin directly over the heart.) Following topical application, nitroglycerin is absorbed through the skin and then into the blood. Effects begin in 20 to 60 minutes and may persist up to 12 hours.

Nitroglycerin ointment (2%) is dispensed from a tube, and the length of the ribbon squeezed from the tube determines dosage. (One inch contains about 15 mg of nitroglycerin.) The usual adult dosage is 1 to 2 inches applied every 4 to 8 hours. The ointment should be spread over an area at least 2.5 inches by 3.5 inches and then covered with plastic wrap. Sites of application should be rotated to minimize skin irritation. As with other long-acting formulations, uninterrupted use can cause tolerance.

Intravenous Infusion. Intravenous nitroglycerin is employed only rarely to treat angina pectoris. When used for angina, IV nitroglycerin is limited to patients who have failed to respond to other medications. Additional uses of IV nitroglycerin include treatment of heart failure associated with acute MI, treatment of perioperative hypertension, and production of controlled hypotension for surgery.

Intravenous nitroglycerin has a very short duration, and hence continuous infusion is required. The infusion rate is 5 mcg/min initially and then is increased gradually until an adequate response has been achieved. Heart rate and blood pressure must be monitored continuously.

Stock solutions of nitroglycerin must be diluted for IV use. Since ampules of nitroglycerin prepared by different manufacturers can differ in both volume and nitroglycerin concentration, the label must be read carefully when dilutions are made.

Administer using a glass IV bottle and the administration set provided by the manufacturer. Nitroglycerin absorbs into standard polyvinyl chloride tubing, and hence this tubing should be avoided.

Discontinuing Nitroglycerin

Long-acting preparations (transdermal patches, topical ointment, sustained-release oral tablets or capsules) should be discontinued slowly. If they are withdrawn abruptly, vasospasm may result.

Summary of Therapeutic Uses

Acute Therapy of Angina. For acute treatment of angina pectoris, nitroglycerin is administered in sublingual tablets and a translingual spray. Both formulations can be used to abort an ongoing anginal attack and to provide prophylaxis in anticipation of exertion.

Sustained Therapy of Angina. For sustained prophylaxis against angina, nitroglycerin is administered in the following formulations: transdermal patches, topical ointment, and sustained-release oral capsules.

Intravenous Therapy. Intravenous nitroglycerin is indicated for perioperative control of blood pressure, production of controlled hypotension during surgery, and treatment of heart failure associated with acute MI. In addition, IV nitroglycerin is used to treat unstable angina and chronic angina when symptoms cannot be controlled with preferred medications.

Isosorbide Mononitrate and Isosorbide Dinitrate

Both of these drugs have pharmacologic actions identical to those of nitroglycerin. Both drugs are used for angina, both are taken orally, and both produce headache, hypotension, and reflex tachycardia. Differences between them relate only to route of administration and time course of action. Time course determines whether a particular drug or dosage form will be used for acute therapy, sustained prophylaxis, or both. As with nitroglycerin, tolerance can develop to long-acting preparations. To avoid tolerance, the dosing schedule for long-acting preparations should allow at least 12 drug-free hours a day. Time courses are summarized in Table 51-2. Trade names and dosages are summarized in Table 51-3. A fixed-dose combination of isosorbide dinitrate plus hydralazine, soled as BiDiL, is discussed in Chapter 48 (Drugs for Heart Failure).

Amyl Nitrite

Amyl nitrite is an ultrashort-acting agent used to treat acute episodes of angina pectoris. The drug has the same mechanism as nitroglycerin. Amyl nitrite is a volatile liquid dispensed in glass ampules. For administration, 1 ampule (0.18 or 0.3 mL) is crushed, allowing the volatile compound to be inhaled. Effects begin within 30 seconds and terminate in 3 to 5 minutes. Amyl nitrite is highly flammable and hence should not be used near flame. The drug is reputed to intensify sexual orgasm and has been abused for that purpose (see Chapter 40).

BETA BLOCKERS

Beta blockers (eg, propranolol, metoprolol) are first-line drugs for *angina of effort*, but are *not* effective against vasospastic angina. When administered on a fixed schedule, beta blockers can provide sustained protection against effort-induced anginal pain. Exercise tolerance is increased and the frequency and intensity of anginal attacks are lowered. All of the beta blockers appear equally effective. In addition to reducing anginal pain, beta blockers decrease the risk of death, especially in patients with a prior MI.

Beta blockers reduce anginal pain primarily by *decreasing cardiac oxygen demand*. How? Primarily through blockade of beta₁ receptors in the heart, which decreases heart rate and contractility. Beta blockers reduce oxygen demand further by causing a modest reduction in arterial pressure (afterload). In addition to decreasing oxygen demand, beta blockers help increase oxygen supply. How? By slowing heart rate, they increase time in diastole, and thereby increase the time during which blood flows through myocardial vessels. (Recall that blood does not flow in these vessels during systole.) In patients taking vasodilators (eg, nitroglycerin), beta blockers provide the additional benefit of blunting reflex tachycardia.

For treatment of stable angina, dosage should be low initially and then gradually increased. The dosing goal is to reduce resting heart rate to 50 to 60 beats/min, and limit exertional heart rate to about 100 beats/min. Beta blockers should not be withdrawn abruptly, since doing so can increase the incidence and intensity of anginal attacks, and may even precipitate MI.

Beta blockers can produce a variety of adverse effects. Blockade of cardiac beta₁ receptors can produce *bradycardia*, *decreased atrioventricular (AV) conduction*, and *reduction of contractility*. Consequently, beta blockers should not be used by patients with sick sinus syndrome, heart failure, or second-degree or third-degree AV block. Blockade of beta₂ receptors in the lung can promote bronchoconstriction. Accordingly, beta blockers should be avoided by patients with asthma. If an asthmatic individual absolutely must use a beta blocker, a

beta₁-selective agent (eg, metoprolol) should be chosen. Beta blockers can mask signs of hypoglycemia, and therefore must be used with caution in patients with diabetes. Rarely, these drugs cause adverse central nervous system effects, including *insomnia, depression, and bizarre dreams*.

The basic pharmacology of the beta blockers is discussed in Chapter 18.

CALCIUM CHANNEL BLOCKERS

The calcium channel blockers (CCBs) used most frequently are *verapamil, diltiazem, and nifedipine* (a dihydropyridine-type calcium channel blocker). Accordingly, our discussion focuses on these three drugs. *All three* can block calcium channels in VSM, primarily in arterioles. The result is arteriolar dilation and reduction of peripheral resistance (afterload). In addition, all three can relax coronary vasospasm. *Verapamil* and *diltiazem* also block calcium channels in the heart, and can thereby decrease heart rate, AV conduction, and contractility.

Calcium channel blockers are used to treat both stable and variant angina. In *variant angina*, these drugs promote relaxation of coronary artery spasm, thereby *increasing cardiac oxygen supply*. In *stable angina*, they promote relaxation of peripheral arterioles; the resultant decrease in afterload *reduces cardiac oxygen demand*. Verapamil and diltiazem can produce modest additional reductions in oxygen demand by suppressing heart rate and contractility.

The major adverse effects of the CCBs are cardiovascular. Dilation of peripheral arterioles lowers blood pressure, and can thereby induce *reflex tachycardia*. This reaction is greatest with nifedipine and minimal with verapamil and diltiazem. Because of their suppressant effects on the heart, verapamil and diltiazem must be used cautiously in patients taking beta blockers and in patients with bradycardia, heart failure, or AV block. These precautions do not apply to nifedipine or other dihydropyridines.

The basic pharmacology of the CCBs is discussed in Chapter 45.

RANOLAZINE

Actions and Therapeutic Use

Ranolazine [Ranexa] represents the first new class of anti-anginal agents to be approved in more than 25 years. In clinical trials, the drug reduced the number of angina episodes per week and increased exercise tolerance. However, these benefits were modest, and were smaller in women than in men. Unlike most other antianginal drugs, ranolazine does not reduce heart rate, blood pressure, or vascular resistance. However, it *can* prolong the QT interval, and is subject to multiple drug interactions. How does ranolazine work? We know it can reduce accumulation of sodium and calcium in myocardial cells, and might thereby help the myocardium use energy more efficiently. However, the exact mechanism of action is unknown. Despite limited efficacy, many drug interactions, and a risk of dysrhythmias (see below), ranolazine is now approved as a first-line drug for angina. It may be combined with nitrates, beta blockers, amlodipine (a CCB), and other drugs used for angina treatment.

Pharmacokinetics

Absorption from the GI tract is highly variable, but not affected by food. Plasma levels peak 2 to 5 hours after dosing. In the liver, ranolazine undergoes rapid and extensive metabolism, mainly by CYP3A4 (the 3A4 isozyme of cytochrome P450). The drug has a plasma half-life of 7 hours, and is excreted in the urine (75%) and feces (25%), almost entirely as metabolites.

Adverse Effects

QT Prolongation. Ranolazine can cause a dose-related increase in the QT interval, and may thereby increase the risk of torsades de pointes, a serious ventricular dysrhythmia. Accordingly, the drug is contraindicated for patients with pre-existing QT prolongation and for those taking other drugs that can increase the QT interval. In addition, ranolazine is contraindicated for patients at risk of developing high levels of the drug—namely, patients with hepatic impairment or those taking drugs that inhibit CYP3A4. The issue of drug-induced QT prolongation is discussed further in Chapter 7 (Adverse Drug Reactions and Medication Errors).

Elevation of Blood Pressure. In patients with severe renal impairment, ranolazine can raise blood pressure by about 15 mm Hg. Accordingly, blood pressure should be monitored often in these people.

Other Adverse Effects. The most common adverse effects are constipation (8%), dizziness (5%), nausea (4%), and headache (3%).

Drug Interactions

CYP3A4 Inhibitors. Agents that inhibit CYP3A4 can increase levels of ranolazine, and can thereby increase the risk of torsades de pointes. Accordingly, moderate or strong CYP3A4 inhibitors should be avoided. Among these agents are grapefruit juice, HIV protease inhibitors (eg, ritonavir), macrolide antibiotics (eg, erythromycin), azole antifungal drugs (eg, itraconazole), and some calcium channel blockers (but not amlodipine).

QT Drugs. Drugs that prolong the QT interval (eg, quinidine, sotalol) can increase the risk of torsades de pointes in patients taking ranolazine, and hence should be avoided. Table 7-2 (see Chapter 7) presents a comprehensive list of QT drugs.

Calcium Channel Blockers. Most CCBs—but not amlodipine—can inhibit CYP3A4, and can thereby increase levels of ranolazine. Accordingly, when use of ranolazine plus a CCB is indicated, amlodipine is the only CCB that should be used.

Preparations, Dosage, and Administration

Ranolazine [Ranexa] is formulated in extended-release tablets (500 and 1000 mg) that should be swallowed intact, with or without food. Dosing begins at 500 mg twice daily, and may be increased to a maximum of 1000 mg twice daily. Ranolazine may be used in combination with a nitrate, beta blocker, or amlodipine (a CCB), and other drugs for angina.

REVASCULARIZATION THERAPY: CABG AND PCI

If drug therapy of angina fails to control symptoms, surgical revascularization should be considered. The two principal forms of revascularization are coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).

Coronary Artery Bypass Graft Surgery

CABG surgery is used to increase blood flow to ischemic areas of the heart. In this procedure, one end of a segment of healthy blood vessel (internal mammary artery or saphenous vein) is grafted onto the aorta, and the other end is connected to the diseased coronary artery at a point distal to the region of atherosclerotic plaque. Hence, the graft constitutes a shunt whereby blood flow can circumvent the occluded section of a diseased coronary vessel. Following surgery, most patients remain in the hospital for a week, and then recuperate for another 6 weeks at home. Once considered exotic, CABG surgery is now commonplace; more than 300,000 Americans undergo the procedure each year.

Vessel blockage can recur over time, thereby requiring repeat surgery. When an artery is used for the graft, the incidence of reblockage is only 4% after 10 years. In contrast, when a vein is used, the incidence of reblockage is nearly 50% after 10 years.

A relatively new procedure, called *minimally invasive direct coronary artery bypass* (MIDCAB) surgery, is an alternative to CABG surgery for some patients. MIDCAB surgery is much less invasive than CABG surgery, and therefore faster and cheaper. Furthermore, MIDCAB surgery is performed on the beating heart, and hence, heart-lung bypass machinery is not needed. At this time, MIDCAB surgery is used only to bypass blockage in the left ascending coronary artery.

Percutaneous Coronary Intervention

PCI is an alternative to CABG surgery for patients with stable angina. In most cases, PCI consists of balloon angioplasty coupled with placement of a stent, an expandable mesh tube that prevents the artery from collapsing after the balloon is withdrawn. When angioplasty is performed *without* a stent, a miniature catheter containing a deflated balloon is inserted into the femoral artery, threaded up into the aorta, and then manipulated into the occluded coronary artery. The balloon is then inflated, thereby flattening the obstruction and allowing blood to flow. When angioplasty is performed *with* a stent, the deflated balloon is placed within a collapsed stent at the start of the procedure. Then, when the catheter reaches the occluded artery, the balloon is inflated, thereby expanding the stent so that it presses against the arterial wall. With the stents employed today, rates of restenosis are about 10%, compared with 30% to 50% with angioplasty alone.

What causes stent restenosis? And how can we reduce it? Restenosis is caused by proliferation and migration of neointimal cells from the arterial wall. To help prevent restenosis, we now use *drug-eluting stents* (DES), rather than the *bare-metal stents* used in the past. What's a DES? It's a metal stent that has been coated with polymer that contains an antiproliferative drug. Following stent placement, the drug is slowly released over weeks to months, thereby causing sustained suppression of neointimal growth. With DES, the rate of restenosis is about 10%, compared with 20% to 30% with bare-metal stents.

Unfortunately, although DES reduce the risk of *restenosis*, they increase the risk of *late thrombosis* (ie, thrombosis that occurs months or even years after stent placement). Thrombosis occurs because suppression of neointimal proliferation prevents endothelial cells from growing over the stent. As a result, when platelets contact the exposed stent, they are likely to aggregate and trigger formation of a thrombus. To reduce

this risk, patients must undergo prolonged therapy with two oral antiplatelet drugs, typically aspirin combined with clopidogrel [Plavix] or prasugrel [Effient].

In the United States, most stents employ one of three drugs: *paclitaxel*, *sirolimus*, or *everolimus* (an analog of sirolimus). The paclitaxel- and sirolimus-eluting stents are considered first-generation devices, and the everolimus-eluting stent is considered a second-generation device. The everolimus-eluting stent is superior to the paclitaxel-eluting stent with respect to risk of restenosis, late thrombosis, and MI. Outcomes with the everolimus- and sirolimus-eluting stents are about the same, although rates of restenosis may be lower with the everolimus-eluting stent. Of note, outcomes with all three devices are nearly equal for patients with diabetes, who constitute between 20% and 30% of the people who undergo PCI.

Comparison of CABG Surgery with PCI

CABG surgery and PCI are equally safe and almost equally effective. The 5-year survival rate after either procedure is about 90%. However, in other respects, the procedures differ substantially. Compared with PCI, CABG surgery is more traumatic and more expensive, it requires a longer hospital stay, and recovery is slower. On the other hand, CABG surgery is more effective: coronary blood flow is better, relief of angina is superior, exercise tolerance is higher, and patients require less antianginal medication. Moreover, the incidence of reblockage after CABG surgery is lower. At this time, CABG surgery is considered the treatment of choice for patients with multivessel disease. For patients with single-vessel disease, either procedure is generally appropriate; the choice is based on patient preference.

SUMMARY OF TREATMENT MEASURES

Guidelines for Management of Chronic Stable Angina

In 1999, three organizations—the American Heart Association, the American College of Cardiology, and the American College of Physicians—American Society of Internal Medicine—joined forces to produce the first national guidelines on the management of chronic stable angina. The 1999 guidelines were updated in 2002 and again in 2007. Both updates—*ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina*, and *2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the Management of Patients with Chronic Stable Angina*—are available free online at circ.ahajournals.org. The discussion below reflects recommendations in these guidelines.

Treatment of stable angina has two objectives: (1) prevention of MI and death, and (2) reduction of cardiac ischemia and associated anginal pain. Although both goals are desirable, prevention of MI and death is clearly more important. Hence, if two treatments are equally effective at decreasing anginal pain, but one also decreases the risk of death, then the latter is preferred.

Drugs Used to Prevent Myocardial Infarction and Death

We now have medical treatments that can decrease the risk of MI and death in patients with chronic stable angina. Therapy directed at preventing MI and death is a new paradigm in the

management of stable angina, and all practitioners should become familiar with it.

Antiplatelet Drugs. These agents decrease platelet aggregation and thereby decrease the risk of thrombus formation in coronary arteries. The most effective agents are *aspirin*, *clopidogrel*, and *prasugrel*. In patients with stable angina, low-dose aspirin produces a 33% decrease in the risk of adverse cardiovascular events. Benefits of clopidogrel seem equal to those of aspirin, although they are not as well documented. The guidelines recommend that all patients with stable angina take 75 to 162 mg of aspirin daily, unless there is a specific reason not to. Aspirin, clopidogrel, and other antiplatelet drugs are discussed in Chapter 52.

Cholesterol-Lowering Drugs. Elevated cholesterol is a major risk factor for coronary atherosclerosis. Drugs that lower cholesterol can slow the progression of CAD, stabilize atherosclerotic plaques, and even cause plaque regression. Therapies that reduce cholesterol are associated with decreased mortality from coronary heart disease. For example, in patients with established CAD, taking simvastatin can decrease the risk of mortality by 35%. Because of the well-established benefits of cholesterol-lowering therapy, the guidelines recommend that all patients with stable angina receive a cholesterol-lowering drug. The pharmacology of the cholesterol-lowering drugs is discussed in Chapter 50.

Angiotensin-Converting Enzyme (ACE) Inhibitors. There is strong evidence that, in patients with CAD, ACE inhibitors greatly reduce the incidence of adverse outcomes. In the Heart Outcomes Prevention Evaluation (HOPE) trial, for example, ramipril reduced the incidence of stroke, MI, and cardiovascular death. Among one subset of patients—those with diabetes—benefits were particularly striking. Ramipril decreased the risk of stroke by 33%, MI by 22%, and cardiovascular death by 37%. In addition, ramipril reduced the risk of nephropathy, retinopathy, and other microvascular complications of diabetes. Because of these well-documented benefits, the guidelines recommend ACE inhibitors for most patients with established CAD, and especially for those with diabetes. The pharmacology of the ACE inhibitors is discussed in Chapter 44.

Antianginal Agents: Drugs Used to Reduce Anginal Pain

The goal of antianginal therapy is to achieve complete (or nearly complete) elimination of anginal pain, along with a return to normal activities. This should be accomplished with a minimum of adverse drug effects.

The basic strategy of antianginal therapy is to provide baseline protection using one or more long-acting drugs (beta blocker, calcium channel blocker [CCB], long-acting nitrate) supplemented with sublingual nitroglycerin when breakthrough pain occurs. A flow plan for drug selection is shown in Figure 51-3. As indicated, treatment is approached sequentially. Progression from one step to the next is based on patient response. Some patients can be treated with a single long-acting drug, some require two or three, and some require revascularization.

Initial treatment consists of sublingual nitroglycerin plus a long-acting antianginal drug. As indicated in Figure 51-3, beta blockers are the preferred agents for baseline therapy. Why? Because they can decrease mortality, espe-

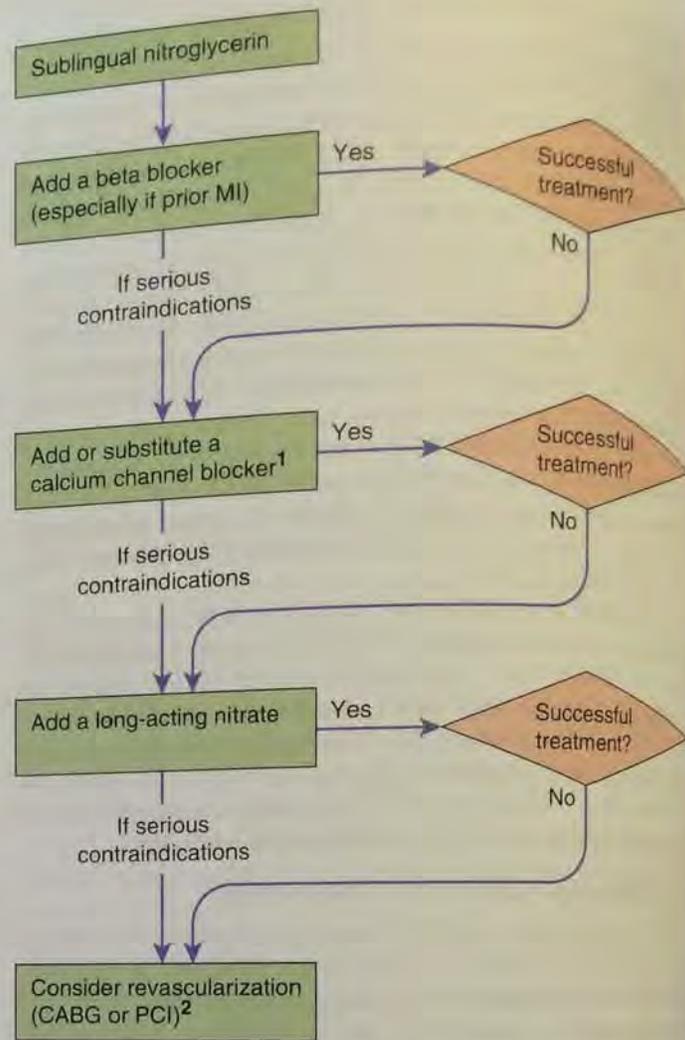


Figure 51-3 • Flow plan for antianginal drug selection in patients with chronic stable angina.

¹Avoid short-acting dihydropyridines.

²At any point in this process, based on coronary anatomy, severity of angina symptoms, and patient preference, it is reasonable to consider evaluation for coronary revascularization (PCI or CABG). Unless a patient is documented to have left main, three-vessel, or two-vessel CAD with significant stenosis of the proximal left anterior descending coronary artery, there is no demonstrated survival advantage associated with CABG or PCI in low-risk patients with chronic stable angina. Accordingly, medical therapy should be attempted in most patients before considering PCI or CABG. (Adapted from Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina]. 2002. Available online at circ.ahajournals.org).

cially in patients with a prior MI. In addition to providing prophylaxis, beta blockers suppress nitrate-induced reflex tachycardia.

If a beta blocker is inadequate, or if there are contraindications to beta blockade, a long-acting CCB should be added or substituted. Because CCBs do not promote bronchoconstriction, they are preferred to beta blockers for patients with asthma. Dihydropyridine-type CCBs (eg, nifedipine) lack

TABLE 51-4 ■ Choosing Between Beta Blockers and Calcium Channel Blockers for Treating Angina in Patients Who Have a Coexisting Condition

Coexisting Condition	Recommended Treatment (Alternative Treatment)	Drugs to Avoid
Medical Conditions		
Systemic hypertension	Beta blockers (long-acting, slow-release CCBs)	
Migraine or vascular headache	Beta blockers (verapamil or diltiazem)	
Asthma or COPD with bronchospasm	Verapamil or diltiazem	Beta blockers
Hyperthyroidism	Beta blockers	
Raynaud's disease	Long-acting, slow-release CCBs	Beta blockers
Type 1 diabetes	Beta blockers, particularly if prior MI, or long-acting, slow-release CCBs	
Type 2 diabetes	Beta blockers or long-acting, slow-release CCBs	
Depression	Long-acting, slow-release CCBs	Beta blockers
Mild peripheral vascular disease	Beta blockers or long-acting, slow-release CCBs	
Severe peripheral vascular disease with ischemia at rest	Long-acting, slow-release CCBs	Beta blockers
Cardiac Dysrhythmias and Conduction Abnormalities		
Sinus bradycardia	Long-acting, slow-release CCBs that do not decrease heart rate	Beta blockers, diltiazem, verapamil
Sinus tachycardia (not due to heart failure)	Beta blockers	
Supraventricular tachycardia	Verapamil, diltiazem, or beta blockers	
AV block	Long-acting, slow-release CCBs that do not slow AV conduction	Beta blockers, diltiazem, verapamil
Rapid atrial fibrillation (with digoxin)	Verapamil, diltiazem, or beta blockers	
Ventricular dysrhythmias	Beta blockers	
Left Ventricular Dysfunction		
Congestive heart failure		
Mild (LVEF $\geq 40\%$)	Beta blockers	
Moderate to severe (LVEF $< 40\%$)	Amlodipine or felodipine (nitrates)	Diltiazem, verapamil
Left-sided valvular heart disease		
Mild aortic stenosis	Beta blockers	
Aortic insufficiency	Long-acting, slow-release dihydropyridine CCBs	
Mitral regurgitation	Long-acting, slow-release dihydropyridine CCBs	
Mitral stenosis	Beta blockers	
Hypertrophic cardiomyopathy	Beta blockers, verapamil, diltiazem	Dihydropyridine CCBs, nitrates

AV = atrioventricular, CCB = calcium channel blocker, COPD = chronic obstructive pulmonary disease, LVEF = left ventricular ejection fraction, MI = myocardial infarction.

Adapted from Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). 2002. Available online at circ.ahajournals.org/.

cardiosuppressant actions, and hence are safer than beta blockers for patients with bradycardia, AV block, or heart failure. When a CCB is to be *combined* with a beta blocker, a dihydropyridine is preferred to verapamil or diltiazem. Why? Because verapamil and diltiazem will intensify the cardiosuppressant actions of the beta blocker, whereas a dihydropyridine CCB will not.

If a CCB is inadequate, or if there are contraindications to calcium channel blockade, a long-acting nitrate (eg, transdermal nitroglycerin) should be added or substituted. However, because tolerance can develop quickly, these nitrate preparations are less well suited than beta blockers or CCBs for continuous protection.

Note that, as we proceed along the drug-selection flow plan, drugs are *added* to the regimen, resulting in treatment with two or more agents. Combination therapy increases our chances of success because oxygen demand is decreased by multiple mechanisms: beta blockers reduce heart rate and contractility; CCBs reduce afterload (by dilating arterioles); and nitrates reduce preload (by dilating veins).

If combined treatment with a beta blocker, CCB, and long-acting nitrate fails to provide relief, CABG surgery or PCI may be indicated. Note that these invasive procedures should be considered only after more conservative treatment has been tried.

How should we treat angina in patients who have a coexisting condition? The antianginal drugs employed—nitrates, beta blockers, and CCBs—are the same ones used in patients who have angina alone. However, when selecting among these drugs, we must consider the coexisting disorder as well as the angina. For example, as noted above, in patients with asthma, CCBs are preferred to beta blockers (because beta blockers promote bronchoconstriction, whereas CCBs do not). Table 51-4 lists over 20 coexisting conditions, and indicates which antianginal agents to use as well as which ones to avoid.

Reduction of Risk Factors

The treatment program should reduce anginal risk factors: smokers should quit; obese patients should lose weight; sedentary patients should get aerobic exercise; and patients with

diabetes, hypertension, or high cholesterol should receive appropriate therapy.

Smoking. Smoking increases the risk of cardiovascular mortality by 50%. Fortunately, smoking cessation greatly decreases cardiovascular risk. Accordingly, all patients who smoke should be strongly encouraged to quit. Smoking cessation is discussed in Chapter 39.

High Cholesterol. As noted, high cholesterol levels increase the risk of adverse cardiovascular events, and therapies that reduce cholesterol reduce that risk. Accordingly, all patients with high cholesterol levels should receive cholesterol-lowering therapy.

Hypertension. High blood pressure increases the risk of cardiovascular mortality, and lowering blood pressure reduces the risk. Accordingly, all patients with hypertension should receive treatment. Blood pressure should be reduced to 140/90 mm Hg or less. In patients with additional risk factors (eg, diabetes, heart failure, retinopathy), the target blood pressure is 130/80 mm Hg or less. Management of hypertension is discussed in Chapter 47.

Diabetes. Both type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes increase the risk of cardiovascular mortality. Type 1 increases the risk 3- to 10-fold; type 2 increases the risk 2- to 4-fold. Although there is good evidence that tight glycemic control decreases the risk of microvascular complications of diabetes, there is little evidence to show that tight glycemic control decreases the risk of cardiovascular complications. Nonetheless, it is prudent to strive for optimal glycemic control.

Obesity. Obesity is associated with an increased risk of coronary disease and mortality; weight reduction is likely to reduce that risk. Accordingly, a program of diet and exercise is recommended for all patients whose body weight exceeds 120% of ideal. Weight reduction is especially important for patients with diabetes, hypertension, and hypertriglyceridemia. Obesity and its management are discussed in Chapter 82.

Physical Inactivity. Increased physical activity has multiple benefits. In patients with chronic stable angina, exercise increases exercise tolerance and the sense of well-being, and decreases anginal symptoms, cholesterol levels, and objective measures of ischemia. Accordingly, the guidelines recommend that patients perform 30 to 60 minutes of a moderate-intensity activity 3 to 4 times a week. Such activities include walking, jogging, cycling, and other aerobic exercises. Exercise by moderate- to high-risk patients should be medically supervised.

Management of Variant Angina

Treatment of vasospastic angina can proceed in three steps. For initial therapy, either a calcium channel blocker or a long-acting nitrate is selected. If either drug alone is inadequate, then combined therapy with a calcium channel blocker *plus* a nitrate should be tried. If the combination fails to control symptoms, CABG surgery may be indicated. Beta blockers are not effective in vasospastic angina.

KEY POINTS

- Anginal pain occurs when cardiac oxygen supply is insufficient to meet cardiac oxygen demand.
- Cardiac oxygen demand is determined by heart rate, contractility, preload, and afterload. Drugs that reduce these factors can help relieve anginal pain.
- Cardiac oxygen supply is determined by myocardial blood flow. Drugs that increase oxygen supply will reduce anginal pain.
- Angina pectoris has three forms: chronic stable angina, variant (vasospastic) angina, and unstable angina.
- The underlying cause of stable angina is coronary artery atherosclerosis.
- The underlying cause of variant angina is coronary artery spasm.
- Drugs relieve pain of stable angina by decreasing cardiac oxygen demand. They do not increase oxygen supply.
- Drugs relieve pain of variant angina by increasing cardiac oxygen supply. They do not decrease oxygen demand.
- Nitroglycerin and other organic nitrates are vasodilators.
- To cause vasodilation, nitroglycerin must first be converted to nitric oxide, its active form. This reaction requires a sulfhydryl source.
- Nitroglycerin relieves pain of stable angina by dilating veins, which decreases venous return, which decreases preload, which decreases oxygen demand.
- Nitroglycerin relieves pain of variant angina by relaxing coronary vasospasm, which increases oxygen supply.
- Nitroglycerin is highly lipid soluble, and therefore is readily absorbed through the skin and oral mucosa.
- Nitroglycerin undergoes very rapid inactivation in the liver. Hence, when the drug is administered orally, most of each dose is destroyed before reaching the systemic circulation.
- When nitroglycerin is administered sublingually, it is absorbed directly into the systemic circulation, and therefore temporarily bypasses the liver. Hence, to produce equivalent effects, sublingual doses can be much smaller than oral doses.
- Nitroglycerin causes three characteristic side effects: headache, orthostatic hypotension, and reflex tachycardia. All three occur secondary to vasodilation.
- Reflex tachycardia from nitroglycerin can be prevented with a beta blocker, verapamil, or diltiazem.
- Continuous use of nitroglycerin can produce tolerance within 24 hours. The mechanism may be depletion of sulfhydryl groups.
- To prevent tolerance, nitroglycerin should be used in the lowest effective dosage, and long-acting formulations should be used on an intermittent schedule that allows at least 8 drug-free hours every day, usually during the night.

- Nitroglycerin preparations that have a rapid onset (eg, sublingual nitroglycerin) are used to abort an ongoing anginal attack and to provide acute prophylaxis when exertion is expected. Administration is PRN.
- Nitroglycerin preparations that have a long duration (eg, patches, sustained-release oral capsules) are used for extended protection against anginal attacks. Administration is on a fixed schedule (but one that allows at least 8 drug-free hours a day).
- Nitroglycerin should be used cautiously with most vasodilators, and must not be used at all with sildenafil [Viagra] and other PDE5 inhibitors.
- Beta blockers prevent pain of stable angina primarily by decreasing heart rate and contractility, which reduces cardiac oxygen demand.
- Beta blockers are administered on a fixed schedule, not PRN.
- Beta blockers are not used for variant angina.
- Calcium channel blockers relieve pain of stable angina by reducing cardiac oxygen demand. Two mechanisms are involved. First, all CCBs relax peripheral arterioles, and thereby decrease afterload. Second, verapamil and diltiazem reduce heart rate and contractility (in addition to decreasing afterload).
- Calcium channel blockers relieve pain of variant angina by increasing cardiac oxygen supply. The mechanism is relaxation of coronary artery spasm.
- When a CCB is combined with a beta blocker, a dihydropyridine (eg, nifedipine) is preferred to verapamil or dil-

tiazem. Why? Because verapamil and diltiazem will intensify cardiosuppression caused by the beta blocker, whereas a dihydropyridine will not.

- Ranolazine appears to reduce anginal pain by helping the heart generate energy more efficiently.
- Ranolazine should not be used alone. Rather, it should be combined with a nitrate, a beta blocker, or the CCB amlodipine.
- Ranolazine increases the QT interval, and may thereby pose a risk of torsades de pointes, a serious ventricular dysrhythmia.
- In patients with chronic stable angina, treatment has two objectives: (1) prevention of MI and death and (2) prevention of anginal pain.
- The risk of MI and death can be decreased with two types of drugs: (1) antiplatelet agents (eg, aspirin, clopidogrel) and (2) cholesterol-lowering drugs.
- Anginal pain is prevented with one or more long-acting antianginal drugs (beta blocker, calcium channel blocker, long-acting nitrate) supplemented with sublingual nitroglycerin when breakthrough pain occurs.
- As a rule, revascularization with CABG surgery or PCI is indicated only after treatment with two or three antianginal drugs has failed.

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Summary of Major Nursing Implications*

NITROGLYCERIN

Preadministration Assessment

Therapeutic Goal

Reduction of the frequency and intensity of anginal attacks.

Baseline Data

Obtain baseline data on the frequency and intensity of anginal attacks, the location of anginal pain, and the factors that precipitate attacks.

The patient interview and physical examination should identify risk factors for angina pectoris, including treatable contributing pathophysiologic conditions (eg, hypertension, hyperlipidemia).

Identifying High-Risk Patients

Use with *caution* in hypotensive patients and patients taking drugs that can lower blood pressure, including alcohol and antihypertensive medications. Use with sildenafil [Viagra] and other PDE5 inhibitors is *contraindicated*.

Implementation: Administration

Routes and Administration

Sublingual Tablets. Use. Prophylaxis or termination of an acute anginal attack.

Technique of Administration. Instruct patients to place the tablet under the tongue and leave it there until fully dissolved; the tablet should not be swallowed.

Instruct patients to call 911 or go to an emergency department if pain is not relieved in 5 minutes. While awaiting emergency care, they can take 1 more tablet, and then a third tablet 5 minutes later.

Instruct patients to store tablets in a dry place at room temperature in their original container, which should be closed tightly after each use. Under these conditions, the tablets should remain effective until the expiration date on the container.

Sustained-Release Oral Capsules. Use. Sustained protection against anginal attacks.

To avoid tolerance, administer only once or twice daily.

Technique of Administration. Instruct patients to swallow these preparations intact, without chewing or crushing.

Transdermal Delivery Systems. Use. Sustained protection against anginal attacks.

Technique of Administration. Instruct patients to apply transdermal patches to a hairless area of skin, using a new patch and a different site each day.

Instruct patients to remove the patch after 12 to 14 hours, allowing 10 to 12 "patch-free" hours each day. This will prevent tolerance.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Translingual Spray. *Use.* Prophylaxis or termination of an acute anginal attack.

Technique of Administration. Instruct patients to direct the spray against the oral mucosa. Warn patients not to inhale the spray.

Topical Ointment. *Use.* Sustained protection against anginal attacks.

Instruct patients to remove any remaining ointment before applying a new dose.

Technique of Administration. (1) Squeeze a ribbon of ointment of prescribed length onto the applicator paper provided; (2) using the applicator paper, spread the ointment over an area at least 2.5 inches by 3.5 inches (application may be made to the chest, back, abdomen, upper arm, or anterior thigh); and (3) cover the ointment with plastic wrap. Avoid touching the ointment.

Instruct patients to rotate the application site to minimize local irritation.

Intravenous. *Uses.* (1) Angina pectoris refractory to more conventional therapy, (2) perioperative control of blood pressure, (3) production of controlled hypotension during surgery, and (4) heart failure associated with acute MI.

Technique of Administration. Perform IV administration using a glass IV bottle and the administration set provided by the manufacturer; avoid standard IV tubing. Check the stock solution label to verify volume and concentration, which can differ between manufacturers. Dilute stock solutions before use.

Administer by continuous infusion. The rate is slow initially (5 mcg/min) and then gradually increased until an adequate response is achieved.

Monitor cardiovascular status constantly.

Terminating Therapy

Warn patients against abrupt withdrawal of long-acting preparations (transdermal systems, topical ointment, sustained-release tablets and capsules).

Implementation: Measures to Enhance Therapeutic Effects

Reducing Risk Factors

Precipitating Factors. Advise patients to avoid activities that are likely to elicit an anginal attack (eg, overexertion, heavy meals, emotional stress, cold exposure).

Weight Reduction. Help overweight patients develop a restricted-calorie diet. The diet should be low in saturated fats, and total fat should not exceed 30% of caloric intake. Target weight is 110% of ideal or less.

Exercise. Encourage patients who have a sedentary lifestyle to establish a regular program of aerobic exercise (eg, walking, jogging, swimming, biking).

Smoking Cessation. Strongly encourage patients to quit smoking.

Contributing Disease States. Ensure that patients with contributing pathology (especially hypertension or hypercholesterolemia) are receiving appropriate treatment.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Instruct patients to keep a record of the frequency and intensity of anginal attacks, the location of anginal pain, and the factors that precipitate attacks.

Minimizing Adverse Effects

Headache. Inform patients that headache will diminish with continued drug use. Advise patients that headache can be relieved with aspirin, acetaminophen, or some other mild analgesic.

Orthostatic Hypotension. Inform patients about symptoms of hypotension (eg, dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when changing from a sitting or supine position to an upright posture.

Reflex Tachycardia. This reaction can be suppressed by concurrent treatment with a beta blocker, verapamil, or diltiazem.

Minimizing Adverse Interactions

Hypotensive Agents, Including PDE5 Inhibitors. Nitroglycerin can interact with other hypotensive drugs to produce excessive lowering of blood pressure. Advise patients to avoid alcohol. Exercise caution when nitroglycerin is used in combination with beta blockers, calcium channel blockers, diuretics, and all other drugs that can lower blood pressure.

Warn patients not to combine nitroglycerin with a PDE5 inhibitor (eg, sildenafil [Viagra]), because life-threatening hypotension can result.

ISOSORBIDE MONONITRATE AND ISOSORBIDE DINITRATE

Both drugs have pharmacologic actions identical to those of nitroglycerin. Differences relate only to dosage forms, routes of administration, and time course of action. Hence, the implications presented for nitroglycerin apply to these drugs as well.

*Patient education information is highlighted as blue text.

Anticoagulant, Antiplatelet, and Thrombolytic Drugs

COAGULATION: PHYSIOLOGY AND PATHOPHYSIOLOGY

Hemostasis

Thrombosis

OVERVIEW OF DRUGS FOR THROMBOEMBOLIC DISORDERS

ANTICOAGULANTS

Heparin and Its Derivatives: Drugs That Activate
Antithrombin

Heparin (Unfractionated)

Low-Molecular-Weight Heparins

Fondaparinux

Warfarin, a Vitamin K Antagonist

Direct Thrombin Inhibitors

Dabigatran Etexilate

Hirudin Analogs

Argatroban

Rivaroxaban, a Direct Factor Xa Inhibitor

Antithrombin

ANTIPLATELET DRUGS

Aspirin

P2Y₁₂ Adenosine Diphosphate Receptor
Antagonists

Glycoprotein IIb/IIIa Receptor Antagonists

Other Antiplatelet Drugs

THROMBOLYTIC (FIBRINOLYTIC) DRUGS

The drugs discussed in this chapter are used to prevent formation of thrombi (intravascular blood clots) and dissolve thrombi that have already formed. These drugs act in several ways: some suppress coagulation, some inhibit platelet aggregation, and some promote clot degradation. They all interfere with normal hemostasis. As a result, they all carry a significant risk of bleeding.

COAGULATION: PHYSIOLOGY AND PATHOPHYSIOLOGY

Hemostasis

Hemostasis is the physiologic process by which bleeding is stopped. Hemostasis occurs in two stages: (1) formation of a platelet plug, followed by (2) reinforcement of the platelet plug with fibrin. Both processes are set in motion by blood vessel injury.

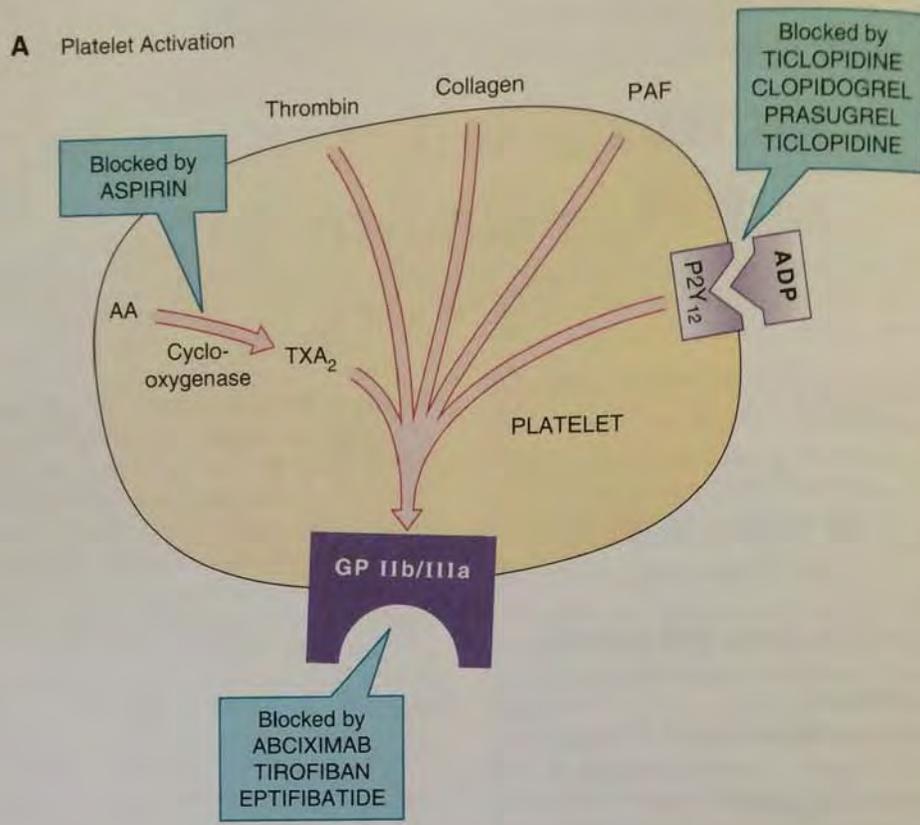
Stage One: Formation of a Platelet Plug. Platelet aggregation is initiated when platelets come in contact with collagen on the exposed surface of a damaged blood vessel. In response to contact with collagen, platelets adhere to the site of vessel injury. Adhesion initiates platelet *activation*, which in turn leads to massive platelet *aggregation*.

Platelet aggregation is a complex process that ends with formation of *fibrinogen bridges* between *glycoprotein IIb/IIIa (GP IIb/IIIa) receptors* on adjacent platelets (Fig. 52-1). In order for these bridges to form, GP IIb/IIIa receptors must first undergo activation—that is, they must undergo a configurational change that allows them to bind with fibrinogen. As indicated in Figure 52-1A, activation of GP IIb/IIIa can be stimulated by multiple factors, including thromboxane A₂ (TXA₂), thrombin, collagen, platelet activation factor, and ADP. Under the influence of these factors, GP IIb/IIIa changes its shape, binds with fibrinogen, and thereby causes aggregation (see Fig. 52-1B). The aggregated platelets constitute a plug that stops bleeding. This plug is unstable, however, and must be reinforced with *fibrin* if protection is to last.

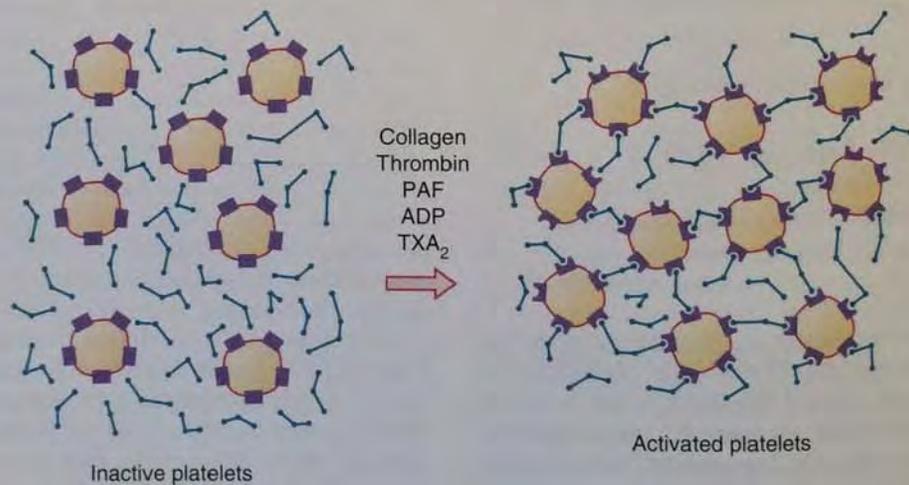
Stage Two: Coagulation. Coagulation is defined as production of *fibrin*, a thread-like protein that reinforces the platelet plug. Fibrin is produced by two convergent pathways (Fig. 52-2), referred to as the *contact activation pathway* (also known as the *intrinsic pathway*) and the *tissue factor pathway* (also known as the *extrinsic pathway*). As shown in Figure 52-2, the two pathways converge at factor Xa, after which they employ the same final series of reactions. In both pathways, each reaction in the sequence amplifies the reaction that follows. Hence, once this sequence is initiated, it becomes self-sustaining and self-reinforcing.

The *tissue factor pathway* is turned on by trauma to the vascular wall, which triggers release of tissue factor,* also known as *tissue thromboplastin*. Tissue factor then combines with and thereby activates factor VII, which in turn activates factor X, which then catalyzes the conversion of *prothrombin* (factor II) into *thrombin* (factor IIa). As shown in Figure 52-2, thrombin then does three things. First, it catalyzes the conversion of fibrinogen into fibrin. Second, it catalyzes the conversion of factor V into *its* active form (Va), a compound that greatly increases the activity of factor Xa, even though it has no direct catalytic activity of its own. Third, thrombin catalyzes the conversion of factor VIII into *its* active form (VIIIa), a compound that greatly increases the activity of factor IXa in the contact activation pathway.

*FYI: The term *tissue factor* refers not to a single compound but rather to a complex of several compounds, including a proteolytic enzyme and phospholipids released from tissue membranes.



B Platelet Aggregation



Inactive GP IIb/IIIa receptor
 Active GP IIb/IIIa receptor
 Fibrinogen

Figure 52-1 ■ Mechanism of platelet aggregation and actions of antiplatelet drugs.
A, Multiple factors—TXA₂, thrombin, collagen, PAF, and ADP—promote activation of the GP IIb/IIIa receptor. Each platelet has 50,000 to 80,000 GP IIb/IIIa receptors, although only one is shown.
B, Activation of the GP IIb/IIIa receptor permits binding of fibrinogen, which then causes aggregation by forming cross-links between platelets. After aggregation occurs, the platelet plug is reinforced with fibrin (not shown). (AA = arachidonic acid, ADP = adenosine diphosphate, GP IIb/IIIa = glycoprotein IIb/IIIa receptor, PAF = platelet activation factor, P2Y₁₂ = P2Y₁₂ ADP receptor, TXA₂ = thromboxane A₂.)

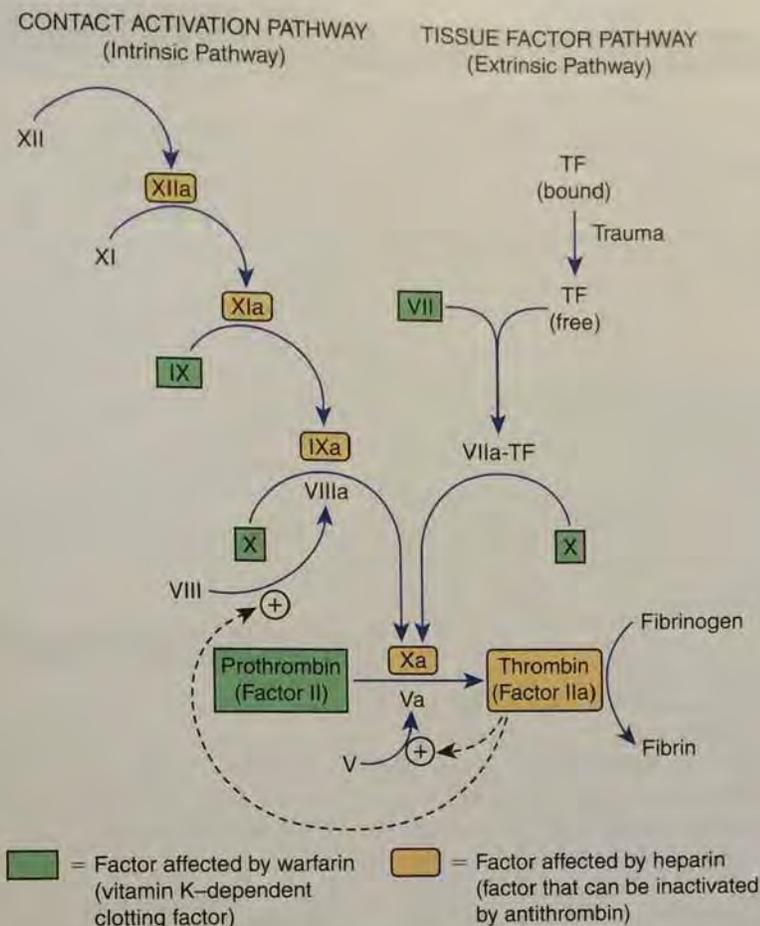


Figure 52-2 ■ Outline of coagulation pathways showing factors affected by warfarin and heparin.

TF = tissue factor. Common names for factors shown in roman numerals: V = proaccelerin, VII = proconvertin, VIII = antihemophilic factor, IX = Christmas factor, X = Stuart factor, XI = plasma thromboplastin antecedent, and XII = Hageman factor. The letter "a" after a factor's name (eg, factor VIIIa) indicates the active form of the factor.

The *contact activation pathway* is turned on when blood makes contact with collagen that has been exposed as a result of trauma to a blood vessel wall. Collagen contact stimulates conversion of factor XII into its active form, XIIa (see Figure 52-2). Factor XIIa then activates factor XI, which activates factor IX, which activates factor X. After this, the contact activation pathway is the same as the tissue factor pathway. As noted, factor VIIIa, which is produced under the influence of thrombin, greatly increases the activity of factor IXa, even though it has no direct catalytic activity of its own.

Important to our understanding of anticoagulant drugs is the fact that *four coagulation factors—factors VII, IX, X, and II (prothrombin)—require vitamin K for their synthesis.* These factors appear in green boxes in Figure 52-2. The significance of the vitamin K-dependent factors will become apparent when we discuss warfarin, an oral anticoagulant.

Keeping Hemostasis Under Control. To protect against widespread coagulation, the body must inactivate any clotting factors that stray from the site of vessel injury. Inactivation is accomplished with *antithrombin*, a protein that forms a complex with clotting factors, and thereby inhibits their activity. The clotting factors that can be neutralized by antithrombin

appear in yellow in Figure 52-2. As we shall see, antithrombin is intimately involved in the action of *heparin*, an injectable anticoagulant drug.

Physiologic Removal of Clots. As healing of an injured vessel proceeds, removal of the clot is eventually necessary. The body accomplishes this with *plasmin*, an enzyme that degrades the fibrin meshwork of the clot. Plasmin is produced through the activation of its precursor, *plasminogen*. The *fibrinolytic drugs* (eg, alteplase) act by promoting conversion of plasminogen into plasmin.

Thrombosis

A thrombus is a blood clot formed within a blood vessel or within the heart. Thrombosis (thrombus formation) reflects pathologic functioning of hemostatic mechanisms.

Arterial Thrombosis. Formation of an arterial thrombus begins with adhesion of platelets to the arterial wall. (Adhesion is stimulated by damage to the wall or rupture of an atherosclerotic plaque.) Following adhesion, platelets release ADP and TXA₂, and thereby attract additional platelets to the evolving thrombus. With continued platelet aggregation, oc-

TABLE 52-1 Overview of Drugs for Thromboembolic Disorders

Generic Name	Trade Name	Route	Action	Therapeutic Use
ANTICOAGULANTS				
Vitamin K Antagonist				
Warfarin	Coumadin	PO	Anticoagulants decrease formation of fibrin	Used primarily to prevent thrombosis in veins and the atria of the heart
Heparin and Its Derivatives: Drugs That Activate Antithrombin				
Heparin (unfractionated)		subQ, IV		
LMW heparins				
Dalteparin	Fragmin	subQ		
Enoxaparin	Lovenox	subQ		
Tinzaparin	Innohep	subQ		
Fondaparinux	Arixtra	subQ		
Direct Thrombin Inhibitors				
Hirudin Analogs				
Bivalirudin	Angiomax	IV		
Desirudin	Iprivask	subQ		
Lepirudin	Refludan	IV		
Other Direct Thrombin Inhibitors				
Apixaban*	Eliquis	PO		
Argatroban	Acova	IV		
Dabigatran	Pradaxa, Pradax ⁺	PO		
Direct Factor Xa Inhibitor				
Rivaroxaban	Xarelto	PO		
Antithrombin (AT)				
Recombinant human AT	ATryn	IV		
Plasma-derived AT	Thrombate III	IV		
ANTIPLATELET DRUGS				
Cyclooxygenase Inhibitor				
Aspirin		PO	Antiplatelet drugs suppress platelet aggregation	Used primarily to prevent thrombosis in arteries
P2Y₁₂ Adenosine Diphosphate Receptor Antagonists				
Clopidogrel	Plavix	PO		
Prasugrel	Effient	PO		
Ticagrelor	Brilinta	PO		
Ticlopidine	Ticlid	PO		
Glycoprotein IIb/IIIa Receptor Antagonists				
Abciximab	ReoPro	IV		
Eptifibatid	Integrilin	IV		
Tirofiban	Aggrastat	IV		
Other Antiplatelet Drugs				
Dipyridamole	Persantine	PO		
Cilostazol	Pletal	PO		
THROMBOLYTIC (FIBRINOLYTIC) DRUGS				
Alteplase	Activase	IV	Thrombolytic drugs promote breakdown of fibrin in thrombi	Used to dissolve newly formed thrombi
Retaplast	Retavase	IV		
Tenecteplase	TNKase	IV		

LMW = low molecular weight.

*Investigational in the United States.

clusion of the artery takes place. As blood flow comes to a stop, the coagulation cascade is initiated, causing the original plug to undergo reinforcement with fibrin. The consequence of an arterial thrombus is localized tissue injury owing to lack of perfusion.

Venous Thrombosis. Venous thrombi develop at sites where blood flow is slow. Stagnation of blood initiates the coagulation cascade, resulting in the production of fibrin,

which enmeshes red blood cells and platelets to form the thrombus. The typical venous thrombus has a long tail that can break off to produce an *embolus*. Such emboli travel within the vascular system and become lodged at faraway sites, frequently the pulmonary arteries. Hence, unlike an arterial thrombus, whose harmful effects are localized, injury from a venous thrombus occurs secondary to embolization at a site distant from the original thrombus.

OVERVIEW OF DRUGS FOR THROMBOEMBOLIC DISORDERS

The drugs considered in this chapter fall into three major groups: (1) anticoagulants, (2) antiplatelet drugs, and (3) thrombolytic drugs, also known as fibrinolytic drugs. *Anticoagulants* (eg, heparin, warfarin, dabigatran) disrupt the coagulation cascade, and thereby suppress production of fibrin. *Antiplatelet drugs* (eg, aspirin, clopidogrel) inhibit platelet aggregation. *Thrombolytic drugs* (eg, alteplase) promote lysis of fibrin, and thereby cause dissolution of thrombi. Drugs that belong to these groups are listed in Table 52-1.

Although the anticoagulants and the antiplatelet drugs both suppress thrombosis, they do so by different mechanisms. As a result, they differ in their effects and applications. The *antiplatelet drugs* are most effective at preventing *arterial* thrombosis, whereas *anticoagulants* are most effective against *venous* thrombosis.

ANTICOAGULANTS

By definition, anticoagulants are drugs that *reduce formation of fibrin*. Two basic mechanisms are involved. One anticoagulant—warfarin—inhibits the *synthesis* of clotting factors, including factor X and thrombin. All other anticoagulants inhibit the *activity* of clotting factors: either factor Xa, thrombin, or both.

Traditionally, anticoagulants have been grouped into two major classes: *oral anticoagulants* and *parenteral anticoagulants*. This scheme was reasonable because, until recently,

all oral anticoagulants belonged to just one pharmacologic class: the vitamin K antagonists, of which warfarin is the principal member. Today, however, anticoagulants in two other pharmacologic classes—direct factor Xa inhibitors and direct thrombin inhibitors—can also be administered by mouth (see Table 52-1). Hence, grouping the anticoagulants by route of administration makes less sense than in the past. Accordingly, in this chapter, these drugs are grouped only by pharmacologic class, and not by whether they are given orally or by injection.

HEPARIN AND ITS DERIVATIVES: DRUGS THAT ACTIVATE ANTITHROMBIN

All drugs in this section share the same mechanism of action. Specifically, they greatly enhance the activity of *antithrombin*, a protein that inactivates two major clotting factors: *thrombin* and *factor Xa*. In the absence of thrombin and factor Xa, production of fibrin is reduced, and hence clotting is suppressed.

Our discussion focuses on three preparations: *unfractionated heparin*, the *low-molecular-weight (LMW) heparins*, and *fondaparinux*. Although all three activate antithrombin, they do not have equal effects on thrombin and factor Xa. Specifically, heparin reduces the activity of thrombin and factor Xa more or less equally; the LMW heparins reduce the activity of factor Xa more than they reduce the activity of thrombin; and fondaparinux causes selective inhibition of factor Xa, having no effect on thrombin. Properties of the three preparations are summarized in Table 52-2.

TABLE 52-2 ■ Comparison of Drugs That Activate Antithrombin

Property	Unfractionated Heparin	Low-Molecular-Weight Heparins	Fondaparinux
Molecular weight range	3000–30,000	1000–9000	1728
Mean molecular weight	12,000–15,000	4000–5000	1728
Mechanism of action	Activation of antithrombin, resulting in the inactivation of factor Xa and thrombin	Activation of antithrombin, resulting in preferential inactivation of factor Xa, plus some inactivation of thrombin	Activation of antithrombin, resulting in selective inactivation of factor Xa
Routes	IV, subQ	subQ only	subQ only
Nonspecific binding	Widespread	Minimal	Minimal
Laboratory monitoring	aPTT monitoring is essential	No aPTT monitoring required	No aPTT monitoring required
Dosage	Dosage must be adjusted on the basis of aPTT	Dosage is fixed	Dosage is fixed
Setting for use	Hospital	Hospital or home	Hospital or home
Cost	\$3/day for heparin itself, but hospitalization and aPTT monitoring greatly increase the real cost	\$35/day for LMW heparin (enoxaparin [Lovenox]), but home use and absence of aPTT monitoring greatly reduce the real cost	\$59/day for fondaparinux, but home use and absence of aPTT monitoring greatly reduce the real cost

aPTT = activated partial thromboplastin time, LMW = low molecular weight.

Heparin (Unfractionated)

Heparin is a rapid-acting anticoagulant administered only by injection. Heparin differs from warfarin (an oral anticoagulant) in several respects, including mechanism, time course, indications, and management of overdose.

Source

Heparin is present in various mammalian tissues. The heparin employed clinically is prepared from two sources: lungs of cattle and intestines of pigs. The anticoagulant activity of heparin from either source is equivalent. Although heparin occurs naturally, its physiologic role is unknown.

Chemistry

Heparin is not a single molecule, but rather a mixture of long polysaccharide chains, with molecular weights that range from 3000 to 30,000. The active region is a unique pentasaccharide (five-sugar) sequence found randomly along the chain. An important feature of heparin's structure is the presence of many negatively charged groups. Because of these negative charges, heparin is highly polar, and hence cannot readily cross membranes.

Mechanism of Anticoagulant Action

Heparin suppresses coagulation by helping antithrombin inactivate clotting factors, primarily thrombin and factor Xa. As shown in Figure 52-3, binding of heparin to antithrombin produces a conformational change in antithrombin that greatly enhances its ability to inactivate both thrombin and factor Xa. However, the process of inactivating these two clotting factors is not identical. In order to inactivate thrombin, heparin must simultaneously bind with both thrombin and antithrombin, thereby forming a ternary complex (see Fig. 52-3). In contrast, in order to inactivate factor Xa, heparin binds only with antithrombin; heparin itself does not bind with factor Xa.

By activating antithrombin, and thereby promoting the inactivation of thrombin and factor Xa, heparin ultimately suppresses formation of fibrin. Since fibrin forms the framework of thrombi in veins, heparin is especially useful for prophylaxis of venous thrombosis. Because thrombin and factor Xa are inhibited as soon as they bind with the heparin-antithrombin complex, the anticoagulant effects of heparin develop quickly (within minutes of IV administration). This contrasts with warfarin, whose full effects are not seen for days.

Pharmacokinetics

Absorption and Distribution. Because of its polarity and large size, heparin is unable to cross membranes, including those of the GI tract. Consequently, heparin cannot be absorbed if given orally, and therefore must be given by injection (IV or subQ). Since it cannot cross membranes, heparin does not traverse the placenta and does not enter breast milk.

Protein and Tissue Binding. Heparin binds nonspecifically to plasma proteins, mononuclear cells, and endothelial cells. As a result, plasma levels of free heparin can be highly variable. Because of this variability, intensive monitoring is required (see below).

Metabolism and Excretion. Heparin undergoes hepatic metabolism followed by renal excretion. Under normal conditions, the half-life is short (about 1.5 hours). However, in patients with hepatic or renal impairment, the half-life is increased.

Time Course. Therapy is initiated with a bolus IV injection, and effects begin immediately. Duration of action is brief

(hours) and varies with dosage. Effects are prolonged in patients with hepatic or renal impairment.

Therapeutic Uses

Heparin is a preferred anticoagulant for use during pregnancy (because it doesn't cross the placenta) and in situations that require rapid onset of anticoagulant effects, including pulmonary embolism (PE), evolving stroke, and massive deep vein thrombosis (DVT). In addition, heparin is used for patients undergoing open heart surgery and renal dialysis; during these procedures, heparin serves to prevent coagulation in devices of extracorporeal circulation (heart-lung machines, dialyzers). Low-dose therapy is used to prevent postoperative venous thrombosis. Heparin may also be useful for treating disseminated intravascular coagulation, a complex disorder in which fibrin clots form throughout the vascular system and in which bleeding tendencies may be present; bleeding can occur because massive fibrin production consumes available supplies of clotting factors. Heparin is also used as an adjunct to thrombolytic therapy of acute myocardial infarction (MI).

Adverse Effects

Hemorrhage. Bleeding develops in about 10% of patients and is the principal complication of treatment. Hemorrhage can occur at any site and may be fatal. Patients should be monitored closely for signs of blood loss. These include reduced blood pressure, increased heart rate, bruises, petechiae, hematomas, red or black stools, cloudy or discolored urine, pelvic pain (suggesting ovarian hemorrhage), headache or faintness (suggesting cerebral hemorrhage), and lumbar pain (suggesting adrenal hemorrhage). If bleeding develops, heparin should be withdrawn. Severe overdose can be treated with protamine sulfate (see below).

The risk of hemorrhage can be decreased in several ways. First, dosage should be carefully controlled so that the activated partial thromboplastin time (see below) does not exceed 2 times the control value. In addition, candidates for heparin therapy should be screened for risk factors (see Warnings and Contraindications). Finally, antiplatelet drugs (eg, aspirin, clopidogrel) should be avoided.

Spinal/Epidural Hematoma. Heparin and all other anticoagulants pose a risk of spinal or epidural hematoma in patients undergoing spinal puncture or spinal/epidural anesthesia. Pressure on the spinal cord caused by the bleed can result in prolonged or permanent paralysis. Risk of hematoma is increased by

- Use of an indwelling epidural catheter
- Use of other anticoagulants (eg, warfarin, dabigatran)
- Use of antiplatelet drugs (eg, aspirin, clopidogrel)
- History of traumatic or repeated epidural or spinal puncture
- History of spinal deformity, spinal injury, or spinal surgery

Patients should be monitored for signs and symptoms of neurologic impairment. If impairment develops, immediate intervention is needed.

Heparin-Induced Thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is a potentially fatal immune-mediated disorder characterized by reduced platelet counts (thrombocytopenia) and a seemingly paradoxical increase in thrombotic events. The underlying cause is development of antibodies against heparin-platelet protein complexes. These antibodies

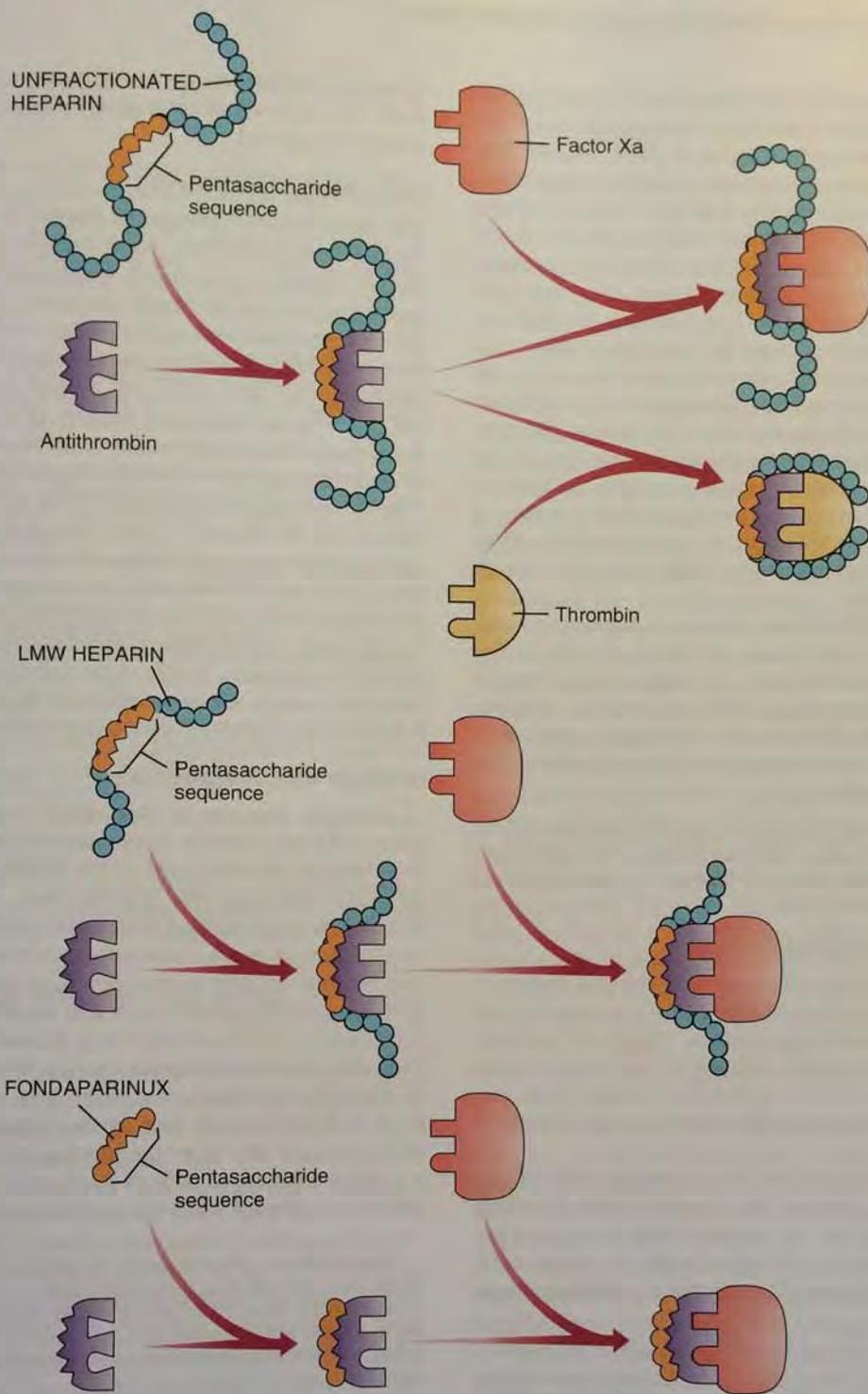


Figure 52-3 ■ Mechanism of action of heparin, LMW heparins, and fondaparinux.

All three drugs share a pentasaccharide sequence that allows them to bind with—and thereby activate—antithrombin, a protein that inactivates two major clotting factors: thrombin and factor Xa. All three drugs enable antithrombin to inactivate factor Xa, but only heparin also facilitates inactivation of thrombin.

Upper Panel: Unfractionated heparin binds with antithrombin, thereby causing a conformational change in antithrombin that greatly increases its ability to interact with factor Xa and thrombin. As shown, when the heparin-antithrombin complex binds with thrombin, heparin changes its conformation such that both heparin and antithrombin come in contact with thrombin. Formation of this ternary complex is necessary for thrombin inactivation. Inactivation of factor Xa is different: It only requires contact between activated antithrombin and factor Xa; contact between heparin and factor Xa is unnecessary.

Middle Panel: Low-molecular-weight (LMW) heparins have the same pentasaccharide sequence as unfractionated heparin, and hence can bind with and thereby activate antithrombin. However, in contrast to unfractionated heparin, which promotes inactivation of both thrombin and factor Xa, most molecules of LMW heparin can only inactivate factor Xa; they are unable to inactivate thrombin. Why? Because most molecules of LMW heparin are too small to form a ternary complex with thrombin and antithrombin.

Lower Panel: Fondaparinux is a synthetic pentasaccharide identical in structure to the antithrombin binding sequence found in unfractionated heparin and LMW heparins. Being even smaller than LMW heparins, fondaparinux is too small to form a ternary complex with thrombin, and hence can only inactivate factor Xa.

activate platelets and damage the vascular endothelium, thereby promoting both thrombosis and a rapid loss of circulating platelets. Thrombus formation poses a risk of DVT, PE, cerebral thrombosis, and MI. Ischemic injury secondary to thrombosis in the limbs may require amputation of an arm or leg. Coronary thrombosis can be fatal. The primary treatment for HIT is discontinuation of heparin and, if anticoagulation is still needed, substitution of a nonheparin anticoagulant (eg, lepirudin, argatroban). The incidence of HIT is between 1% and 3% among patients who receive heparin for more than 4 days.

HIT should be suspected whenever platelet counts fall significantly or when thrombosis develops despite adequate anticoagulation. Accordingly, to reduce the risk of HIT, patients should be monitored for signs of thrombosis and for reductions in platelets. Platelet counts should be determined frequently (2 to 3 times a week) during the first 3 weeks of heparin use, and monthly thereafter. If severe thrombocytopenia develops (platelet count below 100,000/mm³), heparin should be discontinued.

Hypersensitivity Reactions. Because commercial heparin is extracted from animal tissues, these preparations may be contaminated with antigens that can promote allergy. Possible allergic responses include chills, fever, and urticaria. Anaphylactic reactions are rare. To minimize the risk of severe reactions, patients should receive a small test dose of heparin prior to the full therapeutic dose.

Other Adverse Effects. Subcutaneous dosing may produce *local irritation* and *hematoma*. *Vasospastic reactions* that persist for several hours may develop after 1 or more weeks of treatment. Long-term, high-dose therapy may cause *osteoporosis*.

Warnings and Contraindications

Warnings. Heparin must be used with extreme caution in all patients who have a high likelihood of bleeding. Among these are individuals with hemophilia, increased capillary permeability, dissecting aneurysm, peptic ulcer disease, severe hypertension, or threatened abortion. Heparin must also be used cautiously in patients with severe disease of the liver or kidneys.

Contraindications. Heparin is contraindicated for patients with thrombocytopenia and uncontrollable bleeding. In addition, heparin should be avoided both during and immediately after surgery of the eye, brain, or spinal cord. Lumbar puncture and regional anesthesia are additional contraindications.

Drug Interactions

In heparin-treated patients, platelet aggregation is the major remaining defense against hemorrhage. Aspirin and other drugs that depress platelet function will weaken this defense, and hence must be employed with caution.

Protamine Sulfate for Heparin Overdose

Protamine sulfate is an antidote to severe heparin overdose. Protamine is a small protein that has multiple positively charged groups. These groups bond ionically with the negative groups on heparin, thereby forming a heparin-protamine complex that is devoid of anticoagulant activity. Neutralization of heparin occurs immediately and lasts for 2 hours, after which additional protamine may be needed. Protamine is administered by slow IV injection (no faster than 20 mg/min or 50 mg in 10 minutes). Dosage is based on the fact that 1 mg

of protamine will inactivate 100 units of heparin. Hence, for each 100 units of heparin in the body, 1 mg of protamine should be injected.

Laboratory Monitoring

The objective of anticoagulant therapy is to reduce blood coagulability to a level that is low enough to prevent thrombosis but not so low as to promote spontaneous bleeding. Because heparin levels can be highly variable, achieving this goal is difficult, and requires careful control of dosage based on frequent tests of coagulation. The laboratory test employed most commonly is the *activated partial thromboplastin time* (aPTT). The normal value for the aPTT is 40 seconds. At therapeutic levels, heparin *increases* the aPTT by a factor of 1.5 to 2, making the aPTT 60 to 80 seconds. Since heparin has a rapid onset and brief duration, if an aPTT value should fall outside the therapeutic range, coagulability can be quickly corrected through an adjustment in dosage: if the aPTT is too long (more than 80 seconds), the dosage should be lowered; conversely, if the aPTT is too short (less than 60 seconds), the dosage should be increased. Measurements of aPTTs should be made frequently (every 4 to 6 hours) during the initial phase of therapy. Once an effective dosage has been established, measuring aPTT once a day will suffice.

Unitage and Preparations

Unitage. Heparin is prescribed in units, not in milligrams. The heparin unit is an index of anticoagulant activity. In 2009, the method used in the United States to measure heparin's anticoagulant activity was changed, and now matches the method used in Canada and Europe. Because the new method employs a new reference standard for anticoagulant activity, heparin preparations available now have about 10% less activity per unit than preparations made in the past. Nonetheless, the Food and Drug Administration (FDA) did not change dosing recommendations. Why? First, the potency of the old preparations varied by plus or minus 10% from batch to batch anyway. And second, heparin dosage is titrated on the basis of laboratory monitoring, and hence, even if there is a small decrease in activity per heparin unit, dosage can be adjusted as needed when the test results come in.

Preparations. Heparin sodium is supplied in single-dose vials; multidose vials; and unit-dose, preloaded syringes that have their own needles. Concentrations range from 1000 to 40,000 units/mL. Heparin sodium for use in heparin locks [Hep-Lock, HepFlush-10] is supplied in *dilute* solutions (10 and 100 units/mL) that are too weak to produce systemic anticoagulant effects.

Dosage and Administration

General Considerations. Heparin is administered by injection only. Two routes are employed: *intravenous* (either intermittent or continuous) and *subcutaneous*. Intramuscular injection causes hematoma and must not be done. Heparin is not administered orally. Why? Because heparin is too large and too polar to permit intestinal absorption.

Dosage varies with the application. Postoperative prophylaxis of thrombosis, for example, requires relatively small doses. In other situations, such as open heart surgery, much larger doses are needed. The dosages given below are for "general anticoagulant therapy." As a rule, the aPTT should be employed as a guideline for dosage titration; increases in the aPTT of 1.5- to 2-fold are therapeutic. Since heparin is formu-

lated in widely varying concentrations, you must read the label carefully to ensure that dosing is correct.

Intermittent IV Therapy. Intermittent IV heparin is administered via an indwelling needle with a rubber-capped port (heparin lock). Therapy is initiated with a dose of 10,000 units. Subsequent doses of 5000 to 10,000 units are given every 4 to 6 hours. The aPTT should be taken 1 hour before each injection until dosage is stabilized. To avoid venous injury, the site of the heparin lock should be moved every 2 or 3 days. When heparin is administered intermittently, plasma levels of the drug will fluctuate, possibly causing alternating periods of excessive and insufficient anticoagulation.

Continuous IV Infusion. Intravenous infusion provides steady levels of heparin, and therefore is preferred to intermittent injections. Dosing consists of a bolus (5000 units), followed by infusion of 20,000 to 40,000 units over 24 hours. During the initial phase of treatment, the aPTT should be measured once every 4 hours and the infusion rate adjusted accordingly. To decrease the risk of overdose, when heparin solutions are prepared, the amount made up should be sufficient for no more than a 6-hour infusion. Heparin should be infused using an electric pump, and the rate should be checked every 30 to 60 minutes.

Deep SubQ Injection. Subcutaneous injections are made deep into the fatty layer of the abdomen (but not within 2 inches of the umbilicus). The heparin solution should be drawn up using a 20- to 22-gauge needle. This needle is then discarded and replaced with a small needle ($\frac{1}{2}$ to $\frac{5}{8}$ inch, 25 or 26 gauge) to make the injection. Following administration, firm but gentle pressure should be applied to the injection site for 1 to 2 minutes. The initial subQ dose is 10,000 to 20,000 units (preceded immediately by an IV loading dose of 5000 units). The initial subQ dose is followed by either (1) 8000 to 10,000 units every 8 hours or (2) 15,000 to 20,000 units every 12 hours. Dosage is adjusted on the basis of aPTTs taken 4 to 6 hours after each injection. The injection site should be rotated.

Low-Dose Therapy. Heparin in low doses is given for prophylaxis against postoperative thromboembolism. The initial dose (5000 units subQ) is given 2 hours prior to surgery. Additional doses of 5000 units are given every 8 to 12 hours for 7 days (or until the patient is ambulatory). Low-dose heparin is also employed as adjunctive therapy for patients with MI. During low-dose therapy, monitoring of the aPTT is not usually required.

Low-Molecular-Weight Heparins

Group Properties

Low-molecular-weight (LMW) heparins are simply heparin preparations composed of molecules that are shorter than those found in unfractionated heparin. LMW heparins are as effective as unfractionated heparin and are easier to use. Why? Because LMW heparins can be given using a fixed dosage and don't require aPTT monitoring. As a result, LMW heparins can be used at home, whereas unfractionated heparin must be given in a hospital. Because of these advantages, LMW heparins are now considered first-line therapy for prevention and treatment of DVT. In the United States, three LMW heparins are available: enoxaparin [Lovenox], dalteparin [Fragmin], and tinzaparin [Innohep]. Differences between LMW heparins and unfractionated heparin are summarized in Table 52-2.

Production. LMW heparins are made by depolymerizing unfractionated heparin (ie, breaking unfractionated heparin into smaller pieces). Molecular weights in LMW preparations range between 1000 and 9000, with a mean of 4000 to 5000. In comparison, molecular weights in unfractionated heparin range between 3000 and 30,000, with a mean of 12,000 to 15,000.

Mechanism of Action. Anticoagulant activity of LMW heparin is mediated by the same active pentasaccharide sequence that mediates anticoagulant action of unfractionated heparin. However, because LMW heparin molecules are short, they do not have quite the same effect as unfractionated heparin. Specifically, whereas unfractionated heparin is

equally good at inactivating factor Xa and thrombin, LMW heparins preferentially inactivate factor Xa, being much less able to inactivate thrombin. Why the difference? In order to inactivate thrombin, a heparin chain must not only contain the pentasaccharide sequence that activates antithrombin, it must also be long enough to provide a binding site for thrombin. This binding site is necessary because inactivation of thrombin requires simultaneous binding of thrombin with heparin and antithrombin (see Fig. 52-3). In contrast to unfractionated heparin chains, most (but not all) LMW heparin chains are too short to allow thrombin binding, and hence LMW heparins are less able to inactivate thrombin.

Therapeutic Use. LMW heparins are approved for (1) prevention of DVT following abdominal surgery, hip replacement surgery, or knee replacement surgery; (2) treatment of established DVT, with or without PE; and (3) prevention of ischemic complications in patients with unstable angina, non-Q-wave MI, and ST-elevation MI (STEMI). In addition, these drugs have been used extensively *off label* to prevent DVT after general surgery and in patients with multiple trauma and acute spinal injury. When used for prophylaxis or treatment of DVT, LMW heparins are at least as effective as unfractionated heparin, and possibly more effective.

Pharmacokinetics. Compared with unfractionated heparin, LMW heparins have higher bioavailability and longer half-lives. Bioavailability is higher because LMW heparins do not undergo nonspecific binding to proteins and tissues, and hence are more available for anticoagulant effects. Half-lives are prolonged (up to 6 times longer than that of unfractionated heparin) because LMW heparins undergo less binding to macrophages, and hence undergo slower clearance by the liver. Because of increased bioavailability, plasma levels of LMW heparin are highly predictable. As a result, these drugs can be given using a fixed dosage, with no need for routine monitoring of coagulation. Because of their long half-lives, LMW heparins can be given just once or twice a day.

Administration, Dosing, and Monitoring. All LMW heparins are administered subQ. Dosage is based on body weight. Because plasma levels of LMW heparins are predictable for any given dose, these drugs can be employed using a fixed dosage without laboratory monitoring. This contrasts with unfractionated heparin, which requires dosage adjustments on the basis of aPTT measurements. Because LMW heparins have an extended half-life, dosing can be done once or twice daily. For prophylaxis of DVT, dosing is begun in the perioperative period and continued 5 to 10 days.

Adverse Effects and Interactions. Bleeding is the major adverse effect. However, the incidence of bleeding complications is less than with unfractionated heparin. Despite the potential for bleeding, LMW heparins are considered safe for outpatient use. Like unfractionated heparin, LMW heparins can cause immune-mediated *thrombocytopenia*. As with unfractionated heparin, overdose with LMW heparins can be treated with protamine sulfate.

Like unfractionated heparin, LMW heparins can cause *severe neurologic injury*, including permanent paralysis, when given to patients undergoing *spinal puncture* or *spinal or epidural anesthesia*. The risk of serious harm is increased by concurrent use of antiplatelet drugs (eg, aspirin, clopidogrel) or anticoagulants (eg, warfarin, dabigatran). Patients should be monitored closely for signs of neurologic impairment.

Cost. LMW heparins cost more than unfractionated heparin (eg, about \$63/day for dalteparin vs. \$8/day for unfractionated heparin). However, since LMW heparins can be used at home and don't require aPTT monitoring, the overall cost of treatment is lower than with unfractionated heparin.

Individual Preparations

In the United States, three LMW heparins are available: enoxaparin, dalteparin, and tinzaparin. Additional LMW heparins are available in other countries. Each preparation is unique. Hence clinical experience with one may not apply fully to the others.

Enoxaparin. Enoxaparin [Lovenox] was the first LMW heparin available in the United States. The drug is prepared by depolymerization of unfractionated porcine heparin. Molecular weights range between 2000 and 8000. Enoxaparin is used widely: In the United States, hospitals spend more money on Lovenox than any other drug.

Enoxaparin is approved for prevention of DVT following hip and knee replacement surgery or abdominal surgery in patients considered at high risk of thromboembolic complications (eg, obese patients, those over age 40, and those with malignancy or a history of DVT or pulmonary embolism). The drug is also approved for preventing ischemic complications in patients with unstable angina, non-Q-wave MI, or STEMI.

In the event of overdose, hemorrhage can be controlled with protamine sulfate. The dosage is 1 mg of protamine sulfate for each milligram of enoxaparin administered.

Administration and Dosage. Enoxaparin is administered by deep subQ injection. For patients with normal renal function (or moderate renal impairment), dosages are as follows:

- *Prevention of DVT after hip or knee replacement surgery*—30 mg every 12 hours starting 12 to 24 hours after surgery and continuing 7 to 10 days.
- *Prevention of DVT after abdominal surgery*—40 mg once daily, beginning 2 hours before surgery and continuing 7 to 10 days.
- *Treatment of established DVT*—1 mg every 12 hours for 7 days.
- *Patients with unstable angina or non-Q-wave MI*—1 mg/kg every 12 hours (in conjunction with oral aspirin, 100 to 325 mg once daily) for 2 to 8 days.
- *Patients with acute STEMI*—30 mg/kg by IV bolus plus 1 mg/kg subQ, followed by 1 mg/kg subQ every 12 hours for up to 8 days.

For patients with severe renal impairment, dosage should be reduced.

Dalteparin. Dalteparin [Fragmin] was the second LMW heparin approved in the United States. The drug is prepared by depolymerization of porcine heparin. Molecular weights range between 2000 and 9000, the mean being 5000. Approved indications are prevention of DVT following hip replacement surgery or abdominal surgery in patients considered at high risk of thromboembolic complications, prevention of ischemic complications in patients with unstable angina or non-Q-wave MI, and management of symptomatic venous thromboembolism (VTE). Administration is by deep subQ injection. Dosages are as follows:

- *Prevention of DVT after hip replacement surgery*—2500 units 1 or 2 hours before surgery, 2500 units that evening (at least 6 hours after the first dose), and then 5000 units once daily for 5 to 10 days.
- *Prevention of DVT after abdominal surgery*—2500 units once daily for 5 to 10 days, starting 1 to 2 hours before surgery.
- *Patients with unstable angina or non-Q-wave MI*—120 units/kg (but not more than 10,000 units total) every 12 hours for 5 to 8 days. Concurrent therapy with aspirin (75 to 165 mg/day) is required.
- *Patients with symptomatic VTE*—200 units/kg (but not more than 18,000 units total) once daily for 1 month, then 150 units/kg (but not more than 18,000 IU total) once daily for months 2 through 6.

Overdose is treated with 1 mg of protamine sulfate for every 100 units of dalteparin administered.

Tinzaparin. Tinzaparin [Innohep] is indicated for acute symptomatic DVT (with or without PE) and should be used in conjunction with warfarin. Tinzaparin has a mean molecular weight of 6500 and a half-life of 3 to 4 hours. Excretion is renal. In clinical trials, bleeding developed in 0.8% of patients and thrombocytopenia in 1%. Eight men experienced priapism (persistent erection). In elderly patients with renal impairment, tinzaparin increases the risk of death, and hence should not be used in this population. Tinzaparin is supplied in 2-mL vials containing 20,000 units/mL. Administration is by subQ injection in the abdominal region. The recommended dosage is 175 units/kg once daily for 6 or more days. Warfarin should be initiated when appropriate, usually 1 to 3 days after starting tinzaparin. When warfarin has taken effect, tinzaparin can be discontinued. Overdose is treated with 1 mg of protamine sulfate for every 100 units of dalteparin administered.

Fondaparinux

Actions. Fondaparinux [Arixtra], approved in 2001, is a synthetic, subQ anticoagulant that enhances the activity of antithrombin, to cause selective inhibition of factor Xa. The result is reduced production of thrombin, and hence reduced coagulation. Note that fondaparinux differs from the heparin preparations, which cause inactivation of thrombin as well as factor Xa.

Fondaparinux is closely related in structure and function to heparin and the LMW heparins. Structurally, fondaparinux is a pentasaccharide identical to the antithrombin-binding region of the heparins. Hence, like the heparins, fondaparinux is able to induce a conformational change in antithrombin, thereby increasing antithrombin's activity—but only against factor Xa, not against thrombin. Why is fondaparinux selective for factor Xa? Because the drug is quite small—even smaller than the LMW heparins. As a result, it is too small to form a complex with both antithrombin and thrombin, and hence cannot reduce thrombin activity (see Fig. 52-3).

Fondaparinux has no effect on prothrombin time, aPTT, bleeding time, or platelet aggregation.

Therapeutic Use. Fondaparinux is approved for (1) preventing DVT following hip fracture surgery, hip replacement surgery, knee replacement surgery, or abdominal surgery; (2) treating acute PE (in conjunction with warfarin); and (3) treating acute DVT (in conjunction with warfarin). The drug is somewhat more effective than enoxaparin (an LMW heparin) at preventing DVT, but may cause slightly more bleeding. Anticoagulation may persist for 2 to 4 days after the last dose. Like the LMW heparins, fondaparinux is administered using a fixed dosage, and does not require routine laboratory monitoring.

Pharmacokinetics. Fondaparinux is administered subQ. Bioavailability is 100%. Plasma levels peak 2 hours after dosing. The drug is eliminated by the kidneys with a half-life of 17 to 21 hours. The half-life is increased in patients with renal impairment.

Adverse Effects. As with other anticoagulants, bleeding is the biggest concern. The risk is increased by advancing age and renal impairment. Fondaparinux should be used with caution in patients with moderate renal impairment, defined as creatinine clearance (CrCl) of 30 to 50 mL/min, and avoided in patients with severe renal impairment, defined as CrCl below 30 mL/min. The drug should also be avoided in patients weighing less than 50 kg. Why? Because low body weight increases bleeding risk. Following surgery, at least 6 hours should elapse before starting fondaparinux. Aspirin and other drugs that interfere with hemostasis should be used with caution. In contrast to overdose with heparin or LMW heparins, overdose with fondaparinux cannot be treated with protamine sulfate.

Fondaparinux does not promote immune-mediated HIT, although it still can lower platelet counts. During clinical trials, thrombocytopenia developed in 3% of patients. Platelet counts should be monitored and, if they fall below 100,000/mm³, fondaparinux should be discontinued.

In patients undergoing anesthesia using an epidural or spinal catheter, fondaparinux (as well as other anticoagulants) can cause spinal or epidural hematoma, which can result in permanent paralysis. However, in clinical trials, when fondaparinux was administered no sooner than 2 hours after catheter removal, no hematomas were reported.

Preparations, Dosage, and Administration. Fondaparinux [Arixtra] is available in single-dose, pre-filled syringes (2.5, 5, 7.5, and 10 mg). Dosing is done once a day by subQ injection.

For prevention of DVT, the recommended dosage is 2.5 mg once a day, starting 6 to 8 hours after surgery. The usual duration is 5 to 9 days.

For treatment of acute DVT or acute PE, dosage is based on body weight as follows: for patients under 50 kg, 5 mg once daily; for patients 50 to 100 kg, 7.5 mg once daily, and for patients over 100 kg, 10 mg once daily. The usual duration is 5 to 9 days.

WARFARIN, A VITAMIN K ANTAGONIST

Warfarin [Coumadin, Jantoven], a vitamin K antagonist, is our oldest *oral* anticoagulant. The drug is similar to heparin in some respects and quite different in others. Like heparin, warfarin is used to prevent thrombosis. In contrast to heparin, warfarin has a delayed onset, which makes it inappropriate for emergencies. However, because it doesn't require injection, warfarin is well suited for long-term prophylaxis. Like heparin, warfarin carries a significant risk of hemorrhage, which is amplified by the many drug interactions to which warfarin is subject.

History

The history of warfarin underscores its potential for harm. Warfarin was discovered after a farmer noticed that his cattle bled after eating spoiled clover silage. The causative agent was identified as bishydroxycoumarin (dicumarol). Research into derivatives of dicumarol led to the synthesis of warfarin. When warfarin was first developed, clinical use was ruled out owing to concerns about hemorrhage. So, instead of becoming a medicine, warfarin was used to kill rats. The drug proved especially effective in this application and remains one of our most widely used rodenticides. Clinical interest in warfarin was renewed following the report of a failed suicide attempt using huge doses of a warfarin-based rat poison. The clinical trials triggered by that event soon demonstrated that warfarin could be employed safely to treat humans.

Mechanism of Action

Warfarin suppresses coagulation by decreasing production of four clotting factors, namely, factors VII, IX, X, and prothrombin. These factors are known as *vitamin K-dependent clotting factors*, because an active form of vitamin K is needed to make them. Warfarin works by inhibiting *vitamin K epoxide reductase complex 1* (VKORC1), the enzyme needed to convert vitamin K to the required active form. Because of its mechanism, warfarin is referred to as a *vitamin K antagonist*, a term that is somewhat misleading. Why? Because the term implies antagonism of vitamin K *actions*, not antagonism of vitamin K *activation*. In therapeutic doses, warfarin reduces production of vitamin K-dependent clotting factors by 30% to 50%.

Pharmacokinetics

Absorption, Distribution, and Elimination. Warfarin is readily absorbed after oral dosing. Once in the blood, about 99% of warfarin binds to albumin. Warfarin molecules that remain free (unbound) can readily cross membranes, including those of the placenta and milk-producing glands. Warfarin is inactivated in the liver, mainly by CYP2C9, the 2C9 isozyme of cytochrome P450. Metabolites are excreted in the urine and feces.

Time Course. Although warfarin acts quickly to inhibit clotting factor *synthesis*, noticeable *anticoagulant effects* are delayed. Why? Because warfarin has no effect on clotting factors already in circulation. Hence, until these clotting factors decay, coagulation remains unaffected. Since decay of clotting factors occurs with a half-life of 6 hours to 2.5 days (depending on the clotting factor under consideration), initial responses may not be evident until 8 to 12 hours after the first dose. Peak effects take several days to develop.

After warfarin is discontinued, coagulation remains inhibited for 2 to 5 days. Why? Because warfarin has a long half-life (1.5 to 2 days), and hence synthesis of new clotting factors remains suppressed, despite stopping dosing.

Therapeutic Uses

Overview of Uses. Warfarin is employed most frequently for long-term prophylaxis of thrombosis. Specific indications are (1) prevention of venous thrombosis and associated PE, (2) prevention of thromboembolism in patients with prosthetic heart valves, and (3) prevention of thrombosis in patients with atrial fibrillation. The drug has also been used to reduce the risk of recurrent transient ischemic attacks (TIAs) and recurrent MI. Because onset of effects is delayed, warfarin is not useful in emergencies. When rapid action is needed, anticoagulant therapy can be initiated with heparin.

Atrial Fibrillation. Use in atrial fibrillation requires comment. As discussed in Chapter 49 (Antidysrhythmic Drugs), atrial fibrillation carries a high risk of stroke secondary to clot formation in the atrium. (If the clot becomes dislodged, it can travel to the brain and block an artery, thereby causing ischemic stroke.) So, when people have atrial fibrillation, anticoagulant therapy is given long term to prevent clot formation. Until recently, warfarin was the only oral anticoagulant available, and hence has been the reference standard for stroke prevention. However, two new oral anticoagulants—dabigatran [Pradaxa, Pradax[®]] and rivaroxaban [Xarelto]—which are much easier to use than warfarin, are likely to displace warfarin as the treatment of choice for many patients.

Monitoring Treatment

The anticoagulant effects of warfarin are evaluated by monitoring *prothrombin time* (PT)—a coagulation test that is especially sensitive to alterations in vitamin K-dependent factors. The average pretreatment value for PT is 12 seconds. Treatment with warfarin prolongs PT.

Traditionally, PT test results had been reported as a *PT ratio*, which is simply the ratio of the patient's PT to a control PT. However, there is a serious problem with this form of reporting: Test results can vary widely among laboratories. The underlying cause of variability is thromboplastin, a critical reagent employed in the PT test. To ensure that test results from different laboratories are comparable, results are now reported in terms of an *international normalized ratio* (INR). The INR is determined by multiplying the observed PT ratio by a correction factor specific to the particular thromboplastin preparation employed for the test.

The objective of treatment is to raise the INR to an appropriate value. Recommended INR ranges are summarized in Table 52-3. As indicated, an INR of 2 to 3 is appropriate for most patients—although for some patients the target INR is 3 to 4.5. If the INR is below the recommended range, warfarin dosage should be increased. Conversely, if the INR is above the recommended range, dosage should be reduced. Unfortunately, since warfarin has a delayed onset and prolonged duration of action, the INR cannot be altered quickly: Once the dosage has been changed, it may take a week or more to reach the desired INR.

PT must be determined frequently during warfarin therapy. PT should be measured daily during the first 5 days of treatment, twice a week for the next 1 to 2 weeks, once a week for the next 1 to 2 months, and every 2 to 4 weeks thereafter. In

TABLE 52-3 ■ Monitoring Warfarin Therapy: Recommended Ranges of Prothrombin Time-Derived Values

Condition Being Treated	Recommended Ranges	
	Observed PT Ratio*	INR [†]
Acute myocardial infarction [‡]	1.3–1.5	2–3
Atrial fibrillation [‡]	1.3–1.5	2–3
Valvular heart disease [‡]	1.3–1.5	2–3
Pulmonary embolism	1.3–1.5	2–3
Venous thrombosis [§]	1.3–1.5	2–3
Tissue heart valves [‡]	1.3–1.5	2–3
Mechanical heart valves	1.5–2	3–4.5
Systemic embolism		
Prevention	1.3–1.5	2–3
Recurrent	1.5–2	3–4.5

*Observed PT ratio = ratio of patient's PT to a control PT value. In this table, the reagent used to determine the control PT value is one of the preparations of rabbit brain thromboplastin employed in the United States. Had a different preparation of thromboplastin been used, the observed PT ratio could be very different.

[†]INR = international normalized ratio. This value is calculated from the observed PT ratio. The INR is equivalent to the PT ratio that would have been obtained if the patient's PT has been compared to a PT value obtained using the International Reference Preparation, a standardized human brain thromboplastin prepared by the World Health Organization. In contrast to PT ratios, INR values are comparable from one laboratory to the next throughout the United States and the rest of the world.

[‡]For prevention of ischemic stroke and systemic embolism.

[§]Prophylaxis in high-risk surgery; treatment.

addition, PT should be determined whenever a drug that interacts with warfarin is added to or deleted from the regimen.

Concurrent therapy with heparin can influence PT values. To minimize this influence, blood for PT determinations should be drawn no sooner than 5 hours after an IV injection of heparin, and no sooner than 24 hours after a subQ injection.

PT can now be monitored at home. Several devices are available, including *CoaguChek* and the *ProTime Microcoagulation System*. These small, hand-held machines are easy to use, provide reliable results, and determine PT and INR values. In addition, the ProTime meter can be programmed by the prescriber with upper and lower INR values appropriate for the individual patient. When this is done, the meter will display either *In Range*, *INR High*, or *INR Low*, depending on the degree of anticoagulation. Home monitoring is more convenient than laboratory monitoring and gives patients a sense of empowerment. In addition, it improves anticoagulation control. In theory, home monitoring should help reduce bleeding (from excessive anticoagulation) and thrombosis (from insufficient anticoagulation). The CoaguChek meter costs about \$1300 and the ProTime meter costs about \$2000. Each test costs about \$10.

Adverse Effects

Hemorrhage. Bleeding is the major complication of warfarin therapy. Hemorrhage can occur at any site. Patients should be monitored closely for signs of bleeding (reduced

blood pressure, increased heart rate, bruises, petechiae, hematomas, red or black stools, cloudy or discolored urine, pelvic pain, headache, and lumbar pain). If bleeding develops, warfarin should be discontinued. Severe overdose can be treated with *vitamin K* (see below). Patients should be encouraged to carry identification (eg, Medic Alert bracelet) to inform emergency personnel of warfarin use. Of note, compared with warfarin, the newer oral anticoagulants—rivaroxaban and dabigatran—pose a significantly lower risk of serious bleeds.

Several measures can reduce the risk of bleeding. Candidates for treatment must be carefully screened for risk factors (see *Warnings and Contraindications* below). Prothrombin time must be measured frequently. A variety of drugs can potentiate warfarin's effects (see below), and hence must be used with care. Patients should be given detailed verbal and written instructions regarding signs of bleeding, dosage size and timing, and scheduling of PT tests. When a patient is incapable of accurate self-medication, a responsible individual must supervise treatment. Patients should be advised to make a record of each dose, rather than relying on memory. A soft toothbrush can reduce gingival bleeding. An electric razor can reduce cuts from shaving.

Warfarin intensifies bleeding during surgery. Accordingly, surgeons must be informed of warfarin use. Patients anticipating elective procedures should discontinue warfarin several days prior to the appointment. If an emergency procedure must be performed, injection of vitamin K can help suppress bleeding.

Does warfarin increase bleeding during dental surgery? Yes, but not that much. Accordingly, most patients needn't interrupt warfarin for dental procedures, including dental surgery. However, it is important that the INR be in the target range.

Fetal Hemorrhage and Teratogenesis from Use During Pregnancy. Warfarin can cross the placenta and affect the developing fetus. Fetal hemorrhage and death have occurred. In addition, warfarin can cause gross malformations, central nervous system (CNS) defects, and optic atrophy. Accordingly, *warfarin is classified in FDA Pregnancy Risk Category X: The risks to the developing fetus outweigh any possible benefits of treatment.* Women of child-bearing age should be informed about the potential for teratogenesis and advised to postpone pregnancy. If pregnancy occurs, the possibility of termination should be discussed. If an anticoagulant is needed during pregnancy, heparin, which does not cross the placenta, should be employed.

Use During Lactation. Warfarin enters breast milk. Women should be advised against breast-feeding.

Other Adverse Effects. Adverse effects other than hemorrhage are uncommon. Possible undesired responses include skin necrosis, alopecia, urticaria, dermatitis, fever, GI disturbances, and red-orange discoloration of urine, which must not be confused with hematuria. Long-term warfarin use (more than 12 months) may weaken bones, and thereby increase the risk of fractures.

Drug Interactions

General Considerations. Warfarin is subject to a large number of clinically significant adverse interactions—perhaps more than any other drug. As a result of interactions, anticoagulant effects may be reduced to the point of permitting thrombosis, or they may be increased to the point of causing hemorrhage. Patients must be informed about the potential for

TABLE 52-4 ■ Interactions Between Warfarin and Other Drugs

Drug Category	Mechanism of Interaction	Representative Interacting Drugs		
Drugs that <i>increase</i> the effects of warfarin	Displacement of warfarin from albumin	Aspirin and other salicylates Sulfonamides		
	Inhibition of warfarin degradation	Acetaminophen Amiodarone Azole antifungal agents Cimetidine Disulfiram Trimethoprim-sulfamethoxazole		
	Decreased synthesis of clotting factors	Certain parenteral cephalosporins, including cefoperazone and cefamandole		
Drugs that <i>promote bleeding</i>	Inhibition of platelet aggregation	Abciximab Aspirin and other salicylates Cilostazol Clopidogrel Dipyridamole Eptifibatid Prasugrel Ticagrelor Ticlopidine Tirofiban		
		Inhibition of clotting factors and/or thrombin	Antimetabolites Argatroban Bivalirudin Dabigatran Desirudin Fondaparinux Heparins Lepirudin Rivaroxaban	
			Promotion of ulcer formation	Aspirin Glucocorticoids Indomethacin Phenylbutazone
Drugs that <i>decrease</i> the effects of warfarin	Induction of drug-metabolizing enzymes	Carbamazepine Phenobarbital Phenytoin Rifampin		
	Promotion of clotting factor synthesis	Oral contraceptives Vitamin K ₁		
	Reduction of warfarin absorption	Cholestyramine Colestipol		

hazardous interactions and instructed to avoid *all* drugs not specifically approved by the prescriber. This prohibition includes prescription drugs and over-the-counter products.

Interactions between warfarin and other drugs are summarized in Table 52-4. As indicated, the interactants fall into three major categories: (1) *drugs that increase anticoagulant effects*, (2) *drugs that promote bleeding*, and (3) *drugs that decrease anticoagulant effects*. The major mechanisms by which anticoagulant effects can be *increased* are (1) displacement of warfarin from plasma albumin and (2) inhibition of the hepatic enzymes that degrade warfarin. The major mechanisms for *decreasing* anticoagulant effects are (1) acceleration of warfarin degradation through induction of hepatic drug-metabolizing enzymes, (2) increased synthesis of clotting factors, and (3) inhibition of warfarin absorption. Mechanisms

by which drugs can *promote bleeding*, and thereby complicate anticoagulant therapy, include (1) inhibition of platelet aggregation, (2) inhibition of the coagulation, and (3) generation of GI ulcers.

The existence of an interaction between warfarin and another drug does not absolutely preclude using the combination. The interaction does mean, however, that the combination must be used with due caution. The potential for harm is greatest when an interacting drug is being added to or withdrawn from the regimen. At these times, prothrombin time must be monitored, and the dosage of warfarin adjusted to compensate for the impact of removing or adding an interacting drug.

Specific Interacting Drugs. Of the many drugs listed in Table 52-4, a few are especially likely to produce interactions of clinical significance. Four are discussed below.

Heparin. The interaction of heparin with warfarin is obvious: Being an anticoagulant itself, heparin directly increases the bleeding tendencies brought on by warfarin. Combined therapy with heparin plus warfarin must be performed with care.

Aspirin. Aspirin inhibits platelet aggregation. By blocking aggregation, aspirin can suppress formation of the platelet plug that initiates hemostasis. To make matters worse, aspirin can act directly on the GI tract to cause ulcers, thereby initiating bleeding. Hence, when the antifibrin effects of warfarin are coupled with the antiplatelet and ulcerogenic effects of aspirin, the potential for hemorrhagic disaster is big. Accordingly, patients should be warned specifically against using any product that contains aspirin, unless the provider has prescribed aspirin therapy. Drugs similar to aspirin (eg, indomethacin, ibuprofen) should be avoided as well.

Nonaspirin Antiplatelet Drugs. Like aspirin, other antiplatelet drugs can increase the risk of bleeding with warfarin. Accordingly, these drugs (eg, clopidogrel, dipyridamole, ticlopidine, abciximab) should be used with caution.

Acetaminophen. In the past, acetaminophen was considered safe for patients on warfarin. In fact, acetaminophen was routinely recommended as an aspirin substitute for patients who needed a mild analgesic. Now, however, it appears that acetaminophen can increase the risk of bleeding: Compared with nonusers of acetaminophen, those who take just 4 regular-strength tablets a day for a week are 10 times more likely to have a dangerously high INR. Unlike aspirin, which promotes bleeding by inhibiting platelet aggregation, acetaminophen is believed to inhibit warfarin degradation, thereby raising warfarin levels. At this time, the interaction between acetaminophen and warfarin has not been proved. Nonetheless, when the drugs are combined, the INR should be monitored closely.

Other Notable Interactions. Several drugs, including *phenobarbital*, *carbamazepine*, and *rifampin*, are powerful inducers of hepatic drug-metabolizing enzymes. As a result, these drugs can accelerate warfarin degradation, thereby decreasing anticoagulant effects. Accordingly, if one of these drugs is added to the regimen, warfarin dosage must be increased. Of equal importance, when an inducer is withdrawn, causing rates of drug metabolism to decline, a compensatory decrease in warfarin dosage must be made.

Intravaginal miconazole can intensify the anticoagulant effects of warfarin. (Miconazole is the antifungal agent found in Monistat brand vaginal suppositories and cream, used for vaginal candidiasis [yeast infection].) One woman using the combination reported bruising, bleeding gums, and a nosebleed. We have long known that *systemic* miconazole (as well as other azole antifungal agents) can inhibit the metabolism of warfarin, and can thereby cause warfarin levels to rise. Apparently, intravaginal miconazole can be absorbed in amounts sufficient to do the same. Because of this interaction, women taking warfarin should not use intravaginal miconazole. If the drugs must be used concurrently, anticoagulation should be monitored closely and warfarin dosage reduced as indicated.

Like the azole antifungal agents, *cimetidine* (a drug for ulcers) and *disulfiram* (a drug for alcoholism) can inhibit warfarin metabolism, and can thereby increase anticoagulant effects.

Vitamin K increases clotting factor synthesis, and can thereby decrease anticoagulant effects.

Sulfonamide antibacterial drugs can displace warfarin from albumin, and thereby increase anticoagulant effects.

Leflunomide [Arava], a drug for arthritis, can significantly increase the INR in just a few days, probably by inhibiting warfarin degradation. Case reports suggest that two other antiarthritic agents—*glucosamine* and *chondroitin*—may also potentiate warfarin action.

Warnings and Contraindications

Like heparin, warfarin is contraindicated for patients with severe thrombocytopenia or uncontrollable bleeding and for patients undergoing lumbar puncture, regional anesthesia, or

surgery of the eye, brain, or spinal cord. Also like heparin, warfarin must be used with extreme caution in patients at high risk of bleeding, including those with hemophilia, increased capillary permeability, dissecting aneurysm, GI ulcers, and severe hypertension, and in women anticipating abortion. In addition, warfarin is contraindicated in the presence of vitamin K deficiency, liver disease, and alcoholism—conditions that can disrupt hepatic synthesis of clotting factors. Warfarin is also contraindicated during pregnancy and lactation.

Vitamin K₁ for Warfarin Overdose

The effects of warfarin overdose can be overcome with vitamin K₁ (phytonadione). Vitamin K₁ antagonizes warfarin's actions and can thereby reverse warfarin-induced inhibition of clotting factor synthesis. (Vitamin K₃—menadione—has no effect on warfarin action.)

Vitamin K may be given orally or IV; subQ administration is less effective and should be avoided. Intravenous vitamin K acts faster than oral vitamin K, but can cause severe anaphylactoid reactions, characterized by flushing, hypotension, and cardiovascular collapse. To reduce this risk, vitamin K should be diluted and infused slowly.

As a rule, small doses—2.5 mg PO or 0.5 to 1 mg IV—are preferred. Why? Because large doses (eg, 10 mg PO) can cause prolonged resistance to warfarin, thereby hampering restoration of anticoagulation once bleeding is under control.

If vitamin K fails to control bleeding, levels of clotting factors can be raised quickly by infusing fresh whole blood, fresh-frozen plasma, or plasma concentrates of vitamin K-dependent clotting factors.

What About Dietary Vitamin K?

Like medicinal vitamin K, dietary vitamin K can reduce the anticoagulant effects of warfarin. Rich dietary sources include mayonnaise, canola oil, soybean oil, and green leafy vegetables. Must patients avoid these foods? No. But they should keep intake of vitamin K constant. If vitamin K intake does increase, then warfarin dosage should be increased as well. Conversely, if vitamin K intake decreases, the warfarin dosage should decrease too.

Contrasts Between Warfarin and Heparin

Although heparin and warfarin are both anticoagulants, they differ in important ways. Whereas warfarin is given orally, heparin is given by injection. Although both drugs decrease fibrin formation, they do so by different mechanisms: heparin inactivates thrombin and factor Xa, whereas warfarin inhibits synthesis of clotting factors. Heparin and warfarin differ markedly with respect to time course of action: effects of heparin begin and fade rapidly, whereas effects of warfarin begin slowly but then persist several days. Different tests are used to monitor therapy: changes in aPTT are used to monitor heparin treatment; changes in PT are used to monitor warfarin. Finally, these drugs differ with respect to management of overdose: protamine is given to counteract heparin; vitamin K₁ is given to counteract warfarin. These differences are summarized in Table 52-5.

Dosage

Basic Considerations. Dosage requirements for warfarin vary widely among individuals, and hence dosage must be tailored to each patient. Traditionally, dosage ad-

TABLE 52-5 Summary of Contrasts Between Heparin and Warfarin

	Heparin	Warfarin
Mechanism of action	Activates antithrombin, which then inactivates thrombin and factor Xa	Inhibits synthesis of vitamin K-dependent clotting factors, including prothrombin and factor X
Route	IV or subQ	PO
Onset	Rapid (minutes)	Slow (hours)
Duration	Brief (hours)	Prolonged (days)
Monitoring	aPTT*	PT (INR) [†]
Antidote for overdose	Protamine	Vitamin K ₁

*aPTT = activated partial thromboplastin time.

[†]PT = prothrombin time. Test results are reported as an INR (international normalized ratio).

adjustments have been done empirically (ie, by trial and error). Dosing is usually begun at 2 to 5 mg/day. Maintenance dosages, which typically range from 2 to 10 mg/day, are determined by the target INR value. For most patients, dosage should be adjusted to produce an INR between 2 and 3.

Genetics and Dosage Adjustment. Patients with variant genes that code for VKORC1 and CYP2C9 are at increased risk of warfarin-induced bleeding, and hence require reduced doses. As noted above, VKORC1 is the target enzyme that warfarin inhibits, and CYP2C9 is the enzyme that metabolizes warfarin. Variations in VKORC1 increase the enzyme's sensitivity to inhibition by warfarin, and variations in CYP2C9 delay warfarin breakdown. With either variation, effects of warfarin are increased. To reduce the risk of bleeding, the FDA now recommends—but does not require—that patients undergo genetic testing for these variants. Dosage reductions based on this information can be determined using the online calculator at www.warfarindosing.org.

Preparations

Warfarin sodium [Coumadin, Jantoven] is available in tablets (1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg) for oral use. In addition, warfarin is available in a formulation for parenteral dosing, which is not commonly done.

DIRECT THROMBIN INHIBITORS

The anticoagulants discussed in this section work by direct inhibition of thrombin. Hence, they differ from the heparin-like anticoagulants, which inhibit thrombin indirectly (by enhancing the activity of antithrombin). One of the direct thrombin inhibitors—dabigatran—is administered PO; another—desirudin—is administered subQ; and three others—bivalirudin, lepirudin, and argatroban—are administered by continuous IV infusion. Only the subQ and PO drugs are suitable for outpatient use.

Dabigatran Etexilate

Dabigatran etexilate [Pradaxa, Pradax[®]], approved in 2010, is an oral prodrug that undergoes rapid conversion to *dabigatran*, a reversible, direct thrombin inhibitor. Compared with warfarin—our oldest oral anticoagulant—dabigatran has five major advantages: rapid onset; no need to monitor anticoagulation; few drug-food interactions; lower risk of major bleeding; and, since responses are predictable, the same dose can be used for all patients, regardless of age or weight. Contrasts between dabigatran and warfarin are summarized in Table 52-6.

Mechanism of Action

Dabigatran is a direct, reversible inhibitor of thrombin. The drug binds with and inhibits thrombin that is free in the blood as well as thrombin that is bound to clots. In contrast, heparin inhibits only free thrombin. By inhibiting thrombin, dabigatran (1) prevents the conversion of fibrinogen into fibrin and (2) prevents the activation of factor XIII, and thereby prevents the conversion of soluble fibrin into insoluble fibrin.

Therapeutic Use

Atrial Fibrillation. In the United States, dabigatran is approved only for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.* Approval was based on the RE-LY trial, in which over 18,000 patients were randomized to receive either dabigatran (110 or 150 mg twice daily) or warfarin (dosage adjusted to produce an INR of 2 to 3). At the lower dabigatran dose (110 mg twice daily), the incidence of bleeding with dabigatran was less than with warfarin, but protection against stroke was less too. By contrast, at the higher dose (150 mg twice daily), the incidence of bleeding with dabigatran equaled that with warfarin, but the incidence of stroke or embolism was significantly lower. On the basis of these results, the FDA concluded that, for patients with atrial fibrillation, the benefit/risk profile of dabigatran was better at 150 mg twice daily than at 110 mg twice daily, and hence they approved the higher dose for these patients.

Knee or Hip Replacement. Dabigatran is approved in Canada, but not the United States, for prevention of venous thromboembolism (VTE) following knee or hip replacement surgery. The dosage is 220 mg once daily, following an initial dose of 110 mg. The formulation employed—110-mg capsules—is not available in the United States.

Pharmacokinetics

Dabigatran etexilate is well absorbed from the GI tract, both in the presence and absence of food. (Food delays absorption, but does not reduce the extent of absorption.) Plasma levels peak about 1 hour after dosing in the absence of food, and 3 hours after dosing in the presence of food. In the blood, plasma esterases rapidly convert dabigatran etexilate to dabigatran, the drug's active form. Protein binding in blood is low (about 35%). Dabigatran is not metabolized by hepatic enzymes. Elimination is primarily renal. The half-life is 13 hours in patients with normal renal function (creatinine clearance [CrCl] 50 mL/min or higher), and increases to 18 hours in patients with moderate renal impairment (CrCl 30 to 50 mL/min).

*In Canada and Europe, dabigatran etexilate is also approved for prevention of VTE following hip and knee surgery.

TABLE 52-6 ■ Properties of the Oral Anticoagulants

	Warfarin [Coumadin]	Rivaroxaban [Xarelto]	Dabigatran Etexilate [Pradaxa, Pradax ⁺]
Mechanism	Decreased synthesis of vitamin K–dependent clotting factors	Inhibition of factor Xa	Direct inhibition of thrombin
Indications:			
Atrial fibrillation	Yes	Yes	No
Heart valve replacement	Yes	No	Yes*
Knee or hip replacement	Yes	Yes	Yes*
Onset	Delayed (days)	Rapid (hours)	Rapid (hours)
Duration	Prolonged	Short	Short
Antidote available	Yes (oral/parenteral vitamin K)	No	No
Drug-food interactions	Many	Few	Few
INR testing needed	Yes	No	No
Dosage	Adjusted based on INR	Fixed	Fixed
Doses/day	One	One	Two
Clinical experience	Extensive	Limited	Limited
Advantages, summary	<ul style="list-style-type: none"> • Decades of clinical experience • Precise dosage timing not critical, owing to long duration • Antidote available for overdose 	<ul style="list-style-type: none"> • Rapid onset • Fixed dosage • No blood tests needed • Less bleeding and hemorrhagic stroke • Few drug-food interactions 	Same as rivaroxaban
Disadvantages, summary	<ul style="list-style-type: none"> • Delayed onset • Blood tests required • No fixed dosage • Many drug-food interactions 	<ul style="list-style-type: none"> • Dosing on time is important, owing to short duration • No antidote to overdose • Limited clinical experience 	Same as rivaroxaban <i>plus</i> GI disturbances are common

*Dabigatran etexilate is approved for preventing venous thromboembolism following knee and hip replacement surgery in Canada and Europe, but not in the United States.

Adverse Effects

Bleeding. Like all other anticoagulants, dabigatran can cause bleeding. In the RE-LY trial, about 17% of patients taking 150 mg of dabigatran twice daily experienced bleeding of any intensity, and 3% experienced major bleeding. Patients who develop pathologic bleeding should stop taking the drug. Compared with warfarin, dabigatran is safer, posing a much lower risk of hemorrhagic stroke and other major bleeds.

We don't have a specific antidote to reverse dabigatran-related bleeding. In the event of life-threatening hemorrhage, treatment with recombinant factor VIIa may be tried. In addition, because dabigatran is not highly protein bound, dialysis can remove much of the drug (about 60% over 2 to 3 hours). Because dabigatran is eliminated primarily in the urine, maintaining adequate diuresis is important.

Owing to bleeding risk, dabigatran should be stopped before elective surgery. For patients with normal renal function (CrCl 50 mL/min or higher), dosing should stop 1 or 2 days before surgery. For patients with renal impairment (CrCl below 50 mL/min), dosing should stop 3 to 5 days before surgery.

Gastrointestinal Disturbances. About 35% of patients experience *dyspepsia* (abdominal pain, bloating, nausea, vomiting) and/or *gastritis-like symptoms* (esophagitis, gastroesophageal reflux disease, gastric hemorrhage, erosive gastritis, hemorrhagic gastritis, GI ulcer). Symptoms of *dyspepsia* can be reduced by taking dabigatran with food, and by using an acid-suppressing drug (proton pump inhibitor or hista-

mine₂ receptor blocker). If these measures don't help, patients may try a switch to warfarin, which carries a much lower risk of adverse GI effects.

Drug Interactions

Dabigatran is not metabolized by hepatic P450 enzymes, nor is it an inhibitor or inducer of these enzymes. Accordingly, dabigatran does not have metabolic interactions with other drugs.

Dabigatran etexilate is a substrate for intestinal *P-glycoprotein*, the transporter protein that can pump dabigatran and other drugs back into the intestine. Drugs that inhibit *P-glycoprotein* can increase dabigatran absorption and blood levels, and drugs that induce *P-glycoprotein* can decrease dabigatran absorption and blood levels. Combined use with a *P-glycoprotein inhibitor* (eg, ketoconazole, amiodarone, verapamil, quinidine) could cause bleeding from excessive dabigatran levels, and hence these combinations should be avoided. Combined use with a *P-glycoprotein inducer* appears to be safe, even though it might reduce beneficial effects somewhat.

Bleeding risk is increased by other drugs that impair hemostasis.

Preparations, Dosage, Administration, and Storage

Preparations. In the United States, dabigatran etexilate [Pradaxa] is available in two strengths: 75- and 150-mg capsules. In Canada, dabigatran etexilate [Pradax⁺] is available in three strengths: 75-, 110-, and 150-mg capsules.

Administration. Dosing may be done with or without food. Patients should swallow the capsules intact. If the capsules are crushed, chewed, or opened, absorption will be increased by 75%, thereby posing a risk of bleeding.

Dosage for Atrial Fibrillation. The usual dosage is 150 mg twice daily. If a dose is missed, it should be taken as soon as possible on the same day. However, if the missed dose cannot be taken at least 6 hours before the next scheduled dose, the missed dose should be skipped.

In patients with significant renal impairment (CrCl 15 to 30 mL/min), the dosage is 75 mg twice a day. For patients with greater renal impairment (CrCl below 15 mL/min), no dosing recommendation can be made.

Switching from Warfarin to Dabigatran. Discontinue warfarin, wait until the INR falls below 2, and then start dabigatran.

Switching from Dabigatran to Warfarin. Because onset of warfarin's effects is delayed, warfarin should be started *before* stopping dabigatran, based on CrCl as follows:

- CrCl above 50 mL/min—start warfarin 3 days before stopping dabigatran.
- CrCl 31 to 50 mL—start warfarin 2 days before stopping dabigatran.
- CrCl 15 to 30 mL—start warfarin 1 day before stopping dabigatran.
- CrCl below 15 mL/min—no recommendation can be made.

Storage. Dabigatran is unstable, especially when exposed to moisture. To maintain efficacy, the drug must be stored in the manufacturer-supplied bottle, which has a desiccant cap. Patients should open just one bottle at a time, and should not distribute dabigatran to any other container, such as a weekly pill organizer. Current labeling says that, once the bottle is opened, dabigatran should be used within 30 days. However, recent evidence indicates that dabigatran capsules maintain efficacy for 60 days, provided they are stored in the original container—away from excessive moisture, heat, and cold—with the cap tightly closed after each use.

Hirudin Analogs

Bivalirudin

Actions and Use. Bivalirudin [Angiomax], an IV direct thrombin inhibitor, has actions like those of dabigatran. The drug is a synthetic, 20-amino acid peptide chemically related to *hirudin*, an anticoagulant isolated from the saliva of leeches.

Bivalirudin is given in combination with aspirin to prevent clot formation in patients undergoing coronary angioplasty. At this time, the standard therapy for these patients is aspirin combined with a platelet glycoprotein (GP) IIb/IIIa inhibitor combined with low-dose, unfractionated heparin. Bivalirudin, an alternative to heparin in this regimen, has been studied only in combination with aspirin; it has not been studied in combination with GP IIb/IIIa inhibitors. In one trial—the Hirulog Angioplasty Study—bivalirudin plus aspirin was compared with heparin plus aspirin. Bivalirudin was at least as effective as heparin at preventing ischemic complications (MI, abrupt vessel closure, death), and caused fewer bleeding complications. In a subgroup of patients—those with postinfarction angina—bivalirudin was significantly more effective than heparin.

Adverse Effects. The most common side effects are back pain (42%), nausea (15%), hypotension (12%), and headache (12%). Other relatively common effects (incidence greater than 5%) include vomiting, abdominal pain, pelvic pain, anxiety, nervousness, insomnia, bradycardia, and fever.

Bleeding is the effect of greatest concern. However, compared with heparin, bivalirudin causes fewer incidents of major bleeding (3.7% vs. 9.3%), and fewer patients require transfusions (2% vs. 5.7%). Coadministration of bivalirudin with heparin, warfarin, or thrombolytic drugs increases the risk of bleeding.

Pharmacokinetics. With IV dosing, anticoagulation begins immediately. Drug levels are maintained by continuous infusion. Bivalirudin is eliminated primarily by renal excretion, and partly by proteolytic cleavage. The half-life is short (25 minutes) in patients with normal renal function, but may be longer in patients with renal impairment. Coagulation returns to baseline about 1 hour after stopping the infusion. Anticoagulation can be monitored by measuring activated clotting time.

Comparison with Heparin. Bivalirudin is just as effective as heparin and has several advantages: it works independently of antithrombin, inhibits clot-bound thrombin as well as free thrombin, and causes less bleeding and fewer ischemic events. However, the drug also has two disadvantages. First, there is little information on using bivalirudin with GP IIb/IIIa inhibitors, the antiplatelet drugs employed most commonly during angioplasty. In the absence of such data, cardiologists may be reluctant to switch from heparin. Second, bivalirudin is more expensive than heparin: One single-use vial, good for a full course of treatment, costs about \$420, compared with \$10 for an equivalent course of heparin. However, the manufacturer estimates that reductions in bleeding and ischemic complications would save, on average, \$300 to \$1000 per patient, which would more than offset the greater cost of

bivalirudin. The bottom line? Bivalirudin works as well as heparin, is safer, and may be equally cost effective—and hence is considered an attractive alternative to heparin for use during angioplasty.

Preparations, Dosage, and Administration. Bivalirudin [Angiomax] is supplied as a lyophilized powder (250 mg) for reconstitution in sterile water. Dosing consists of an initial IV bolus (0.75 mg/kg) followed by continuous infusion (1.75 mg/kg/hr) for the duration of the procedure, and up to 4 hours after. If necessary, bivalirudin may be infused for up to 20 additional hours at a rate of 0.2 mg/kg/hr. Treatment should begin just prior to angioplasty. Dosage should be reduced in patients with severe renal impairment. All patients should take aspirin (300 to 325 mg).

Lepirudin

Like bivalirudin, lepirudin [Refludan] is an IV anticoagulant that works by direct inhibition of thrombin. The drug is indicated for prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). As discussed above, when HIT develops, the primary treatment is to withdraw heparin and substitute a nonheparin anticoagulant—usually lepirudin or argatroban. In clinical trials, lepirudin produced effective anticoagulation in about 80% of patients, and thereby significantly reduced the risk of death and new thrombotic complications. Like other anticoagulants, lepirudin poses a risk of bleeding. The risk is increased by liver dysfunction, renal insufficiency, recent stroke or surgery, and recent therapy with thrombolytic drugs. Dosing consists of an initial IV bolus (0.4 mg/kg infused over 15 to 20 seconds) followed by a continuous infusion (0.15 mg/kg/hr) for 2 to 10 days. Dosage should be titrated to achieve an aPTT ratio (ie, the ratio between the patient's aPTT and a reference aPTT) of 1.5 to 2.5. Treatment is expensive: One week of therapy costs over \$4700.

Desirudin

Desirudin [Iprivask] is a direct thrombin inhibitor similar to bivalirudin and lepirudin. However, unlike the other two drugs, which are given by IV infusion, desirudin is given by subQ injection. Desirudin is indicated for prevention of DVT in patients undergoing elective hip replacement surgery. In clinical trials, patients experienced fewer thromboembolic events than those given unfractionated heparin or enoxaparin, an LMW heparin.

Desirudin is completely absorbed following subQ injection, achieving peak plasma levels in 1 to 3 hours. Elimination is primarily by renal excretion, and partly by proteolytic cleavage. In patients with normal renal function, the elimination half-life is 2 to 3 hours. By contrast, in those with severe renal impairment, the half-life is greatly prolonged (up to 12 hours).

As with other anticoagulants, hemorrhage is the adverse effect of greatest concern. In clinical trials, the incidence of hemorrhage was 30% in the desirudin group, compared with 33% in the enoxaparin group and 20% in the heparin group. Less serious effects include wound secretion (4%), injection-site mass (4%), anemia (3%), nausea (2%), and deep thrombophlebitis (2%).

In patients undergoing spinal or epidural anesthesia, desirudin may cause spinal or epidural hematoma, which can result in long-term or even permanent paralysis. Hematoma risk is increased by use of other drugs that impair hemostasis (eg, nonsteroidal anti-inflammatory drugs, antiplatelet drugs, warfarin, heparin). Patients should be monitored for signs of neurologic impairment, and given immediate treatment if they develop.

Desirudin [Iprivask] is supplied as a lyophilized powder (15 mg) in single-use vials. Immediately after reconstitution (with 0.5 mL of 3% mannitol in sterile water), the drug is administered by deep subQ injection into the thigh or abdominal wall. For patients with normal renal function, the dosage is 15 mg every 12 hours, beginning 5 to 15 minutes before hip surgery (but after induction of regional block anesthesia, if used). For patients with moderate renal impairment (CrCl 30 to 50 mL/min), dosage is reduced to 5 mg every 12 hours. For those with severe renal impairment (CrCl below 30 mL/min), dosage is reduced to 1.7 mg every 12 hours. For all patients, the usual duration of treatment is 9 to 12 days.

Argatroban

Like bivalirudin and lepirudin, argatroban is an IV anticoagulant that works by direct inhibition of thrombin. Like lepirudin, the drug is indicated for prophylaxis and treatment of thrombosis in patients with HIT. In clinical trials, argatroban reduced development of new thrombosis and permitted restoration of platelet counts. Like other anticoagulants, argatroban poses a risk of hemorrhage. About 12% of patients experience hematuria. Allergic reactions (dyspnea, cough, rash), which develop in 10% of patients, occur almost exclusively in those receiving either thrombolytic drugs (eg, alteplase) or contrast media for coronary angioplasty. Argatroban has a short half-life (about 45 minutes) owing to rapid metabolism by the liver. Treatment is monitored

by measuring the aPTT. When infusion of argatroban is discontinued, the aPTT returns to baseline in 2 to 4 hours.

Argatroban is supplied in 2.5-mL single-dose vials (100 mg/mL) intended for dilution followed by continuous IV infusion. Dosage depends on the setting as follows:

- For prophylaxis and treatment of thrombosis in patients with HIT and normal liver function (but who are not undergoing percutaneous coronary intervention [PCI])—The initial infusion rate is 2 mcg/kg/min. In patients with liver dysfunction, the initial rate is only 0.5 mcg/kg/min. Dosage is adjusted to maintain the aPTT at 1.5 to 3 times the baseline value.
- For prevention of thrombosis in patients with or at risk of HIT who are undergoing PCI—Give an IV bolus (350 mcg/kg) followed by continuous IV infusion (25 mcg/kg/min). Adjust the infusion rate (and perhaps give a second IV bolus) to achieve the desired activated clotting time.

RIVAROXABAN, A DIRECT FACTOR Xa INHIBITOR

Actions and Uses

Rivaroxaban [Xarelto], approved in 2011, is an oral anticoagulant that causes selective inhibition of factor Xa (activated factor X). Unlike fondaparinux, which acts indirectly (see above), rivaroxaban binds directly with the active center of factor Xa, and thereby inhibits production of thrombin. Compared with warfarin, our oldest oral anticoagulant, rivaroxaban has several advantages: rapid onset, fixed dosage, lower bleeding risk, few drug interactions, and no need for INR monitoring. Rivaroxaban has two approved uses: (1) prevention of DVT and PE following total hip or knee replacement surgery, and (2) prevention of stroke in patients with atrial fibrillation. Contrasts with warfarin are summarized in Table 52–6.

Clinical Trials

Knee and Hip Replacement Patients. In a series of trials known as RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism), rivaroxaban was compared with enoxaparin (an LMW heparin) in patients who had undergone hip or knee replacement surgery. The result? Patients who received rivaroxaban (10 mg once daily) were much less likely to experience DVT, VTE, PE, or death, compared with patients who received enoxaparin (40 mg once daily or 30 mg twice daily). With both drugs, the incidence of major bleeding episodes was low (0.2%).

Nonvalvular Atrial Fibrillation Patients. In a trial known as ROCKET AF, rivaroxaban was compared with warfarin for preventing stroke in patients with nonvalvular atrial fibrillation (ie, patients with atrial fibrillation who do not have a prosthetic heart valve or hemodynamically significant valve disease). The result? Rivaroxaban was at least as effective as warfarin, and carried the same risk of major hemorrhagic events of all kinds—but had a lower risk for intracranial bleeds and fatal bleeds.

Pharmacokinetics

Rivaroxaban is administered orally, and bioavailability is high (80% to 90%). Plasma levels peak 2 to 4 hours after dosing. Protein binding in blood is substantial (92% to 95%). Rivaroxaban undergoes partial metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450), and is a substrate for P-glycoprotein, an efflux transporter that helps remove rivaroxaban from the body. Rivaroxaban is eliminated in the urine (36% as unchanged drug) and feces (7% as unchanged drug), with a half-life of 5 to 9 hours. In patients with renal impair-

ment or hepatic impairment, rivaroxaban levels may climb dangerously high.

Adverse Effects

Bleeding. Bleeding is the most common adverse effect, and can occur at any site. Patients have experienced epidural and hematoma, as well as major intracranial, retinal, adrenal, and GI bleeds. Some people have died. Bleeding risk is increased by other drugs that impede hemostasis. How does rivaroxaban compare with warfarin? The risk of hemorrhagic stroke and other major bleeds is significantly lower with rivaroxaban.

In the event of overdose, we have no specific antidote to reverse this drug's anticoagulant effects. However we can prevent further absorption of ingested rivaroxaban with activated charcoal (see Chapter 109). Treatment with several agents—recombinant factor VIIa, prothrombin complex concentrate, or activated prothrombin complex concentrate—can be considered. However, these have not been tested in overdose patients. Because rivaroxaban is highly protein bound, dialysis is unlikely to remove it from the blood.

Spinal/Epidural Hematoma. Like all other anticoagulants, rivaroxaban poses a risk of spinal or epidural hematoma in patients undergoing spinal puncture or epidural anesthesia. Prolonged or permanent paralysis can result. Rivaroxaban should be discontinued at least 18 hours before removing an epidural catheter; once the catheter is out, another 6 hours should elapse before rivaroxaban is restarted. If a traumatic puncture occurs, rivaroxaban should be delayed for at least 24 hours. Anticoagulant-related spinal/epidural hematoma is discussed further above (see *Adverse Effects* under Heparin).

Drug Interactions

Levels of rivaroxaban can be altered by drugs that inhibit or induce CYP3A4 and P-glycoprotein. Specifically, in patients with normal renal function, drugs that inhibit CYP3A4 strongly and also inhibit P-glycoprotein (eg, ketoconazole, itraconazole, ritonavir) can raise rivaroxaban levels enough to increase the risk of bleeding. Similarly, in patients with renal impairment, drugs that inhibit CYP3A4 moderately and also inhibit P-glycoprotein (eg, amiodarone, dronedarone, quinidine, diltiazem, verapamil, ranolazine, macrolide antibiotics) can raise rivaroxaban levels enough to increase the risk of bleeding. Conversely, drugs that induce CYP3A4 strongly and also induce P-glycoprotein (eg, carbamazepine, phenytoin, rifampin, St. John's wort) may reduce rivaroxaban levels enough to increase the risk of thrombotic events. Of note, rivaroxaban itself does not inhibit or induce cytochrome P450 enzymes or P-glycoprotein, and hence is unlikely to alter the effects of other drugs.

Owing to the risk of bleeding, rivaroxaban should not be combined with other anticoagulants. Concurrent use with antiplatelet drugs and fibrinolytics should be done with caution.

Precautions

Renal Impairment. Renal impairment can delay excretion of rivaroxaban, and can thereby increase the risk of bleeding. Accordingly, rivaroxaban should be avoided in patients with severe renal impairment, indicated by a creatinine clearance (CrCl) below 30 mL/min. In patients with moderate renal impairment (CrCl 30 to 50 mL/min), rivaroxaban should be used with caution. If renal failure develops during treatment, rivaroxaban should be discontinued.

Hepatic Impairment. In clinical trials, rivaroxaban levels and anticoagulation were excessive in patients with moderate hepatic impairment. Accordingly, in patients with moderate or severe hepatic impairment, rivaroxaban should not be used.

Pregnancy. Rivaroxaban appears unsafe in pregnancy. The drug increases the risk of pregnancy-related hemorrhage, and may have detrimental effects on the fetus. When pregnant rabbits were given high doses (10 mg/kg or more) during organogenesis, rivaroxaban increased fetal resorption, decreased fetal weight, and decreased the number of live fetuses. However, dosing of rats and rabbits early in pregnancy was not associated with gross fetal malformations. Rivaroxaban is classified in FDA Pregnancy Risk Category C, and should be used only if the benefits are deemed to outweigh the risks to the mother and fetus.

Preparations, Dosage, and Administration

Rivaroxaban [Xarelto] is supplied in tablets (10, 15, and 20 mg). Whether dosing is done with food depends on the setting as follows:

- **Prevention of DVT.** The recommended dosage is 10 mg once a day, with or without food, starting 6 to 10 hours after knee or hip replacement surgery. If a dose is missed, it should be taken as soon as possible, and the next dose should be taken as originally scheduled. Treatment duration is 12 days following knee replacement and 35 days following hip replacement.
- **Nonvalvular Atrial Fibrillation.** Dosing is done once a day with the evening meal. For patients with normal renal function, the dosage is 20 mg once daily, and for patients with moderate renal impairment, the dosage is 15 mg once daily. Patients with severe renal impairment should not use this drug.

ANTITHROMBIN

As discussed earlier, antithrombin (AT) is an endogenous compound that suppresses coagulation, primarily by inhibiting thrombin and factor Xa. Clinically, AT is used to prevent thrombosis in patients with inherited AT deficiency. Currently, we have two AT preparations, marketed as *ATryn* and *Thrombate III*. *Atryn* is made by recombinant DNA technology; *Thrombate III* is made by extraction from human plasma. Nonetheless, the actions of both products are the same: suppression of coagulation mediated by thrombin and factor Xa.

Recombinant Human Antithrombin

Production. Recombinant human AT (rhAT), sold as *ATryn*, is produced in goats that have been given the DNA sequence for human AT, along with genetic instructions that cause the AT to be expressed into their milk. The rhAT produced in goats is nearly identical to endogenous AT: Both compounds have the same sequence of amino acids, but they have different patterns of glycosylation. (Glycosylation refers to sugar derivatives attached to the amino acid backbone of rhAT.) rhAT is the first drug produced in transgenic animals to be approved for use in the United States.

Therapeutic Use. In 2009, the FDA approved rhAT for prevention of perioperative or peripartum thromboembolic events in patients with inherited AT deficiency, a disorder that puts these people at high risk of venous thromboembolism. In fact, to protect against thromboembolism, these people typically require lifelong therapy with an anticoagulant, usually warfarin. During surgery or childbirth, the risk of thrombosis increases. However, there is also an obvious increase in the risk of serious bleeding. Accordingly, when patients with hereditary AT deficiency are facing childbirth or surgery, anticoagulant therapy is usually discontinued—thereby reducing the risk of bleeding, but increasing the risk of thrombosis. To reduce that risk of thrombosis, rhAT is given until anticoagulant therapy can be safely resumed. In clinical trials, rhAT prevented thromboembolism associated with childbirth or surgery in 30 of 31 patients with inherited AT deficiency.

Adverse Effects. The principal concern is hemorrhage. To minimize risk, AT activity should be monitored and, if it rises too high, the rhAT dosage should be reduced. In addition to causing outright hemorrhage, rhAT may cause hematomata, hematuria, and hemarthrosis. Infusion-site reactions are common.

Because rhAT is derived from goats' milk, there is a risk of hypersensitivity reactions. Accordingly, patients should be closely observed during the infusion period. If signs of a hypersensitivity reaction develop (eg, hives, generalized urticaria, wheezing, hypotension), rhAT should be discontinued immediately.

Unlike plasma-derived AT, rhAT poses no risk of hepatitis C and other infections.

Interaction with Heparin. As discussed earlier in the chapter, heparin produces its anticoagulant effects by enhancing the actions of AT. Accordingly, if rhAT is given to a patient taking heparin, anticoagulation will be greatly increased, thereby posing a risk of bleeding. Accordingly, if heparin is used with rhAT, tests for anticoagulation should be performed often, especially during the first hours following the initiation or termination of rhAT use.

Comparison with Plasma-Derived AT. rhAT has two advantages over plasma-derived AT. First, supplies of rhAT are more abundant. Why? Because supplies are not limited by the availability of human volunteers. Second, rhAT is safer. Why? Because plasma-derived AT carries a risk of infection, especially hepatitis C, whereas rhAT carries no such risk.

Preparations, Dosage, and Administration. rhAT [ATryn] is supplied as a powder (1750 units) in single-use vials for reconstitution with 10 mL of sterile water, followed by further dilution prior to IV infusion. Treatment consists of a 15-minute loading infusion followed immediately by a continuous maintenance infusion. The loading infusion should begin prior to delivery or 24 hours prior to surgery, and should continue until normal maintenance coagulation can be re-established. Dosage size is based on the patient's AT activity and body weight. The goal is to maintain AT activity between 80% and 120% of normal. During the maintenance infusion, AT activity should be monitored periodically, and the dosage adjusted accordingly. Treatment with rhAT is hugely expensive: The drug costs \$2.34/unit, and a full course of treatment may require 40,000 units to over 250,000 units. Financial assistance is available from the manufacturer.

Plasma-Derived Antithrombin

Plasma-derived AT [Thrombate III] is made by extraction from the plasma of human volunteers. Thrombate III is like rhAT in most regards: Both drugs share the same indication (prevention of thromboembolic events associated with surgery or childbirth in patients with inherited AT deficiency), both pose a risk of hemorrhage, both increase the anticoagulant effects of heparin, and both are given by IV infusion. The drugs differ primarily in that plasma-derived AT carries a risk of hepatitis C and other infections, whereas rhAT does not. Thrombate III is supplied as a powder (500 units) in single-use vials, and must be reconstituted with sterile water before use. As with rhAT, dosage is based on AT activity and body weight.

ANTIPLATELET DRUGS

Antiplatelet drugs suppress platelet aggregation. Since a platelet core constitutes the bulk of an *arterial thrombus*, the principal indication for the antiplatelet drugs is prevention of thrombosis in *arteries*. In contrast, the principal indication for anticoagulants (eg, heparin, warfarin) is prevention of thrombosis in *veins*.

There are three major groups of antiplatelet drugs: aspirin (a "group" with one member), P2Y₁₂ ADP receptor antagonists, and GP IIb/IIIa receptor antagonists. As indicated in Figure 52-1, aspirin and the P2Y₁₂ ADP receptor antagonists affect only one pathway in platelet activation, and hence their antiplatelet effects are limited. In contrast, the GP IIb/IIIa antagonists block the final common step in platelet activation, and hence have powerful antiplatelet effects. Properties of the major classes of antiplatelet drugs are summarized in Table 52-7.

Aspirin

The basic pharmacology of aspirin is discussed in Chapter 71. Consideration here is limited to aspirin's role in preventing arterial thrombosis.

Mechanism of Antiplatelet Action. Aspirin suppresses platelet aggregation by causing *irreversible inhibition of cyclooxygenase*, an enzyme required by platelets to synthesize thromboxane A₂ (TXA₂). As noted, TXA₂ is one of the factors

TABLE 52-7 • Properties of the Major Classes of Antiplatelet Drugs

	Aspirin, a Cyclooxygenase Inhibitor	P2Y ₁₂ Adenosine Diphosphate (ADP) Receptor Blockers	Glycoprotein (GP) IIb/IIIa Receptor Blockers
Representative drug	Aspirin	Clopidogrel [Plavix]	Tirofiban [Aggrastat]
Mechanism of antiplatelet action	Irreversibly inhibits cyclooxygenase, and thereby blocks synthesis of TXA ₂	Irreversibly blocks receptors for ADP*	Reversibly blocks receptors for GP IIb/IIIa
Route	PO	PO	IV infusion
Duration of effects	Effects persist 7–10 days after the last dose	Effects persist 7–10 days after the last dose*	Effects stop within 4 hr of stopping the infusion
Cost	\$3/month	\$87/month	\$1000/course

TXA₂ = thromboxane A₂.

*A new ADP receptor blocker—ticagrelor [Brilinta]—causes reversible ADP receptor blockade, and hence effects wear off faster than with clopidogrel.

that can promote platelet activation. In addition to activating platelets, TXA₂ acts on vascular smooth muscle to promote vasoconstriction. Both actions promote hemostasis. By inhibiting cyclooxygenase, aspirin suppresses both TXA₂-mediated vasoconstriction and platelet aggregation, thereby reducing the risk of arterial thrombosis. Since inhibition of cyclooxygenase by aspirin is irreversible, and since platelets lack the machinery to synthesize new cyclooxygenase, the effects of a single dose of aspirin persist for the life of the platelet (7 to 10 days).

In addition to inhibiting the synthesis of TXA₂, aspirin can inhibit synthesis of prostacyclin by the blood vessel wall. Since prostacyclin has effects that are exactly opposite to those of TXA₂—namely, suppression of platelet aggregation and promotion of vasodilation—suppression of prostacyclin synthesis can partially offset the beneficial effects of aspirin therapy. Fortunately, aspirin is able to inhibit synthesis of TXA₂ at doses that are lower than those needed to inhibit synthesis of prostacyclin. Accordingly, if we keep the dosage of aspirin low (325 mg/day or less), we can minimize inhibition of prostacyclin production while maintaining inhibition of TXA₂ production.

Indications for Antiplatelet Therapy. Antiplatelet therapy with aspirin has multiple indications of proven efficacy, namely

- *Ischemic stroke* (to reduce the risk of death and nonfatal stroke)
- *Transient ischemic attacks* (to reduce the risk of death and nonfatal stroke)
- *Chronic stable angina* (to reduce the risk of MI and sudden death)
- *Unstable angina* (to reduce the combined risk of death and nonfatal MI)
- *Coronary stenting* (to prevent reocclusion)
- *Acute MI* (to reduce the risk of vascular mortality)
- *Previous MI* (to reduce the combined risk of death and nonfatal MI)
- *Primary prevention of MI* (to prevent a first MI in men and in women age 65 and older)

In all of these situations, prophylactic therapy with aspirin can reduce morbidity, and possibly mortality. Primary prevention of MI is discussed further immediately below.

Primary Prevention of MI. In January of 2002, the U.S. Preventive Services Task Force (USPSTF) issued updated guidelines on the use of aspirin for primary prevention of MI. The USPSTF noted that the benefit/risk ratio is most favorable for people at high risk of MI, defined as a 3% (or higher) risk of a cardiovascular event within the next 5 years.* For these people, daily aspirin lowers the risk of MI by 28%. Conversely, for people without cardiovascular disease, benefits are minimal. Furthermore, although aspirin lowers the risk of MI, it does *not* reduce the risk of death. Cardiovascular risk is based on five factors—age, gender, cholesterol levels, blood pressure, and smoking status—and can be calculated using an online risk assessment tool, such as those at www.med-decisions.com and www.intmed.mcu.edu/clinical/heartrisk.html. Although the optimal aspirin dosage for primary prevention is unknown, low doses (eg, 81 mg/day) appear as effective as higher ones.

Adverse Effects. Even in low doses, aspirin increases the risk of GI bleeding and hemorrhagic stroke. Among middle-aged people taking aspirin for 5 years, the estimated rate of major GI bleeding episodes is 2 to 4 per 1000 patients, and the rate of hemorrhagic stroke is 0 to 2 episodes per 1000 patients. Use of enteric-coated or buffered aspirin may *not* reduce the risk of GI bleeding. Benefits of treatment must be weighed against bleeding risks. If GI bleeding occurs, adding a proton pump inhibitor (eg, omeprazole [Prilosec]) to reduce gastric acidity can help.

Dosing. Dosage for preventing cardiovascular events should be low. Maximal inhibition of platelet cyclooxygenase, and hence maximal effects on platelet function, can be produced in a few days by taking 81 mg/day. Dosages above 81 mg/day offer no increase in benefits, but do increase the risk of GI bleeding and stroke. Accordingly, for *chronic therapy*, a dosage of 81 mg/day is probably adequate. A higher dosage (eg, 325 mg/day) is indicated for *initial treatment* of an acute event, such as MI, in order to establish full antiplatelet effects rapidly—after which 81 mg/day can be taken for maintenance.

*Data from the Women's Health Study, released in 2005, show that aspirin does *not* prevent a first MI in middle-aged women, but does protect women 65 and older.

P2Y₁₂ Adenosine Diphosphate Receptor Antagonists

Drugs in this class block P2Y₁₂ ADP receptors on the platelet surface, and thereby prevent ADP-stimulated aggregation (see Fig. 52-1). Four P2Y₁₂ ADP receptor antagonists are available. Three of them—clopidogrel, prasugrel, and ticlopidine—cause irreversible receptor blockade, and the fourth—ticagrelor—causes reversible receptor blockade. Clopidogrel, prasugrel, and ticagrelor are used for secondary prevention of atherothrombotic events in patients with acute coronary syndromes (ACS), defined as unstable angina or myocardial infarction (MI). Ticlopidine is approved for stroke prevention in patients at risk. All four drugs are taken orally, and all four can cause serious bleeding.

Clopidogrel

Clopidogrel [Plavix] is an oral antiplatelet drug with effects much like those of aspirin. The drug is taken to prevent stenosis of coronary stents, and for secondary prevention of MI, ischemic stroke, and other vascular events. Clopidogrel is among the best-selling drugs in the world. In 2009, global sales totaled \$6.6 billion.

Antiplatelet Actions. Clopidogrel blocks P2Y₁₂ ADP receptors on platelets, and thereby prevents ADP-stimulated platelet aggregation. As with aspirin, antiplatelet effects are irreversible, and hence persist for the life of the platelet. Effects begin 2 hours after the first dose, and plateau after 3 to 7 days of treatment. At the recommended dosage, platelet aggregation is inhibited by 40% to 60%. Platelet function and bleeding time return to baseline 7 to 10 days after the last dose.

Pharmacokinetics. Clopidogrel is rapidly absorbed from the GI tract, both in the presence and absence of food. Bioavailability is about 50%. Clopidogrel is a *prodrug* that undergoes metabolism to its active form, primarily by hepatic CYP2C19 (the 2C19 isozyme of cytochrome P450). People with variant forms of the CYP2C19 gene are *poor metabolizers* of clopidogrel, and hence may not benefit adequately from the drug.

Therapeutic Use. Clopidogrel is used widely to prevent blockage of coronary artery stents, and to reduce thrombotic events—MI, ischemic stroke, and vascular death—in patients with ACS and in those with atherosclerosis documented by recent MI, recent stroke, or established peripheral arterial disease. In patients with ACS, clopidogrel should always be combined with aspirin (75 to 325 mg once daily).

Should clopidogrel be used in poor metabolizers? Probably not. As noted, people with variant forms of the CYP2C19 gene cannot reliably convert clopidogrel to its active form. When treated with standard dosages of clopidogrel, these poor metabolizers exhibit a higher rate of cardiovascular events compared with normal metabolizers. Poor metabolizers can be identified by testing a blood or saliva sample for CYP2C19 variants, or by simply measuring the platelet response to treatment. Unfortunately, even with this information, the course of action is not clear. Yes, we could give poor metabolizers higher doses—but doses that might be safe and effective have not been established. As an alternative, poor metabolizers could be treated with either prasugrel [Effient] or ticagrelor [Brilinta], two other P2Y₁₂ ADP receptor antagonists discussed below.

Adverse Effects. Clopidogrel is generally well tolerated. Adverse effects are about the same as with aspirin. The most common complaints are abdominal pain (6%), dyspepsia (5%), diarrhea (5%), and rash (4%).

Bleeding. Like all other antiplatelet drugs, clopidogrel poses a risk of serious bleeding. However, compared with aspirin, clopidogrel causes less GI bleeding (2% vs. 2.7%) and less intracranial hemorrhage (0.4% vs. 0.5%). Owing to bleeding risk, clopidogrel should be discontinued 5 days prior to elective surgery. If possible, major bleeding should be managed without discontinuing clopidogrel, since discontinuation would increase the risk of a thrombotic event.

Patients should be told about the risk of bleeding, and warned that they may bruise or bleed more easily, and that bleeding will take longer than usual to stop. Also, patients should be informed about signs of bleeding (eg, blood in the urine, black tarry stools, vomitus that looks like coffee grounds) and instructed to contact the prescriber if these develop. Finally, patients who develop these symptoms should be warned not to stop clopidogrel until the prescriber says they should.

Thrombotic Thrombocytopenic Purpura (TTP). Rarely, patients develop TTP, a potentially fatal condition characterized by thrombocytopenia, hemolytic anemia, neurologic symptoms, renal dysfunction, and fever. Most cases occur during the first 2 weeks of treatment. TTP is a serious disorder that requires urgent treatment, including plasmapheresis.

Drug Interactions. Drugs That Promote Bleeding. Clopidogrel should be used with caution in patients taking other drugs that promote bleeding (eg, heparin, warfarin, aspirin, and nonaspirin nonsteroidal anti-inflammatory drugs [NSAIDs]).

Proton Pump Inhibitors (PPIs). Omeprazole [Prilosec, Losec⁺] and other PPIs suppress secretion of gastric acid (see Chapter 78), and hence are often combined with clopidogrel to protect against GI bleeding. Unfortunately, PPIs may also reduce the antiplatelet effects of clopidogrel. Why? Because PPIs inhibit CYP2C19, the enzyme that converts clopidogrel to its active form. Hence the dilemma: If clopidogrel is used alone, there is a significant risk of GI bleeding; however, if clopidogrel is combined with a PPI to reduce the risk of GI bleeding, antiplatelet effects may be reduced as well. After considering the available evidence, three organizations—the American College of Cardiology, the American Heart Association, and the American College of Gastroenterology—issued a consensus document on the problem. This document, published in November 2010, concludes that, although PPIs may reduce the antiplatelet effects of clopidogrel somewhat, there is no evidence that the reduction is large enough to be clinically relevant. Accordingly, for patients who have risk factors for GI bleeding (eg, advanced age, use of NSAIDs or anticoagulants), the benefits of combining a PPI with clopidogrel probably outweigh any risk from reduced antiplatelet effects—and hence combining a PPI with clopidogrel is probably OK for these people. Conversely, for patients who lack risk factors for GI bleeding, combined use of clopidogrel with a PPI may reduce the benefits of clopidogrel without offering any meaningful GI protection—and hence combining a PPI with clopidogrel in these patients should probably be avoided. When a PPI is used with clopidogrel, pantoprazole [Protonix] would be a good choice. Why? Because, compared with other PPIs, pantoprazole causes less inhibition of CYP2C19.

CYP2C19 Inhibitors (Other Than PPIs). Like the PPIs, several other drugs can inhibit CYP2C19. Among these are cimetidine [Tagamet], fluoxetine [Prozac], fluvoxamine [Luvox], fluconazole [Diflucan], ketoconazole [Nizoral], voriconazole [Vfend], etravirine [Intelence], felbamate [Felbatol], and ticlopidine [Ticlid]. Since these drugs may reduce the antiplatelet effects of clopidogrel (by reducing its activation), use of alternative drugs is preferred.

Preparations, Dosage, and Administration. Clopidogrel [Plavix] is available in 75-mg tablets. The usual maintenance dosage is 75 mg once a day, taken with or without food. A 300-mg loading dose may be used for some patients. The optimal duration of treatment is unknown. Dosage needn't be changed for elderly patients or those with renal impairment. Patients being treated for ACS should take daily aspirin (75 to 325 mg). Clopidogrel should be withdrawn 5 days before elective surgery, and then resumed as soon as possible.

Prasugrel

Actions and Uses. Prasugrel [Effient], a close relative of clopidogrel, is an oral antiplatelet drug approved for prevention of thrombotic events in patients with ACS. Like clopidogrel, prasugrel is a prodrug that undergoes conversion to an active metabolite, which then blocks P2Y₁₂ ADP receptors on platelets, causing irreversible inhibition of platelet aggregation. Prasugrel is more effective than clopidogrel and has fewer drug interactions, but causes more major bleeding.

Clinical Trial. In a trial known as TRITON-TIMI, prasugrel was compared directly with clopidogrel. The trial enrolled over 13,000 patients with ACS who were scheduled for coronary angioplasty, also known as percutaneous coronary intervention (PCI). The goal with both drugs was to prevent thrombotic complications, including stent restenosis. The result? Patients taking prasugrel experienced fewer thrombotic events, but more major bleeding.

Pharmacokinetics. Prasugrel is rapidly absorbed after oral dosing, both in the presence and absence of food. Activation takes place in two steps. The process begins with hydrolysis by esterases in the intestine, and ends with conversion to the active metabolite in the liver, primarily by CYP3A4 and CYP2B6, two isozymes of cytochrome P450. (Note that activation of prasugrel differs from activation of clopidogrel, which is mediated by CYP2C19.) The entire activation process is fast: Plasma levels of the active metabolite peak about 30 minutes after dosing. Elimination of the active form is primarily by hepatic metabolism, followed by excretion in the urine and feces. The active metabolite has a half-life of 7 hours. In patients who weigh less than 60 kg, total exposure to the active metabolite is 30% to 40% higher than in heavier patients. Accordingly, these lighter patients may need a dosage reduction.

Adverse Effects. The principal adverse effect is *bleeding*, which occurs more often with prasugrel than with clopidogrel. According to results of TRITON-TIMI, among patients not undergoing coronary artery bypass surgery (CABG), the incidence of major bleeding is 2.4% with prasugrel versus 1.8% with clopidogrel, and the incidence of life-threatening bleeding is 0.4% versus 0.1%. Among patients who require CABG surgery, the incidence of major bleeding is greatly increased: 18.8% with prasugrel, versus 2.7% with clopidogrel. Accordingly, if CABG surgery is anticipated, prasugrel should not be started. Prasugrel should be avoided by patients at increased risk of bleeding, including patients with active pathologic bleeding, patients over the age of 75, and patients with a history of transient ischemic attacks or stroke. If possible, major bleeding should be managed without discontinuing prasugrel, since discontinuation would increase the risk of a thrombotic event.

Rarely, patients experience *hypersensitivity reactions*, including potentially life-threatening angioedema. Onset may occur within hours of the first dose, or after 5 to 10 days of treatment.

Data from TRITON-TIMI suggest that prasugrel may increase the risk of *cancer*. Among patients using the drug, there was a 62% increase in the rate of new and worsening solid tumors. However, we don't know of any plausible mechanism of tumor promotion. The FDA is monitoring for more cancer cases.

Drug Interactions. Other drugs that promote bleeding (eg, warfarin, heparin, fibrinolytic drugs, chronic NSAIDs) will increase the risk of a serious bleed, and hence should be used with great caution. PPIs, which may slow the activation of clopidogrel (by inhibiting CYP2C19), do *not* prevent the activation of prasugrel. Also, according to the prasugrel package insert, drugs that induce or inhibit CYP3A4 do *not* have a significant impact on prasugrel activity.

Preparations, Dosage, and Administration. Prasugrel [Effient] is supplied in 5- and 10-mg tablets for oral dosing, with or without food. Treat-

ment consists of a 60-mg loading dose, followed by once-daily 10-mg maintenance doses. For patients who weigh less than 60 kg, maintenance doses may be reduced to 5 mg. All patients should take aspirin daily (80 to 325 mg).

Ticagrelor

Actions and Uses. Ticagrelor [Brilinta], approved in 2011, is a P2Y₁₂ ADP receptor antagonist indicated for prevention of thrombotic events in patients with ACS. The drug inhibits platelet aggregation by blocking P2Y₁₂ ADP receptors on the platelet surface. In contrast to clopidogrel and prasugrel, which cause *irreversible* receptor blockade, ticagrelor causes *reversible* blockade, and hence the effects of ticagrelor wear off faster.

Clinical Trial. In a trial known as PLATO, ticagrelor was compared directly with clopidogrel in patients with recent-onset ACS (within the previous 24 hours). The trial randomized over 18,000 patients to receive either ticagrelor (180 mg once followed by 90 mg twice daily) or clopidogrel (300 mg once followed by 75 mg once daily). All patients also took a daily aspirin. The results? Compared with clopidogrel, ticagrelor produced a greater reduction in MI, stroke, stent restenosis, and cardiovascular death. Unfortunately, these advantages were offset by a greater risk of hemorrhagic events, including fatal intracranial bleeding.

Pharmacokinetics. Ticagrelor is administered by mouth, and food has little effect on absorption. Plasma levels peak 1.5 hours after dosing. Bioavailability is 36%. Unlike clopidogrel and prasugrel, which are prodrugs, ticagrelor is active as administered. In the liver, CYP3A4 converts much of each dose to an active metabolite. Later, the parent drug and active metabolite undergo inactivation by CYP3A4, followed by excretion in the feces (58%) and urine (26%). The elimination half-life is 7 hours for ticagrelor itself and 9 hours for the active metabolite.

Adverse Effects. The most common adverse effects are bleeding and dyspnea. Other adverse effects include headache (6.5%), cough (4.9%), dizziness (4.5%), nausea (4.3%), noncardiac chest pain (3.7%), diarrhea (3.7%), and bradycardia, including ventricular pauses.

Bleeding. Like all other antiplatelet drugs, ticagrelor poses a risk of serious bleeding. In the PLATO study, serious non-CABG bleeding developed in 4.5% of patients taking ticagrelor, compared with 3.8% of patients taking clopidogrel. However, the incidence of CABG-related bleeding was the same with both drugs. Because of bleeding risk, ticagrelor should be discontinued 5 days prior to elective surgery, and then resumed as soon as possible after the surgery is done.

Dyspnea. In the PLATO study, dyspnea developed in 13.8% of patients taking ticagrelor, compared with 7.8% of patients taking clopidogrel. Dyspnea was usually mild to moderate, and often resolved despite continued drug use. Ticagrelor-related dyspnea does not require any specific intervention.

Ventricular Pauses. Ticagrelor can cause ventricular pauses. In the PLATO trial, ventricular pauses were relatively common early in treatment (6% with ticagrelor vs. 3.5% with clopidogrel), but were much less common after 1 month (2.2% with ticagrelor vs. 1.6% with clopidogrel).

Drug Interactions. **Aspirin.** Aspirin in low doses—75 to 100 mg/day—enhances the effects of ticagrelor. However, higher doses—more than 100 mg/day—actually *reduce* the benefits of ticagrelor. Accordingly, patients should be warned against taking more than 100 mg of aspirin a day.

Drugs That Promote Bleeding. Anticoagulants (eg, warfarin, heparin, dabigatran), fibrinolytics (eg, alteplase, reteplase), and antiplatelet drugs (eg, aspirin, abciximab) will increase the risk of a serious bleed, and hence should be used with great caution.

Inhibitors and Inducers of CYP3A4. Because ticagrelor and its active metabolite are eliminated by CYP3A4, drugs that induce CYP3A4 (eg, rifampin, phenytoin, phenobarbital, carbamazepine) can reduce the therapeutic effects of both compounds, and drugs that inhibit CYP3A4 (eg, ketoconazole, itraconazole, clarithromycin, telithromycin, ritonavir, saquinavir) can increase the risk of toxicity (by allowing both compounds to accumulate to dangerous levels).

Statins. Ticagrelor inhibits CYP3A4, and can thereby increase levels of *simvastatin* and *lovastatin*. To avoid toxicity, dosages of these statins should not exceed 40 mg/day.

Digoxin. Ticagrelor and its active metabolite can inhibit P-glycoprotein, a transport molecule that promotes renal, hepatic, and intestinal elimination of drugs (see Chapter 4). P-glycoprotein inhibition is of particular concern with digoxin, a heart drug with a low margin of safety. To avoid toxicity, digoxin levels should be checked during initial ticagrelor use, and whenever ticagrelor dosage is changed.

Contraindications and Precautions. Ticagrelor is contraindicated for patients with active pathologic bleeding, a history of intracranial hemorrhage, or severe hepatic impairment. In patients with moderate hepatic impairment, ticagrelor should be used with caution (because levels of ticagrelor

itself and its active metabolite could become excessive, thereby increasing the risk of bleeding).

Preparations, Dosage, and Administration. Ticagrelor [Brilinta] is supplied in 90-mg tablets for dosing with or without food. Following an initial loading dose (180 mg), patients take 90 mg twice daily. All patients should also take daily aspirin (75 to 100 mg).

Ticlopidine

Actions. Ticlopidine [Ticlid] is a chemical relative of clopidogrel, but causes more adverse hematologic effects. Like clopidogrel, ticlopidine causes irreversible inhibition of platelet aggregation.

Uses. Ticlopidine has only one approved indication: prevention of thrombotic stroke. The drug is at least as beneficial as aspirin, but much more expensive. More importantly, ticlopidine can cause life-threatening adverse effects. Accordingly, the drug should be reserved for patients who have not responded to aspirin or cannot use aspirin because of intolerance.

Pharmacokinetics. Ticlopidine is well absorbed following oral administration. Antiplatelet effects begin within 48 hours and become maximal in about a week. The drug undergoes extensive hepatic metabolism followed by renal excretion. Ticlopidine has a long half-life (4 to 5 days). Effects persist for 7 to 10 days after drug withdrawal (ie, until new platelets have been synthesized).

Adverse Effects. Hematologic Effects. Ticlopidine can cause life-threatening hematologic reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura (TTP).

Neutropenia develops in 2.4% of patients, and is sometimes severe. Rarely, agranulocytosis develops. Both effects reverse within 1 to 3 weeks after drug withdrawal.

TTP occurs in 0.02% of patients with coronary stents who are taking ticlopidine. The mortality rate is 20% to 30%. TTP is characterized by thrombocytopenia, fever, anemia, renal dysfunction, and neurologic disturbances. The risk is highest during the first few weeks of treatment. After 12 weeks, the risk is very low. Patients should be instructed to report potential signs of TTP (eg, unusual bleeding, bruising, rash).

To reduce the risk from hematologic reactions, complete blood counts and a white cell differential should be obtained every 2 weeks during the first 12 weeks of treatment, and at any sign of infection. Ticlopidine should be withdrawn if neutropenia, agranulocytosis, or TTP develops.

Other Adverse Effects. The most common side effects are *GI disturbances* (diarrhea, abdominal pain, flatulence, nausea, dyspepsia) and *dermatologic reactions* (rash, purpura, pruritus).

Preparations, Dosage, and Administration. Ticlopidine [Ticlid] is available in 250-mg tablets. The recommended dosage is 250 mg twice a day, taken with food.

Glycoprotein IIb/IIIa Receptor Antagonists

Group Properties

The GP IIb/IIIa receptor antagonists, sometimes called “super aspirins,” are the most effective antiplatelet drugs on the market. Three agents are available: abciximab, tirofiban, and eptifibatide.

All three are administered IV, usually in combination with aspirin and low-dose heparin. Treatment is expensive, costing \$1000 or more for a brief course. Dosages are summarized in Table 52-8.

Actions. The GP IIb/IIIa antagonists cause reversible blockade of platelet GP IIb/IIIa receptors, and thereby inhibit the final step in aggregation (see Fig. 52-1). As a result, these drugs can prevent aggregation stimulated by all factors, including collagen, thromboxane A₂ (TXA₂), ADP, thrombin, and platelet activation factor.

Therapeutic Use. The GP IIb/IIIa antagonists are used short term to prevent ischemic events in patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI).

Acute Coronary Syndromes. ACS have two major manifestations: unstable angina and non-Q-wave MI. In both cases, symptoms result from thrombosis triggered by disruption of atherosclerotic plaque. When added to traditional drugs for ACS (heparin and aspirin), GP IIb/IIIa antagonists reduce the risk of ischemic complications.

Percutaneous Coronary Intervention. GP IIb/IIIa antagonists reduce the risk of rapid reocclusion following coronary artery revascularization with PCI (balloon or laser angioplasty, or atherectomy using an intra-arterial rotating blade). Reocclusion is common because PCI damages the arterial wall, and thereby encourages platelet aggregation.

Properties of Individual GP IIb/IIIa Antagonists

Abciximab. Description and Use. Abciximab [ReoPro] is a purified Fab fragment of a monoclonal antibody. The drug binds to platelets in the vicinity of GP IIb/IIIa receptors, and thereby prevents the receptors from binding fibrinogen. Abciximab, in conjunction with aspirin and heparin, is approved for IV therapy of ACS and for patients undergoing PCI. In addition, studies indicate it can accelerate revascularization in patients undergoing thrombolytic therapy for acute MI. Antiplatelet effects persist for 24 to 48 hours after stopping the infusion. The cost of a single course of treatment is about \$1200. Dosages for ACS and PCI are summarized in Table 52-8.

Adverse Effects and Interactions. Abciximab doubles the risk of major bleeding, especially at the PCI access site in the femoral artery. The drug may also cause GI, urogenital,

TABLE 52-8 • Dosages for Glycoprotein IIb/IIIa Receptor Antagonists

Application	Tirofiban [Aggrastat]	Eptifibatide [Integrilin]	Abciximab [ReoPro]
Acute coronary syndromes (ACS)	0.4 mcg/kg/min for 30 min, then 0.1 mcg/kg/min for 48–108 hr	180-mcg/kg bolus, then 2 mcg/kg/min for up to 72 hr	0.25-mg/kg bolus, then 10 mcg/kg/min for 18–24 hr
Percutaneous coronary intervention* (PCI) following treatment for ACS	Continue 0.1 mcg/kg/min for the procedure and 12–24 hr after	Consider decreasing the infusion rate to 0.5 mcg/kg/min for the procedure and 20–24 hr after	Continue 10 mcg/kg/min for the procedure and 1 hr after
PCI without prior treatment for ACS	Not FDA approved for this application	135-mcg/kg bolus prior to procedure, then 0.5 mcg/kg/min for 20–24 hr	0.25-mg/kg bolus 10–60 min before the procedure, then 0.125 mcg/kg/min (max. 10 mcg/min) for 12 hr

FDA = Food and Drug Administration.

*Balloon or laser angioplasty, or atherectomy.

and retroperitoneal bleeds. However, it does not increase the risk of fatal hemorrhage or hemorrhagic stroke. In the event of severe bleeding, infusion of abciximab and heparin should be discontinued. Other drugs that impede hemostasis will increase bleeding risk.

Eptifibatide. Eptifibatide [Integrilin] is a small peptide that causes reversible and highly selective inhibition of GP IIb/IIIa receptors. The drug is approved for patients with ACS and those undergoing PCI. Antiplatelet effects reverse within 4 hours of stopping the infusion. The most important adverse effect is bleeding, which occurs most often at the site of PCI catheter insertion, and in the GI and urinary tracts. As with other GP IIb/IIIa inhibitors, the risk of bleeding is increased by concurrent use of other drugs that impede hemostasis. Dosages are summarized in Table 52-8.

Tirofiban. Tirofiban [Aggrastat] causes selective and reversible inhibition of GP IIb/IIIa receptors. The drug—neither an antibody nor a peptide—was modeled after a platelet inhibitor isolated from the venom of the saw-scaled viper, a snake indigenous to Africa. Like other GP IIb/IIIa inhibitors, tirofiban is used to reduce ischemic events associated with ACS and PCI. Platelet function returns to baseline within 4 hours of stopping the infusion. Bleeding is the primary adverse effect. The risk of bleeding can be increased by other drugs that suppress hemostasis. Dosages for ACS and PCI are summarized in Table 52-8.

Other Antiplatelet Drugs

Dipyridamole

Dipyridamole [Persantine] suppresses platelet aggregation, perhaps by increasing plasma levels of adenosine. The drug is approved only for prevention of thromboembolism following heart valve replacement. For this application, dipyridamole is always combined with warfarin. The recommended dosage is 75 to 100 mg 4 times a day. A fixed-dose combination of dipyridamole and aspirin is indicated for recurrent stroke (see below).

Dipyridamole plus Aspirin

Actions and Use. Dipyridamole combined with aspirin is available in a fixed-dose formulation sold as *Aggrenox*. The product is used to prevent recurrent ischemic stroke in patients who have had a previous stroke or transient ischemic attack (TIA). Both drugs— aspirin and dipyridamole—suppress platelet aggregation. However, since they do so by different mechanisms, the combination is more effective than either drug alone.

Clinical Trial. The benefit of combining aspirin and dipyridamole was demonstrated in the second *European Stroke Prevention Study* (ESPS-2), a randomized controlled trial that enrolled over 6000 patients who had suffered a prior ischemic stroke or TIA. Some patients took aspirin alone (25 mg twice daily), some took dipyridamole alone (200 mg twice daily), some took both drugs, and some took placebo. The result? After 24 months, the incidence of fatal or nonfatal ischemic stroke was reduced by 16% with dipyridamole alone, 18% with aspirin alone, and 37% with the combination. Unfortunately, ESPS-2 was tainted by scientific scandal (one investigator, who later resigned, was charged with creating and falsifying data). Although all fraudulent data were discarded prior to publication, some authorities remain skeptical of the results.

Adverse Effects. The most common adverse effects of the combination are headache, dizziness, and GI disturbances (nausea, vomiting, diarrhea, abdominal pain, dyspepsia). Of course, bleeding is a concern: The product can cause hemorrhage (3.2% vs. 1.5% with placebo), nosebleed (2.4% vs. 1.5%), and purpura (1.4% vs. 0.4%). The aspirin in *Aggrenox* poses a risk of GI bleeding from peptic ulcers.

Preparations, Dosage, and Administration. *Aggrenox* capsules contain 25 mg of aspirin and 200 mg of extended-release dipyridamole. The recommended dosage is 2 capsules a day—one in the morning and one at night. The cost is about \$90 a month, compared with \$3 a month for aspirin alone. It is important to note that the daily dose of aspirin (50 mg) is lower than the dose recommended to prevent MI (at least 80 mg/day). Accordingly, supplemental aspirin may be needed.

Cilostazol

Actions and Therapeutic Use. Cilostazol [Pletal], a platelet inhibitor and vasodilator, is indicated for *intermittent claudication*. (Intermittent claudication is a syndrome characterized by pain, cramping, and weakness of the calf muscles brought on by walking and relieved by resting a few minutes. The underlying cause is atherosclerosis in the legs.) Cilostazol suppresses platelet aggregation by inhibiting type 3 phosphodiesterase (PDE3) in platelets, and promotes vasodilation by inhibiting PDE3 in blood vessels (primarily in the legs). Inhibition of platelet aggregation is greater than with aspirin,

ticlopidine, or dipyridamole. Full effects take up to 12 weeks to develop, but reverse quickly (within 48 hours) following drug withdrawal.

Adverse Effects. Cilostazol causes a variety of untoward effects. The most common is headache (34%). Others include diarrhea (19%), abnormal stools (15%), palpitations (10%), dizziness (10%), and peripheral edema (7%).

Other drugs that inhibit PDE3 have increased mortality in patients with heart failure. Whether cilostazol represents a risk is unknown. Nonetheless, heart failure is a contraindication to cilostazol use.

Drug and Food Interactions. Cilostazol is metabolized by hepatic CYP3A4, and hence cilostazol levels can be increased by CYP3A4 inhibitors, (eg, ketoconazole, itraconazole, erythromycin, fluoxetine, fluvoxamine, nefazodone, sertraline, and grapefruit juice). Metabolism of cilostazol can also be inhibited by omeprazole.

Preparations, Dosage, and Administration. Cilostazol [Pletal] is available in 50- and 100-mg tablets. The usual dosage is 100 mg twice daily, available in 50- and 100-mg tablets. The usual dosage is 100 mg twice daily, taken 30 minutes before or 2 hours after breakfast and the evening meal. Dosage should be reduced to 50 mg twice daily in patients taking omeprazole and drugs or foods that inhibit CYP3A4.

THROMBOLYTIC (FIBRINOLYTIC) DRUGS

As their name implies, thrombolytic drugs are given to remove thrombi that have already formed. This contrasts with the anticoagulants, which are given to prevent thrombus formation. In the United States, three thrombolytic drugs are available: alteplase, reteplase, and tenecteplase.* These drugs are employed acutely and only for severe thrombotic disease: acute MI, pulmonary embolism, and ischemic stroke. Principal differences among the drugs concern specific uses, duration of action, and ease of dosing. All thrombolytics pose a risk of serious bleeding, and hence should be administered only by clinicians skilled in their use. Because of their mechanism, thrombolytic drugs are also known as *fibrinolytics* (and informally as *clot busters*). Properties of individual agents are summarized in Table 52-9.

Alteplase (tPA)

Description and Mechanism. Alteplase [Activase, Cathflo Activase]—also known as *tissue plasminogen activator* (tPA)—is identical to naturally occurring human tPA. The drug is manufactured using recombinant DNA technology.

How does alteplase work? The drug first binds with *plasminogen* to form an active complex. The alteplase-plasminogen complex then catalyzes the conversion of other plasminogen molecules into *plasmin*, an enzyme that digests the fibrin meshwork of clots. In addition to digesting fibrin, plasmin degrades fibrinogen and other clotting factors. These actions don't contribute to lysis of thrombi, but they do increase the risk of hemorrhage.

Therapeutic Uses. Alteplase has three major indications: (1) acute MI, (2) acute ischemic stroke, and (3) acute massive pulmonary embolism. In all three settings, timely intervention is essential: The sooner alteplase is administered, the better the outcome.

The importance of early intervention was first demonstrated in GUSTO-I (Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries), a huge trial that evaluated the benefits of two thrombolytic drugs—alteplase (tPA) and streptokinase—in patients with acute MI. Results for alteplase were as follows: Among patients treated within

*A fourth thrombolytic drug—streptokinase—has been withdrawn from the U.S. market.

TABLE 52-9 ■ Properties of Thrombolytic (Fibrinolytic) Drugs

	Alteplase (tPA)	Tenecteplase	Retepase
Trade name	Activase, Cathflo Activase	TNKase	Retavase
Description	A compound identical to human tPA	Modified form of tPA with a prolonged half-life	A compound that contains the active sequence of amino acids present in tPA
Source	All three drugs are made using recombinant DNA technology		
Mechanism	All three promote conversion of plasminogen to plasmin, an enzyme that degrades the fibrin matrix of thrombi		
Indications:			
Acute MI	Yes	Yes	Yes
Acute ischemic stroke	Yes	No	No
Acute pulmonary embolism	Yes	No	No
Clearing a blocked central venous catheter	Yes	No	No
Adverse effect: Bleeding	With all three drugs, bleeding is the primary adverse effect		
Half-life (min)	5	20–24	13–16
Dosage and administration for acute MI	<i>Intravenous:</i> 15-mg bolus, then 50 mg infused over 30 min, then 35 mg infused over 60 min*	<i>Intravenous:</i> Single bolus based on body weight (see text)	<i>Intravenous:</i> 10-unit bolus 2 times, separated by 30 min

MI = myocardial infarction, tPA = tissue plasminogen activator.

*Dosage for patients who weigh more than 67 kg.

2 hours of symptom onset, the death rate was only 5.4%; among those treated 2 to 4 hours after symptom onset, the rate increased to 6.6%; and among those treated 4 to 6 hours after symptom onset, the rate jumped to 9.4%. Clearly, outcomes are best when thrombolytic therapy is started quickly, preferably within 2 to 4 hours of symptom onset, and even earlier if possible. Thrombolytic therapy of acute MI is discussed further in Chapter 53.

In addition to its use for acute thrombotic disease, alteplase can be used to restore patency in a clogged central venous catheter.

Pharmacokinetics. Alteplase is a large molecule that must be administered parenterally, almost always by IV infusion. The drug has a very short half-life (5 minutes) owing to rapid hepatic inactivation. Within 5 minutes of stopping an infusion, 50% of the drug is cleared from the blood. About 80% is cleared within 10 minutes.

Adverse Effect: Bleeding. Bleeding is the major complication of treatment. Intracranial hemorrhage (ICH) is by far the most serious concern. Bleeding occurs for two reasons: (1) plasmin can destroy pre-existing clots, and can thereby promote recurrence of bleeding at sites of recently healed injury; and (2) by degrading clotting factors, plasmin can disrupt coagulation, and can thereby interfere with new clot formation in response to vascular injury. Likely sites of bleeding include recent wounds, sites of needle puncture, and sites at which an invasive procedure has been performed. Anticoagulants and antiplatelet drugs further increase hemorrhage risk. Accordingly, high-dose therapy with these drugs must be avoided until thrombolytic effects of alteplase have abated.

Management of bleeding depends on severity. Oozing at sites of cutaneous puncture can be controlled with a pressure dressing. If severe bleeding occurs, alteplase should be discontinued. Patients who require blood replacement can be

given whole blood or blood products (packed red blood cells, fresh-frozen plasma). As a rule, blood replacement restores hemostasis. However, if this approach fails, excessive fibrinolysis can be reversed with IV *aminocaproic acid* [Amicar], a compound that prevents activation of plasminogen and directly inhibits plasmin.

The risk of bleeding can be lowered by

- Minimizing physical manipulation of the patient
- Avoiding subQ and IM injections
- Minimizing invasive procedures
- Minimizing concurrent use of anticoagulants (eg, heparin, warfarin, dabigatran)
- Minimizing concurrent use of antiplatelet drugs (eg, aspirin, clopidogrel)

Owing to the risk of hemorrhage, alteplase and other thrombolytic drugs must be avoided in patients at high risk for bleeding complications, and must be used with great caution in patients at lower risk of bleeding. A list of absolute and relative contraindications to thrombolytic therapy is presented in Table 52-10.

Preparations. Alteplase is available under two trade names: *Activase* (50 and 100 mg/vial) and *Cathflo Activase* (2 mg/vial). *Activase* is used to treat thrombotic disorders. *Cathflo Activase* is used to clear clogged central venous catheters. Both products are supplied as a powder to be reconstituted with sterile water. After reconstitution, the solution should stand a few minutes to allow dissipation of any large bubbles.

Dosage and Administration. Acute Myocardial Infarction (Activase only). Alteplase is usually given by an "accelerated" or "front-loaded" schedule, in which the infusion time is only 90 minutes, compared with 3 hours as routinely done in the past. Dosage is based on patient weight, but should not exceed 100 mg. Why? Because doses in excess of 100 mg are associated with an increased risk of intracranial bleeding.

For patients who weigh over 67 kg, the total dose is 100 mg, administered in three phases: a 15-mg IV bolus, followed by 50 mg infused over 30 minutes, followed in turn by 35 mg infused over 60 minutes.

TABLE 52-10 ■ Contraindications and Cautions Regarding Thrombolytic Use for Myocardial Infarction**Absolute Contraindications**

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion
- Ischemic stroke within last 3 months *except* ischemic stroke within 4.5 hr*
- Known intracranial neoplasm
- Active internal bleeding (other than menses)
- Suspected aortic dissection

Relative Contraindications/Cautions

- Severe, uncontrolled hypertension on presentation (blood pressure above 180/110 mm Hg)
- History of chronic, severe, poorly controlled hypertension
- History of prior ischemic stroke, dementia, or known intracerebral pathology not covered in absolute contraindications
- Current use of anticoagulants in therapeutic doses (INR 2–3 or greater); known bleeding diathesis
- Traumatic or prolonged (more than 10 min) CPR or major surgery (less than 3 wk ago)
- Recent internal bleeding (within 2–4 wk)
- Noncompressible vascular punctures
- Pregnancy
- Active peptic ulcer

CPR = cardiopulmonary resuscitation, INR = international normalized ratio.

*In 2009, the American Heart Association/American Stroke Association issued revised guidelines that recommend fibrinolytic therapy of ischemic stroke starting up to 4.5 hours after symptom onset, rather than just 3 hours as in the past.

Adapted from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 44:671–719, 2004.

For patients who weigh *under* 67 kg, the *maximum* dose is 100 mg, administered in three phases: a 15-mg IV bolus, followed by 0.75 mg/kg (50 mg max) infused over 30 minutes, followed in turn by 0.5 mg/kg (35 mg max) infused over 60 minutes.

Acute Ischemic Stroke (Activase only). The recommended dosage is 0.9 mg/kg (90 mg max) infused IV over 60 minutes, with 10% of the dose given as an initial IV bolus over 1 minute.

Pulmonary Embolism (Activase only). The recommended dosage is 100 mg infused IV over 2 hours.

Clearing a Central Venous Catheter (Cathflo Activase only). Use a dilute solution (1 mg/mL). Dosage is based on patient weight. For patients who weigh 30 kg or more, instill 2 mg in 2 mL of solution. For patients who weigh 10 kg to 29 kg, instill a volume equal to 110% of the internal volume of the catheter, but no more than 2 mL (2 mg of alteplase).

Tenecteplase

Tenecteplase [TNKase], a variant of human tissue plasminogen activator (tPA, alteplase), is approved only for acute MI. Except for the substitution of three amino acids, the drug is structurally identical to tPA. However, because of this small structural change, the pharmacokinetics of tenecteplase are much different. Specifically, tenecteplase is 80 times more resistant than tPA to circulating inhibitors and has a much longer half-life (20 to 24 minutes vs. 5 minutes for tPA). Like tPA, tenecteplase acts by converting plasminogen into plasmin, an enzyme that digests fibrin clots. Tenecteplase is just as safe and effective as tPA, but much easier to use: Whereas tPA must be infused over 90 minutes, tenecteplase is given as a single IV bolus. As a result, thrombolysis develops faster, and emergency personnel are spared the trouble of monitoring a prolonged infusion. Because tenecteplase is so easy to administer, it has the potential to allow dosing before the patient reaches a hospital.

Tenecteplase was compared with tPA in the second Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) study, which enrolled 16,949 patients. Tenecteplase was given as a 5-second IV bolus; tPA was infused over 90 minutes. The median time between symptom onset and starting treatment was 2.7 hours for tenecteplase and 2.8 hours for tPA. Thirty days after treatment, outcomes were equivalent with respect to mortality (6.2% with each drug), intracranial hemorrhage (0.93% with tenecteplase vs. 0.94% with tPA), and total stroke (1.78% vs. 1.66% with tPA). Of significance, the incidence of major hemorrhage (other than intracranial) was *lower* with tenecteplase (4.7% vs. 5.9%).

Tenecteplase dosage is based on body weight as follows:

- Below 60 kg: dose 30 mg
- 60 to 69.9 kg: dose 35 mg
- 70 to 79.9 kg: dose 40 mg
- 80 to 89.9 kg: dose 45 mg
- Above 90 kg: dose 50 mg

Retepase

Retepase [Retavase] is a derivative of tPA produced by recombinant DNA technology. In contrast to tPA itself, which contains 527 amino acids, reteplase is composed of only 355 amino acids. Like tPA, reteplase converts plasminogen to plasmin, which in turn digests the fibrin matrix of the thrombus. Reteplase has a short half-life (13 to 16 minutes) owing to rapid clearance by the liver and kidneys. As with other thrombolytic drugs, bleeding is the major adverse effect. The risk of bleeding is increased by concurrent use of heparin, aspirin, and other drugs that impair hemostasis.

Reteplase is approved only for acute MI. Treatment consists of two 10-unit doses separated by 30 minutes. Each dose is given by IV bolus injected over a 2-minute interval. Reteplase should not be administered through a line that contains heparin. If a heparin-containing line must be used, it should be flushed before giving reteplase.

KEY POINTS

- Hemostasis occurs in two stages: formation of a platelet plug, followed by coagulation (ie, production of fibrin, a protein that reinforces the platelet plug).
 - Platelet aggregation depends on activation of platelet glycoprotein (GP) IIb/IIIa receptors, which bind fibrinogen to form cross-links between platelets.
 - Fibrin is produced by two pathways—the contact activation pathway (aka intrinsic pathway) and the tissue factor pathway (aka extrinsic pathway)—that converge at clotting factor Xa, which catalyzes formation of thrombin, which in turn catalyzes formation of fibrin.
 - Four factors in the coagulation pathways require an activated form of vitamin K for their synthesis.
 - Plasmin, the active form of plasminogen, serves to degrade the fibrin meshwork of clots.
 - A thrombus is a blood clot formed within a blood vessel or the atria of the heart.
 - Arterial thrombi begin with formation of a platelet plug, which is then reinforced with fibrin.
 - Venous thrombi begin with formation of fibrin, which then enmeshes red blood cells and platelets.
 - Arterial thrombi are best prevented with antiplatelet drugs (eg, aspirin, clopidogrel), whereas venous thrombi are best prevented with anticoagulants (eg, heparin, warfarin, dabigatran).
 - Heparin is a large polymer (molecular weight range, 3000 to 30,000) that carries many negative charges.
 - Heparin suppresses coagulation by helping antithrombin inactivate thrombin and factor Xa.
 - Heparin is administered IV or subQ. Because of its large size and negative charges, heparin is unable to cross membranes, and hence cannot be administered PO.
 - Anticoagulant effects of heparin develop within minutes of IV administration.
 - The major adverse effect of heparin is bleeding.
 - Severe heparin-induced bleeding can be treated with protamine sulfate, a drug that binds heparin and thereby stops it from working.
 - Heparin-induced thrombocytopenia is a potentially fatal condition caused by development of antibodies against heparin–platelet protein complexes.
 - Heparin is contraindicated for patients with thrombocytopenia or uncontrollable bleeding, and must be used with extreme caution in all patients for whom there is a high likelihood of bleeding.
 - Heparin therapy is monitored by measuring the activated partial thromboplastin time (aPTT). The target aPTT is 60 to 80 seconds (ie, 1.5 to 2 times the normal value of 40 seconds).
 - Low-molecular-weight (LMW) heparins are produced by breaking molecules of unfractionated heparin into smaller pieces.
 - In contrast to unfractionated heparin, which inactivates factor Xa and thrombin equally, LMW heparins preferentially inactivate factor Xa.
 - In contrast to unfractionated heparin, LMW heparins do not bind nonspecifically to plasma proteins and tissues.
- As a result, their bioavailability is high, making their plasma levels predictable.
- Because plasma levels of LMW heparins are predictable, these drugs can be administered using a fixed dosage, with no need for routine laboratory monitoring. As a result, LMW heparins can be used at home.
 - Warfarin is our oldest *oral* anticoagulant.
 - Warfarin prevents the activation of vitamin K, and thereby blocks the biosynthesis of vitamin K–dependent clotting factors.
 - Anticoagulant responses to warfarin develop slowly and persist for several days after warfarin is discontinued.
 - Warfarin is used to prevent venous thromboembolism (VTE), and to prevent stroke and systemic embolism in patients with atrial fibrillation.
 - Warfarin therapy is monitored by measuring prothrombin time (PT). Results are expressed as an international normalized ratio (INR). An INR of 2 to 3 is the target for most patients.
 - Bleeding is the major complication of warfarin therapy.
 - Genetic testing for variant genes that code for VKORC1 and CYP2C9 can identify people with increased sensitivity to warfarin, and who therefore may need a dosage reduction.
 - Moderate warfarin overdose is treated with vitamin K.
 - Warfarin must not be used during pregnancy. The drug can cause fetal malformation, CNS defects, and optic atrophy.
 - Warfarin is subject to a large number of clinically significant drug interactions. Drugs can increase anticoagulant effects by displacing warfarin from plasma albumin and by inhibiting hepatic enzymes that degrade warfarin. Drugs can decrease anticoagulant effects by inducing hepatic drug-metabolizing enzymes, increasing synthesis of clotting factors, and inhibiting warfarin absorption. Drugs that promote bleeding, such as heparin and aspirin, will obviously increase the risk of bleeding in patients taking warfarin. Instruct patients to avoid all drugs—prescription and nonprescription—that have not been specifically approved by the prescriber.
 - Dabigatran is an oral anticoagulant that works by direct inhibition of thrombin.
 - Dabigatran is an alternative to warfarin for chronic anticoagulation in patients with atrial fibrillation.
 - Compared with warfarin, dabigatran has five *advantages*: rapid onset, fixed dosage, no need for coagulation testing, few drug/food interactions, and a lower risk of hemorrhagic stroke and other major bleeds.
 - Compared with warfarin, dabigatran has three *disadvantages*: no antidote, limited clinical experience, and more GI disturbances (dyspepsia, ulceration, gastritis, etc.).
 - Rivaroxaban is an oral anticoagulant that works by direct inhibition of factor Xa.
 - Like dabigatran, rivaroxaban is safer than warfarin and easier to use.
 - Aspirin and other antiplatelet drugs suppress thrombus formation in arteries.

- Aspirin inhibits platelet aggregation by causing irreversible inhibition of cyclooxygenase. Since platelets are unable to synthesize new cyclooxygenase, inhibition persists for the life of the platelet (7 to 10 days).
- In its role as an antiplatelet drug, aspirin is given for multiple purposes, including primary prevention of myocardial infarction (MI), acute management of MI, and reduction of cardiovascular events in patients with unstable angina, chronic stable angina, ischemic stroke, or a history of transient ischemic attacks (TIAs).
- When used to suppress platelet aggregation, aspirin is administered in low doses—typically 80 to 325 mg/day.
- Clopidogrel suppresses platelet aggregation by causing irreversible blockade of P2Y₁₂ ADP receptors on the platelet surface.
- Clopidogrel is a prodrug that undergoes conversion to its active form by hepatic CYP2C19.
- Patients with an inherited deficiency in CYP2C19 may have an unreliable response to clopidogrel.

- The major adverse effect of clopidogrel is bleeding.
- The GP IIb/IIIa receptor blockers (eg, abciximab) inhibit the final common step in platelet aggregation, and hence are the most effective antiplatelet drugs available.
- Alteplase (tPA) and other thrombolytic drugs (aka fibrinolytic drugs) are used to dissolve existing thrombi (rather than prevent thrombi from forming).
- Thrombolytic drugs work by converting plasminogen to plasmin, an enzyme that degrades the fibrin matrix of thrombi.
- Thrombolytic therapy is most effective when started early (eg, for acute MI, within 4 to 6 hours of symptom onset, and preferably sooner).
- Thrombolytic drugs carry a significant risk of bleeding. Intracranial hemorrhage is the greatest concern.

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Summary of Major Nursing Implications

HEPARIN

Preadministration Assessment

Therapeutic Goal

The objective is to prevent thrombosis without inducing spontaneous bleeding.

Heparin is the preferred anticoagulant for use during pregnancy and in situations that require rapid onset of effects, including pulmonary embolism, evolving stroke, and massive DVT. Other indications include open heart surgery, renal dialysis, and disseminated intravascular coagulation. Low doses are used to prevent postoperative venous thrombosis and to enhance thrombolytic therapy of MI.

Baseline Data

Obtain baseline values for blood pressure, heart rate, complete blood cell counts, platelet counts, hematocrit, and aPTT.

Identifying High-Risk Patients

Heparin is *contraindicated* for patients with severe thrombocytopenia or uncontrollable bleeding and for patients undergoing lumbar puncture, regional anesthesia, or surgery of the eye, brain, or spinal cord.

Use with *extreme caution* in patients at high risk of bleeding, including those with hemophilia, increased capillary permeability, dissecting aneurysm, GI ulcers, or severe hypertension. Caution is also needed in patients with severe hepatic or renal impairment.

Implementation: Administration

Routes

Intravenous (continuous infusion or intermittent) and subQ. Avoid IM injections!

Administration

General Considerations. Dosage is prescribed in units, not milligrams. Heparin preparations vary widely in concentration; read the label carefully to ensure correct dosing.

Intermittent IV Administration. Administer through a heparin lock every 4 to 6 hours. Determine the aPTT before each dose during the early phase of treatment, and daily thereafter. Rotate the injection site every 2 to 3 days.

Continuous IV Infusion. Administer with a constant infusion pump or some other approved volume-control unit. Policy may require that dosage be double-checked by a second person. Check the infusion rate every 30 to 60 minutes. During the early phase of treatment, the aPTT should be determined every 4 hours. Check the site of needle insertion periodically for extravasation.

Deep SubQ Injection. Perform subQ injections into the fatty layer of the abdomen (but not within 2 inches of the umbilicus). Draw up the heparin solution using a 20- to 22-gauge needle, and then discard that needle and replace it with a small needle ($\frac{1}{2}$ to $\frac{5}{8}$ inch, 25 or 26 gauge) to make the injection. Apply firm but gentle pressure to the injection site for 1 to 2 minutes following administration. Rotate and record injection sites.

Ongoing Evaluation and Interventions

Evaluating Treatment

We evaluate treatment by measuring the aPTT. Heparin should increase the aPTT by 1.5- to 2-fold above baseline.

Minimizing Adverse Effects

Hemorrhage. Heparin overdose may cause hemorrhage. Monitor closely for signs of bleeding. These include reduced blood pressure, elevated heart rate, discolored urine

Summary of Major Nursing Implications*—cont'd

or stool, bruises, petechiae, hematomas, persistent headache or faintness (suggestive of cerebral hemorrhage), pelvic pain (suggestive of ovarian hemorrhage), and lumbar pain (suggestive of adrenal hemorrhage). Laboratory data suggesting hemorrhage include reductions in the hematocrit and blood cell counts. If bleeding occurs, heparin should be discontinued. Severe overdose can be treated with *protamine sulfate* administered by slow IV injection. The risk of bleeding can be reduced by ensuring that the aPTT does not exceed 2 times the baseline value.

Heparin-Induced Thrombocytopenia. HIT, characterized by reduced platelet counts and increased thrombotic events, poses a risk of DVT, pulmonary embolism, cerebral thrombosis, MI, and ischemic injury to the arms and legs. To reduce risk, monitor platelet counts 2 to 3 times a week during the first 3 weeks of heparin use, and monthly thereafter. If severe thrombocytopenia develops (platelet count below $100,000/\text{mm}^3$), discontinue heparin and, if anticoagulation is still needed, substitute another anticoagulant, such as lepirudin or argatroban.

Spinal/Epidural Hematoma. Heparin and all other anticoagulants pose a risk of spinal or epidural hematoma in patients undergoing spinal puncture or spinal/epidural anesthesia. Prolonged or permanent paralysis can result. Risk of hematoma is increased by several factors, including use of an indwelling epidural catheter, use of other anticoagulants (eg, warfarin, dabigatran), and use of antiplatelet drugs (eg, aspirin, clopidogrel). Monitor for signs and symptoms of neurologic impairment. If impairment develops, immediate intervention is needed.

Hypersensitivity Reactions. Allergy may develop to antigens in heparin preparations. To minimize the risk of severe reactions, administer a small test dose prior to the full therapeutic dose.

Minimizing Adverse Interactions

Antiplatelet Drugs. Concurrent use of aspirin, clopidogrel, and other antiplatelet drugs increases the risk of bleeding. Use these agents with caution.

WARFARIN, A VITAMIN K ANTAGONIST

Preadministration Assessment

Therapeutic Goal

The goal is to prevent thrombosis without inducing spontaneous bleeding. Specific indications include prevention of venous thrombosis and associated pulmonary embolism, prevention of thromboembolism in patients with prosthetic heart valves, and prevention of stroke and systemic embolism in patients with atrial fibrillation.

Baseline Data

Obtain a thorough medical history. Be sure to identify use of any medications that might interact adversely with warfarin. Obtain baseline values of vital signs and PT. Genetic testing for variants of CYP2C9 and VKORC1 may be done to identify patients who may require a reduction in warfarin dosage.

Identifying High-Risk Patients

Warfarin is *contraindicated* in the presence of vitamin K deficiency, liver disease, alcoholism, thrombocytopenia, uncontrollable bleeding, pregnancy, and lactation, and for patients undergoing lumbar puncture, regional anesthesia, or surgery of the eye, brain, or spinal cord.

Use with *extreme caution* in patients at high risk of bleeding, including those with hemophilia, increased capillary permeability, dissecting aneurysm, GI ulcers, and severe hypertension.

Use with *caution* in patients with variant forms of CYP2C9 or VKORC1.

Implementation: Administration

Route

Oral.

Administration

For most patients, dosage is adjusted to maintain an INR value of 2 to 3. Maintain a flow chart for hospitalized patients indicating INR values, dosage size, and dosage timing.

Implementation: Measures to Enhance Therapeutic Effects

Promoting Adherence

Safe and effective therapy requires rigid adherence to the dosing schedule. Achieving adherence requires active and informed participation by the patient. **Provide the patient with detailed written and verbal instructions regarding the purpose of treatment, dosage size and timing, and the importance of careful adherence to the dosing schedule. Also, provide the patient with a chart on which to keep an ongoing record of warfarin use.** If the patient is incompetent (eg, mentally ill, alcoholic, senile), ensure that a responsible individual supervises treatment.

Nondrug Measures

Advise the patient to (1) avoid prolonged immobility, (2) elevate the legs when sitting, (3) avoid garments that can restrict blood flow in the legs, (4) participate in exercise activities, and (5) wear support hose. These measures will reduce venous stasis, and will thereby reduce the risk of thrombosis.

Ongoing Evaluation and Interventions

Monitoring Treatment

Evaluate therapy by monitoring PT. Test results are reported as an *international normalized ratio* (INR). For most patients, the target INR is 2 to 3. If the INR is below this range, dosage should be increased. Conversely, if the INR is above this range, dosage should be reduced.

The INR should be determined frequently: daily during the first 5 days, twice a week for the next 1 to 2 weeks, once a week for the next 1 to 2 months, and every 2 to 4 weeks thereafter. In addition, the INR should be determined whenever a drug that interacts with warfarin is added to or withdrawn from the regimen.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

If heparin is being employed concurrently, blood for INR determinations should be drawn no sooner than 5 hours after giving heparin IV, and no sooner than 24 hours after giving heparin subQ.

When appropriate, teach patients how to monitor their PT and INR at home.

Minimizing Adverse Effects

Hemorrhage. Hemorrhage is the major complication of warfarin therapy. Warn patients about the danger of hemorrhage, and inform them about signs of bleeding. These include reduced blood pressure, elevated heart rate, discolored urine or stools, bruises, petechiae, hematomas, persistent headache or faintness (suggestive of cerebral hemorrhage), pelvic pain (suggestive of ovarian hemorrhage), and lumbar pain (suggestive of adrenal hemorrhage). Laboratory data suggesting hemorrhage include reductions in the hematocrit and blood cell counts.

Instruct the patient to withhold warfarin and notify the prescriber if signs of bleeding are noted. Advise the patient to wear some form of identification (eg, Medic Alert bracelet) to alert emergency personnel to warfarin use.

To reduce the incidence of bleeding, advise the patient to avoid excessive consumption of alcohol. Suggest use of a soft toothbrush to prevent bleeding from the gums. Advise patients to shave with an electric razor.

Warfarin intensifies bleeding during surgical procedures. Instruct the patient to make certain the surgeon is aware of warfarin use. Warfarin should be discontinued several days prior to elective procedures. If emergency surgery must be performed, vitamin K₁ can help reduce bleeding.

Warfarin-induced bleeding can be controlled with vitamin K₁. For most patients, oral vitamin K will suffice. For patients with severe bleeding or a very high INR, vitamin K is given by injection (usually IV). The prescriber may advise the patient to keep a supply of vitamin K on hand for use in emergencies, but only after consultation with an informed clinician.

Use in Pregnancy and Lactation. Warfarin can cross the placenta, causing fetal hemorrhage and malformation. Inform women of child-bearing age about potential risks to the fetus, and warn them against becoming pregnant. If pregnancy develops, termination should be considered.

Warfarin enters breast milk and may harm the nursing infant. Warn women against breast-feeding.

Minimizing Adverse Interactions

Inform patients that warfarin is subject to a large number of potentially dangerous drug interactions. Instruct them to avoid all drugs—prescription and nonprescription—that have not been specifically approved by the pre-

scriber. Prior to treatment, take a complete medication history to identify any drugs that might interact adversely with warfarin.

CLOPIDOGREL, A P2Y₁₂ ADENOSINE DIPHOSPHATE RECEPTOR ANTAGONIST

Preadministration Assessment

Therapeutic Goal

Clopidogrel is used to prevent blockage of coronary artery stents, and to reduce thrombotic events—MI, ischemic stroke, and vascular death—in patients with ACS and in those with atherosclerosis documented by recent MI, recent stroke, or established peripheral arterial disease.

Baseline Data

Consider testing for variants of the CYP2C19 gene to determine if the patient is a poor metabolizer of clopidogrel.

Identifying High-Risk Patients

Clopidogrel is *contraindicated* in patients with active pathologic bleeding, including intracranial hemorrhage and bleeding ulcers. Use with *caution* in patients taking other drugs that promote bleeding. *Generally avoid* clopidogrel in poor metabolizers of the drug.

Implementation: Administration

Route

Oral.

Administration

Instruct patients to take clopidogrel once a day, with or without food.

Ongoing Evaluation and Interventions

Promoting Beneficial Effects

Instruct patients being treated for ACS to take aspirin (75 to 325 mg) once daily.

Minimizing Adverse Effects

Bleeding. Clopidogrel poses a risk of serious bleeding. Avoid clopidogrel in patients with active pathologic bleeding, and use with caution in patients taking other drugs that promote bleeding. If possible, manage major bleeding without stopping clopidogrel, since discontinuation would increase the risk of a thrombotic event.

Inform patients about the risk of bleeding, and warn them that:

- You may bruise more easily.
- You may bleed more easily.
- You are more likely to get nosebleeds.
- Bleeding will take longer than usual to stop.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Instruct patients to contact the prescriber if they experience any of these symptoms of bleeding:

- Unexpected bleeding
- Bleeding that lasts a long time
- Blood in the urine, indicated by discoloration (pink, red, brown)
- Blood in stools (indicated by red, black, tarry stools)
- Bruising with no obvious cause
- Vomiting blood, which may look like coffee grounds

Instruct patients that, even if these symptoms occur, they should continue taking clopidogrel until the prescriber says they should stop.

Instruct patients to discontinue clopidogrel 5 days before elective surgery.

Thrombotic Thrombocytopenic Purpura (TTP). Rarely, patients develop TTP, a potentially fatal condition characterized by thrombocytopenia, hemolytic anemia, neurologic symptoms, renal dysfunction, and fever. If TTP is diagnosed, urgent treatment—including plasmapheresis—is required.

Minimizing Adverse Interactions

Drugs That Promote Bleeding. Use with caution in patients taking other drugs that promote bleeding (eg, heparin, warfarin, dabigatran, aspirin, and nonaspirin NSAIDs).

Proton Pump Inhibitors (PPIs). The PPIs can help prevent clopidogrel-related GI bleeding—but may reduce the benefits of clopidogrel by inhibiting CYP2C19, the hepatic enzyme that converts clopidogrel to its active form. In patients with risk factors for GI bleeding (eg, advanced age, use of NSAIDs or anticoagulants), the benefits of combining a PPI with clopidogrel probably outweigh any risk from reduced antiplatelet effects. Conversely, in patients who lack risk factors for GI bleeding, combined use of clopidogrel with a PPI may reduce the benefits of clopidogrel without offering any meaningful GI protection—hence combining a PPI with clopidogrel in these patients should probably be avoided. When a PPI is used with clopidogrel, pantoprazole is a good choice because, compared with other PPIs, pantoprazole causes less inhibition of CYP2C19.

CYP2C19 Inhibitors (Other Than PPIs). Like the PPIs, several other drugs can inhibit CYP2C19. Among these are cimetidine [Tagamet], fluoxetine [Prozac], fluvoxamine [Luvox], fluconazole [Diflucan], ketoconazole [Nizoral], voriconazole [Vfend], etravirine [Intelence], felbamate [Felbatol], and ticlopidine [Ticlid]. Since these drugs may reduce the antiplatelet effects of clopidogrel, using an alternative to these drugs is preferred.

THROMBOLYTIC (FIBRINOLYTIC) DRUGS

Alteplase (tPA)

Retepase

Tenecteplase

Preadministration Assessment

Therapeutic Goal

All three thrombolytic drugs are used for acute MI, and one drug—alteplase—is also used for ischemic stroke and pulmonary embolism, and, in low dosage, for clearing blocked central venous catheters.

Baseline Data

Obtain baseline values for blood pressure, heart rate, platelet counts, hematocrit, aPTT, PT, and fibrinogen level.

Identifying High-Risk Patients

Thrombolytic drugs are *contraindicated* for patients with active bleeding, aortic dissection, acute pericarditis, cerebral neoplasm, cerebral vascular disease, or a history of intracranial bleeding.

Use with *great caution* in patients with relative contraindications, including pregnancy, severe hypertension, ischemic stroke within the prior 6 months, and major surgery within the prior 2 to 4 weeks. See Table 52-10 for a complete list of absolute and relative contraindications.

Implementation: Administration

Route

Intravenous.

Administration (for Acute MI)

Alteplase. Administer as an initial IV bolus followed by a 90-minute IV infusion.

Tenecteplase. Administer as a single IV bolus.

Retepase. Administer as two IV boluses, separated by 30 minutes.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hemorrhage. Thrombolytics may cause bleeding; ICH is the greatest concern. To reduce the risk of major bleeding, minimize manipulation of the patient, avoid subQ and IM injections, minimize invasive procedures, and minimize concurrent use of anticoagulants and antiplatelet drugs. Manage oozing at cutaneous puncture sites with a pressure dressing.

Minimizing Adverse Interactions

Anticoagulants and Antiplatelet Drugs. Anticoagulants (eg, heparin, warfarin, dabigatran) and antiplatelet drugs (eg, aspirin, clopidogrel) increase the risk of bleeding from antithrombotics. Avoid high-dose therapy with these drugs until thrombolytic effects have subsided.

*Patient education information is highlighted as blue text.

Management of ST-Elevation Myocardial Infarction

Pathophysiology of STEMI

Diagnosis of STEMI

Management of STEMI

Routine Drug Therapy

Reperfusion Therapy

Adjuncts to Reperfusion Therapy

Complications of STEMI

Secondary Prevention of STEMI

Myocardial infarction (MI), also known as heart attack, is defined as necrosis of the myocardium (heart muscle) resulting from local ischemia (deficient blood flow). The underlying cause is partial or complete blockage of a coronary artery. When blockage is complete, the area of infarction is much larger than when the blockage is partial. In this chapter, discussion is limited to acute MI caused by *complete* interruption of regional myocardial blood flow. This class of MI is called *ST-elevation MI* (STEMI), because it causes elevation of the ST segment on the electrocardiogram (ECG). Management of STEMI differs from management of non-ST-elevation MI, which occurs when blockage of blood flow is only partial.

In the United States, STEMI strikes about 500,000 people each year and is the most common cause of death. Between 20% and 30% of STEMI victims die before reaching the hospital, another 9.9% die in the hospital, and 7.1% die within a year of hospital discharge. Risk factors for STEMI include advanced age, a family history of MI, sedentary lifestyle, obesity, high serum cholesterol, hypertension, smoking, and diabetes. The objectives of this chapter are to describe the pathophysiology of STEMI and to discuss interventions that can help reduce morbidity and mortality.

PATHOPHYSIOLOGY OF STEMI

Acute MI occurs when blood flow to a region of the myocardium is stopped owing to platelet plugging and thrombus formation in a coronary artery—almost always at the site of a fissured or ruptured atherosclerotic plaque. Myocardial injury is ultimately the result of an imbalance between oxygen demand and oxygen supply.

In response to local ischemia, a dramatic redistribution of ions takes place. Hydrogen ions accumulate in the myocardium and calcium ions become sequestered in mitochondria. The resultant acidosis and functional calcium deficiency alter the distensibility of cardiac muscle. Sodium ions accumulate in myocardial cells and promote edema. Potassium

ions are lost from myocardial cells, thereby setting the stage for dysrhythmias.

Local metabolic changes begin rapidly following coronary arterial occlusion. Within seconds, metabolism shifts from aerobic to anaerobic. High-energy stores of ATP and creatine phosphate become depleted. As a result, contraction ceases in the affected region.

If blood flow is not restored, cell death begins within 20 minutes. Clear indices of cell death—myocyte disruption, coagulative necrosis, elevation of cardiac proteins in serum—are present by 24 hours. By 4 days, monocyte infiltration and removal of dead myocytes weaken the infarcted area, making it vulnerable to expansion and rupture. Structural integrity is partially restored with deposition of collagen, which begins in 10 to 12 days, and ends with dense scar formation by 4 to 6 weeks.

Myocardial injury also triggers ventricular remodeling, a process in which ventricular mass increases and the chambers change in volume and shape. Remodeling is driven in part by local production of angiotensin II. Ventricular remodeling increases the risk of heart failure and death.

The degree of residual cardiac impairment depends on how much of the myocardium was damaged. With infarction of 10% of left ventricular (LV) mass, the ejection fraction is reduced. With 25% LV infarction, cardiac dilation and heart failure occur. With 40% LV infarction, cardiogenic shock and death are likely.

DIAGNOSIS OF STEMI

Acute STEMI is diagnosed by the presence of chest pain, characteristic ECG changes, and elevated serum levels of myocardial cellular components (troponin, creatine kinase). Other symptoms include sweating, weakness, and a sense of impending doom. Of note, about 20% of people with STEMI experience no symptoms.

Chest Pain. Patients undergoing STEMI typically experience severe substernal pressure that they characterize as unbearable crushing or constricting pain. The pain often radiates down the arms and up to the jaw. STEMI can be differentiated from angina pectoris in that pain caused by STEMI lasts longer (20 to 30 minutes) and is not relieved by nitroglycerin. Some patients confuse the pain of STEMI with indigestion.

ECG Changes. Acute STEMI produces changes in the ECG. Why? Because conduction of electrical impulses through the heart becomes altered in the region of injury. Elevation of the ST segment, which defines STEMI, occurs almost immediately in response to acute ischemia (Fig. 53-1). Following a period of ST-segment elevation, a prominent Q wave (more than 40 milliseconds in duration) develops in

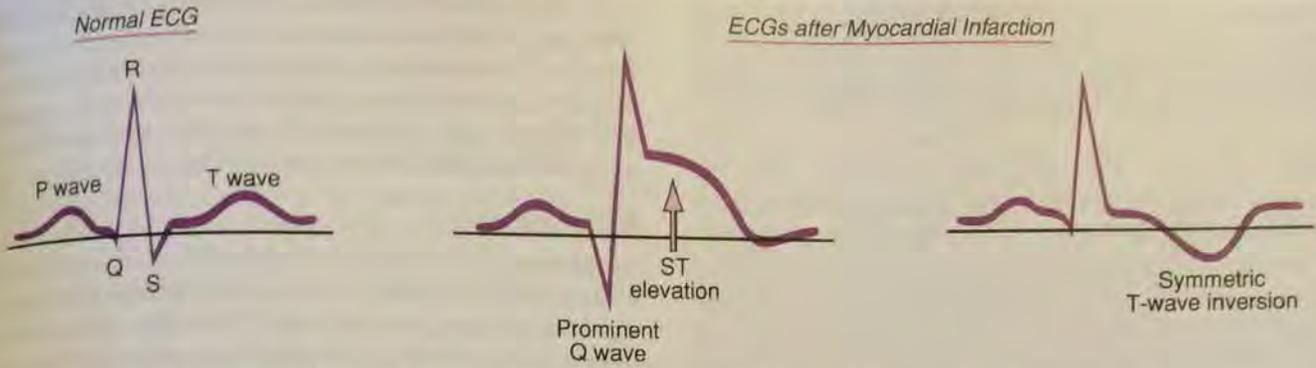


Figure 53-1 • ECG changes associated with ST-elevation myocardial infarction.

the majority of patients. (Q waves are small or absent in the normal ECG.) Over time, the ST segment returns to baseline, after which a symmetric inverted T wave appears. This T-wave inversion may resolve within weeks to months. Q waves may resolve over a period of years.

Biochemical Markers for MI. When myocardial cells undergo necrosis, they release intracellular proteins (eg, cardiac troponins, creatine kinase). Hence, elevations in these proteins in blood can be diagnostic of STEMI.

Today, cardiac-derived troponins—*cardiac troponin I* and *cardiac troponin T*—are considered the best serum markers for STEMI. These proteins are components of the sarcomere, and are distinct from their counterparts in skeletal muscle. Under normal conditions, troponin I and troponin T are undetectable in blood. However, when STEMI occurs, their levels rise dramatically, often to 100-fold or more above the lower limits of detection. Cardiac troponins become detectable 2 to 4 hours after symptom onset, peak in 10 to 24 hours, and return to undetectable in 5 to 14 days. Measurements of troponin I and troponin T are more sensitive than measurements of other biochemical markers for STEMI, and produce fewer false-positive or false-negative results.

Before cardiac troponins became the preferred biomarkers for STEMI, clinicians relied on measurement of the MB isozyme of creatine kinase (CK-MB). Since CK-MB is found primarily in cardiac muscle rather than skeletal muscle, an increase in serum CK-MB is highly suggestive of cardiac injury. Following MI, serum levels of CK-MB begin to rise in 4 to 8 hours, peak in 24 hours, and return to baseline in 36 to 72 hours. In some patients, the increase in CK-MB may be too small to allow a definitive diagnosis, even though significant myocardial injury has occurred.

Heart Association (AHA), and the Society for Cardiovascular Angiography and Interventions (SCAI) have published a series of evidence-based guidelines, including the following:

- ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction)
- 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines
- 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines
- 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

These guidelines are available online at circ.ahajournals.org. The discussion below reflects recommendations in these documents.

Routine Drug Therapy

When a patient presents with suspected STEMI, several interventions should begin immediately. The objective is to minimize possible myocardial necrosis while waiting for a clear diagnosis. Once STEMI has been diagnosed, more definitive therapy—reperfusion—can be implemented (see below).

Oxygen

Supplemental oxygen, administered by nasal cannula, can increase arterial oxygen saturation, and can thereby increase oxygen delivery to the ischemic myocardium. Accordingly, current guidelines recommend giving oxygen to all patients with reduced arterial oxygen saturation (below 90%). However, although oxygen is recommended, and using it seems to

MANAGEMENT OF STEMI

The acute phase of management refers to the interval between the onset of symptoms and discharge from the hospital (usually 6 to 10 days). The goal is to bring cardiac oxygen supply back in balance with oxygen demand. This can be accomplished by reperfusion therapy, which restores blood flow to the myocardium, and by reducing myocardial oxygen demand. The first few hours of treatment are most critical. The major threats to life during acute STEMI are ventricular dysrhythmias, cardiogenic shock, and heart failure.

To aid clinicians in the management of STEMI, the American College of Cardiology (ACC), the American

make sense, the practice is not evidence based. That is, we have no hard evidence to show that oxygen is beneficial. In fact there is some evidence that oxygen may actually be harmful, causing mortality to increase rather than decline.

Aspirin

Aspirin suppresses platelet aggregation, producing an immediate antithrombotic effect. In the Second International Study of Infarct Survival (ISIS-2), aspirin caused a substantial reduction in mortality. Moreover, benefits were synergistic with fibrinolytic drugs: mortality was 13.2% with fibrinolytics alone, and dropped to 8% with the addition of aspirin. Because of these benefits, virtually all patients with evolving STEMI should get aspirin. Therapy should begin immediately after onset of symptoms, and should continue indefinitely. The first dose (162 to 325 mg) should be chewed to allow rapid absorption across the buccal mucosa. Prolonged therapy (with 81 to 162 mg/day) reduces the risk of reinfarction, stroke, and death.

Nonaspirin NSAIDs

According to the 2007 guideline updates, routine use of nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin should be *discontinued*. Why? Because, unlike aspirin, these agents increase the risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture.

Morphine

Intravenous morphine is the treatment of choice for STEMI-associated pain. In addition to relieving pain, morphine can improve hemodynamics. By promoting venodilation, the drug reduces cardiac preload. By promoting modest arterial dilation, morphine may cause some reduction in afterload. The combined reductions in preload and afterload lower cardiac oxygen demand, thereby helping preserve the ischemic myocardium.

Beta Blockers

When given to patients undergoing acute STEMI, beta blockers (eg, atenolol, metoprolol) reduce cardiac pain, infarct size, and short-term mortality. Recurrent ischemia and reinfarction are also decreased. Reduction in myocardial wall tension may decrease the risk of myocardial rupture. Continued use of an oral beta blocker increases long-term survival. Unfortunately, although nearly all patients can benefit from beta blockers, many don't get them. Furthermore, among patients who *do* get a beta blocker, the dosage is often too low.

Benefits result from several mechanisms. As STEMI evolves, traffic along sympathetic nerves to the heart increases greatly, as does the number of beta receptors in the heart. As a result, heart rate and force of contraction rise substantially, thereby increasing cardiac oxygen demand. By preventing beta receptor activation, beta blockers reduce heart rate and contractility, and thereby reduce oxygen demand. They reduce oxygen demand even more by lowering blood pressure. By prolonging diastolic filling time, beta blockers increase coronary blood flow and myocardial oxygen supply. Additional benefits derive from antidysrhythmic actions.

Beta blockers should be used routinely in the absence of specific contraindications (eg, asthma, bradycardia, significant LV dysfunction). The initial dose may be oral or IV; oral dosing is used thereafter. Treatment with an oral beta blocker should begin within 24 hours and should continue for at least 2 to 3 years, and perhaps longer. Beta blockers are especially

good for patients with reflex tachycardia, systolic hypertension, atrial fibrillation, and atrioventricular conduction abnormalities. Contraindications include overt severe heart failure, pronounced bradycardia, persistent hypotension, advanced heart block, and cardiogenic shock. The basic pharmacology of the beta blockers is presented in Chapter 18.

Nitroglycerin

In patients with STEMI, nitroglycerin has several beneficial effects: It can (1) reduce preload, and thereby reduce oxygen demand; (2) increase collateral blood flow in the ischemic region of the heart; (3) control hypertension caused by STEMI-associated anxiety; and (4) limit infarct size and improve LV function. However, despite these useful effects, nitroglycerin does not reduce mortality. Nonetheless, since the drug is easily administered, offers hemodynamic benefits, and helps relieve ischemic chest pain, it continues to be used. According to the current guidelines, patients with ongoing ischemic discomfort should be given sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of three doses, and then be assessed to determine whether IV nitroglycerin should be given. Indications for IV therapy include persisting ischemic discomfort, hypertension, and pulmonary congestion. Nitroglycerin should be avoided in patients with hypotension (systolic pressure below 90 mm Hg), severe bradycardia (heart rate below 50 bpm), marked tachycardia (heart rate above 100 bpm), or suspected right ventricular infarction. In addition, nitroglycerin should be avoided in men who have taken sildenafil or vardenafil for erectile dysfunction within the last 24 hours, or tadalafil within the last 48 hours.

Reperfusion Therapy

The goal of reperfusion therapy is to restore blood flow through the blocked coronary artery. Reperfusion is the most effective way to preserve myocardial function and limit infarct size. How do we accomplish reperfusion? Either with fibrinolytic drugs (also known as thrombolytic drugs) or with percutaneous coronary intervention (PCI), usually balloon angioplasty coupled with placement of a stent. Both options are very effective. However, PCI is generally preferred. The relative advantages of fibrinolytic therapy and primary PCI are summarized in Table 53-1. With either intervention, rapid implementation is essential.

TABLE 53-1 ■ Comparison of Fibrinolytic Therapy with Primary PCI

Advantages of Fibrinolytic Therapy

- More universal access
- Shorter time to treatment
- Results less dependent on physician experience
- Lower system cost

Advantages of Primary PCI

- Higher initial reperfusion rates
- Less residual stenosis
- Lower recurrence rates of ischemia/infarction
- Does not promote intracranial bleeding
- Defines coronary anatomy and LV function
- Can be used when fibrinolytic therapy is contraindicated

LV = left ventricular, PCI = percutaneous coronary intervention

Primary Percutaneous Coronary Intervention

The term *primary PCI* refers to the use of angioplasty, rather than fibrinolytic therapy, to recanalize an occluded coronary artery. In almost all cases, PCI consists of balloon angioplasty coupled with placement of a drug-eluting stent (as discussed in Chapter 51 under *Revascularization Therapy: CABG and PCI*). Under current guidelines, the institutional goal is to implement PCI within 90 minutes of initial patient contact. As discussed below, all patients undergoing PCI should receive an anticoagulant (IV heparin) combined with antiplatelet drugs: aspirin plus either clopidogrel or prasugrel, and perhaps a glycoprotein IIb/IIIa inhibitor.

The success rate with primary PCI is somewhat higher than with fibrinolytic therapy. Moreover, studies indicate that the benefits of PCI last longer. After 30 days, the rate of death, reinfarction, or disabling stroke following PCI is 9.6%, versus 13.6% following fibrinolytic therapy using tissue plasminogen activator (tPA). After 5 years, the rate of all-cause mortality following PCI is 13%, versus 24% with streptokinase—the difference being due entirely to lower cardiovascular mortality in PCI-treated patients. Benefits of primary PCI over fibrinolytic therapy are greatest in high-risk patients.

Fibrinolytic Therapy

Fibrinolytic drugs dissolve clots. How? By converting plasminogen into plasmin, a proteolytic enzyme that digests the fibrin meshwork that holds clots together. In the United States, three fibrinolytic drugs are available: *alteplase (tPA)*, *reteplase*, and *teneceplase*. A fourth agent—streptokinase—has been withdrawn. The basic pharmacology of these drugs is presented in Chapter 52. Discussion here is limited to their use in STEMI.

Fibrinolytic therapy is most effective when presentation is early. When thrombolytics are given soon enough, the occluded artery can be opened in 80% of patients. Current guidelines suggest a target of 30 minutes or less for the time between entering the emergency department and starting fibrinolysis. Clinical trials have shown that timely therapy improves ventricular function, limits infarct size, and reduces mortality. Restoration of blood flow reduces or eliminates chest pain, and often reduces ST elevation. Current guidelines restrict fibrinolytic therapy to patients with ischemic pain that has been present no more than 12 hours. Patients for whom fibrinolytic therapy is contraindicated are listed in Table 53–2.

Under *typical* conditions, all fibrinolytics are equally beneficial. However, under *ideal* conditions (ie, treatment within 4 to 6 hours of pain onset), alteplase is most effective, especially in patients under age 75 as shown in a trial known as GUSTO-I. Unfortunately, alteplase is very expensive.

The major complication of fibrinolytic therapy is bleeding, which occurs in 1% to 5% of patients. Intracranial hemorrhage (ICH) is the greatest concern. ICH has an incidence of 0.5% to 1%, and is most likely in the elderly. Nonetheless, the benefits of fibrinolysis generally outweigh the risks.

As discussed below, all patients undergoing fibrinolytic therapy should receive an anticoagulant (IV heparin) plus antiplatelet drugs (aspirin plus either clopidogrel or prasugrel—but not a glycoprotein IIb/IIIa inhibitor, such as abciximab).

TABLE 53–2 ■ Contraindications and Cautions Regarding Fibrinolytic Use for Myocardial Infarction

Absolute Contraindications

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion
- Ischemic stroke within last 3 months *except* ischemic stroke within 3 hr
- Known intracranial neoplasm
- Active internal bleeding (other than menses)
- Suspected aortic dissection

Relative Contraindications/Cautions

- Severe, uncontrolled hypertension on presentation (blood pressure above 180/110 mm Hg)
- History of chronic, severe, poorly controlled hypertension
- History of prior ischemic stroke, dementia, or known intracerebral pathology not covered in contraindications
- Current use of anticoagulants in therapeutic doses (INR 2–3 or greater); known bleeding diathesis
- Traumatic or prolonged (more than 10 min) CPR or major surgery (less than 3 wk ago)
- Recent internal bleeding (within 2–4 wk)
- Noncompressible vascular punctures
- Pregnancy
- Active peptic ulcer

CPR = cardiopulmonary resuscitation, INR = international normalized ratio.

Adapted from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 44:671–719, 2004.

Adjuncts to Reperfusion Therapy

Heparin

Heparin is a parenteral anticoagulant that was used widely to treat MI before fibrinolytics and primary PCI became available. The drug was shown to decrease mortality, reinfarction, stroke, pulmonary embolism, and deep vein thrombosis. Today, heparin is used in conjunction with fibrinolytics and PCI to reduce the risk of thrombosis. The main complication of heparin is bleeding.

Heparin is recommended for all STEMI patients undergoing fibrinolytic therapy or PCI. For those receiving fibrinolytic drugs, treatment should begin prior to giving the fibrinolytic, and should continue for at least 48 to 72 hours after. For patients undergoing PCI, heparin is given once, immediately before the procedure.

As discussed in Chapter 52, heparin is available as the intact (unfractionated) drug and in low-molecular-weight (LMW) forms. When heparin is used as an adjunct to fibrinolytic therapy, selection of a heparin product depends on duration of use. For treatment lasting less than 48 hours, *unfractionated* heparin can be employed. However, for treatment lasting more than 48 hours, an *LMW* heparin should be chosen. Why? Because prolonged use of unfractionated heparin poses a risk of heparin-induced thrombocytopenia.

Antiplatelet Drugs

Thienopyridines: Clopidogrel and Prasugrel. Clopidogrel [Plavix] and prasugrel [Effient] suppress platelet aggregation by blocking receptors for adenosine diphosphate (see Chapter 52). These drugs are recommended for all MI patients undergoing reperfusion therapy, and even for those who do not undergo reperfusion. In all cases, clopidogrel or prasugrel should be combined with aspirin. In patients undergoing PCI with stenting, duration of treatment should be at least 12 months, unless the risk of bleeding outweighs the benefits of continued drug use. In patients undergoing fibrinolytic therapy, dosing should continue at least 14 days. Which is better, clopidogrel or prasugrel? Current guidelines do not endorse one over the other.

Glycoprotein (GP) IIb/IIIa Inhibitors. As discussed in Chapter 52, the GP IIb/IIIa inhibitors (eg, abciximab [ReoPro]) are powerful, intravenous antiplatelet drugs that inhibit the final step in platelet aggregation. These drugs are recommended for patients undergoing PCI, but not for those undergoing fibrinolytic therapy. Of the three GP IIb/IIIa inhibitors available, abciximab is preferred. Treatment should begin as soon as possible before PCI and should continue for 12 hours after.

Aspirin. As discussed above, *low-dose* aspirin (81 to 162 mg/day) should be taken indefinitely by all people who have had an MI. In addition, *higher-dose* aspirin (162 to 325 mg/day) is recommended for patients who have undergone PCI combined with stent implantation. How long should the higher dose be taken? For at least 1 month by those with a *bare-metal* stent, at least 3 months by those with a *sirolimus-eluting* stent, and at least 6 months by those with a *paclitaxel-eluting* stent—after which all patients should switch to low-dose aspirin and take it indefinitely.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

When used following acute STEMI, angiotensin-converting enzyme (ACE) inhibitors (eg, captopril, lisinopril) decrease short-term mortality in all patients, and long-term mortality in patients with reduced LV function. Benefits derive from reducing preload and afterload, promoting water loss, and favorably altering ventricular remodeling. Because of their benefits, ACE inhibitors are recommended for all STEMI patients in the absence of specific contraindications. Treatment should start within 24 hours of symptom onset and should continue for 6 weeks in all patients, and indefinitely in patients with LV dysfunction. The possibility that long-term therapy may also benefit patients who do not have LV dysfunction is being evaluated in large-scale trials. The major adverse effects of ACE inhibitors are hypotension and cough. Contraindications to ACE inhibitors are hypotension, bilateral renal artery stenosis, renal failure, and a history of ACE inhibitor-induced cough or angioedema. The basic pharmacology of the ACE inhibitors is presented in Chapter 44.

Therapy with angiotensin II receptor blockers (ARBs) in STEMI patients has not been studied as extensively as has therapy with ACE inhibitors. However, one major trial—Valsartan in Acute Myocardial Infarction Trial (VALIANT)—demonstrated that, in patients with post-MI heart failure or LV dysfunction, valsartan (an ARB) was as effective as captopril (an ACE inhibitor) at reducing short-term and long-term mortality. In the current guidelines, ARBs are recommended for STEMI patients who are intolerant of ACE inhibitors and have heart failure or reduced LV function.

Calcium Channel Blockers

Because of their antianginal, vasodilatory, and antihypertensive actions, calcium channel blockers (CCBs) were presumed beneficial for patients with acute STEMI, and hence were once used widely. However, in large-scale controlled trials, these drugs failed to decrease mortality either during or after acute STEMI. Accordingly, CCBs are not recommended for routine use. However, since the effects of CCBs on the heart are nearly identical to those of beta blockers, current guidelines state that it is reasonable to use two of beta blockers, current guidelines state that it is reasonable to use two of CCBs—verapamil or diltiazem—when beta blockers are either ineffective or contraindicated to relieve ongoing ischemia or control a rapid ventricular rate caused by atrial fibrillation or atrial flutter. These drugs should not be used if the patient has heart failure, LV dysfunction, or atrioventricular block.

COMPLICATIONS OF STEMI

Myocardial infarction predisposes the heart and vascular system to serious complications. Among the most severe are ventricular dysrhythmias, cardiogenic shock, and heart failure.

Ventricular Dysrhythmias. These dysrhythmias develop frequently and are the major cause of death following MI. Sudden death from dysrhythmias occurs in 15% of patients during the first hour. Ultimately, ventricular dysrhythmias cause 60% of infarction-related deaths. Acute management of ventricular fibrillation consists of defibrillation followed by IV lidocaine for 24 to 48 hours. Programmed ventricular stimulation with guided antidysrhythmic therapy may be lifesaving for some patients.

Attempts to prevent dysrhythmias by giving antidysrhythmic drugs *prophylactically* have failed to reduce mortality. Worse yet, attempted prophylaxis of ventricular dysrhythmias with two drugs—encainide and flecainide—actually *increased* mortality. Similarly, when quinidine was employed to prevent supraventricular dysrhythmias, it too increased mortality. Therefore, since prophylaxis with antidysrhythmic drugs does not reduce mortality—and may in fact increase mortality—antidysrhythmic drugs should be withheld until a dysrhythmia actually occurs.

Cardiogenic Shock. Shock results from greatly reduced tissue perfusion secondary to impaired cardiac function. Shock develops in 7% to 15% of patients during the first few days after MI and has a mortality rate of up to 90%. Patients at highest risk are those with large infarcts, a previous infarct, a low ejection fraction (less than 35%), diabetes, and advanced age. Drug therapy includes inotropic agents (eg, dopamine, dobutamine) to increase cardiac output and vasodilators (nitroglycerin, nitroprusside) to improve tissue perfusion and reduce cardiac work and oxygen demand. Unfortunately, although these drugs can improve hemodynamic status, they do not seem to reduce mortality. Restoration of cardiac perfusion with PCI or coronary artery bypass grafting may be of value.

Heart Failure. Heart failure secondary to acute MI can be treated with a combination of drugs. A diuretic (eg, furosemide) is given to decrease preload and pulmonary congestion. Inotropic agents (eg, digoxin) increase cardiac output by enhancing contractility. Vasodilators (eg, nitroglycerin, nitroprusside) improve hemodynamic status by reducing preload, afterload, or both. ACE inhibitors (or ARBs), which reduce both preload and afterload, can be especially helpful. Beta blockers may also improve outcome. Drug therapy of heart failure is discussed at length in Chapter 48.

Cardiac Rupture. Weakening of the myocardium predisposes the heart wall to rupture. Following rupture, shock and circulatory collapse develop rapidly. Death is often immediate. Fortunately, cardiac rupture is relatively rare (less than

2% incidence). Patients at highest risk are those with a large anterior infarction. Cardiac rupture is most likely within the first days after MI. Early treatment with vasodilators and beta blockers may reduce the risk of wall rupture.

SECONDARY PREVENTION OF STEMI

As a rule, patients who survive the acute phase of STEMI can be discharged from the hospital after 6 to 10 days. However, they are still at risk of reinfarction (5% to 15% incidence within the first year) and other complications (eg, dysrhythmias, heart failure). Outcome can be improved with risk factor reduction, exercise, and long-term therapy with drugs.

Reduction of risk factors for MI can increase long-term survival. Patients who smoke must be encouraged to quit; the goal is total cessation. Patients with high serum cholesterol should be given an appropriate dietary plan and, if necessary, treated with a cholesterol-lowering drug (usually one of the statins); the goal is an LDL cholesterol level substantially below 100 mg/dL. Patients with high triglyceride levels (200 mg/dL or higher) should be given niacin or a “fibrate”

(eg, gemfibrozil). Overweight patients should reduce; the goal is a body mass index of 18.5 to 29.4 kg/m² (see Chapter 82) and a waist circumference under 35 inches (for women) or under 40 inches (for men). Hypertension and diabetes increase the risk of mortality and must be controlled. For patients with hypertension, blood pressure should be decreased to below 140/90 mm Hg (or below 130/80 mm Hg for those with chronic kidney disease or diabetes). For patients with diabetes, the goal is a level of hemoglobin A_{1c} below 7%.

Exercise training can be valuable for two reasons: it reduces complications associated with prolonged bed rest and it accelerates return to an optimal level of functioning. The goal is 30 minutes of exercise at least 3 to 4 days a week, and preferably 7. Although exercise is safe for most patients, there is concern about cardiac risk and impairment of infarct healing in patients whose infarct is large.

All post-MI patients should take three drugs: (1) a beta blocker, (2) an ACE inhibitor or an ARB, and either (3a) an antiplatelet drug (aspirin or clopidogrel or prasugrel) or (3b) an anticoagulant (warfarin). All three should be taken indefinitely.

Estrogen therapy for postmenopausal women is not effective as secondary prevention and should not be initiated.

KEY POINTS

- Myocardial infarction (MI) is defined as necrosis of the myocardium secondary to acute occlusion of a coronary artery. The usual cause is platelet plugging and thrombus formation at the site of a ruptured atherosclerotic plaque.
- ST-elevation MI (STEMI) is diagnosed by the presence of chest pain, characteristic ECG changes, and elevated serum levels of cardiac troponins.
- Aspirin suppresses platelet aggregation, and thereby decreases mortality, reinfarction, and stroke. All patients should chew a 162- to 325-mg dose upon hospital admission, and should take 81 to 162 mg/day indefinitely after discharge. A higher dose (162 to 325 mg/day) should be used short term (1 to 6 months) by patients who received a stent during PCI.
- In patients undergoing acute STEMI, beta blockers reduce cardiac pain, infarct size, short-term mortality, recurrent ischemia, and reinfarction. Continued use increases long-term survival. All patients should receive a beta blocker in the absence of specific contraindications.
- In addition to aspirin and a beta blocker, three other drugs—oxygen, morphine, and nitroglycerin—are considered routine therapy for suspected STEMI. They should be started, as appropriate, soon after symptom onset.
- Reperfusion therapy, which restores blood flow through blocked coronary arteries, is the most beneficial treatment for STEMI.
- Reperfusion can be accomplished with PCI or with fibrinolytic drugs. Both approaches are highly effective—but PCI is now generally preferred.
- In most cases, PCI consists of balloon angioplasty coupled with placement of a drug-eluting stent.
- Fibrinolytic drugs dissolve clots by converting plasminogen into plasmin, an enzyme that digests the fibrin meshwork that holds clots together.
- Under typical conditions, all fibrinolytic drugs are equally effective. However, when treatment is initiated within 4 to 6 hours of pain onset, alteplase is most effective (but also very expensive).
- The major complication of fibrinolytic therapy is bleeding. Intracranial hemorrhage is the greatest concern.
- Heparin (an anticoagulant) is recommended for all patients undergoing fibrinolytic therapy or PCI.
- A regimen of aspirin (an antiplatelet drug) *combined* with either clopidogrel or prasugrel (two other antiplatelet drugs) is recommended for all patients undergoing reperfusion therapy, either with PCI or with a fibrinolytic drug.
- Glycoprotein IIb/IIIa inhibitors (eg, abciximab) are powerful IV antiplatelet drugs that can enhance the benefits of primary PCI.
- In patients with acute MI, ACE inhibitors decrease mortality, severe heart failure, and recurrent MI. All patients should receive an ACE inhibitor in the absence of specific contraindications. For patients who cannot tolerate ACE inhibitors, an ARB may be used instead.
- To lower the risk of a second MI, all patients should decrease cardiovascular risk factors (eg, smoking, hypercholesterolemia, hypertension, obesity, diabetes); exercise for 30 minutes at least 3 or 4 days a week; and undergo long-term therapy with three drugs: (1) a beta blocker, (2) an ACE inhibitor or an ARB, and (3) either an antiplatelet drug (aspirin or clopidogrel or prasugrel) or warfarin (an anticoagulant).

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Basic Considerations**Pathophysiology****Inheritance Pattern****Clinical Features****Overview of Therapy****Pain Management****Immunization****Preparations Used to Treat Hemophilia****Factor VIII Concentrates****Factor IX Concentrates****Desmopressin****Antifibrinolytic Agents****Managing Patients Who Develop Inhibitors**

Hemophilia is a rare genetic bleeding disorder seen almost exclusively in males. About 70% of cases result from inheriting a defective gene from the mother. The other 30% result from a spontaneous gene mutation.

Hemophilia has two forms: hemophilia A and hemophilia B. In hemophilia A, there is a deficiency of clotting factor VIII (aka antihemophilic factor). In hemophilia B, there is a deficiency of clotting factor IX (aka Christmas factor, named for Stephen Christmas, the first boy diagnosed with the disease). Hemophilia A is about 6 times more prevalent than hemophilia B, occurring in 1 of every 5000 males, compared with 1 of every 30,000 males for hemophilia B.

When hemophilia is managed well, the prognosis is good. Patients starting treatment today can live healthy, near-normal lives. The foundation of treatment is clotting factor replacement, which may be given on a regular schedule (to prevent bleeds from occurring) or "on demand" (to stop an ongoing bleed). Unfortunately, although treatment is highly effective, it is also very expensive: For patients undergoing prophylactic treatment, the cost for clotting factors alone ranges between \$140,000 and \$300,000 a year.

BASIC CONSIDERATIONS**Pathophysiology**

In people with hemophilia, there is a failure of hemostasis, the process by which bleeding is stopped. As discussed in Chapter 52, hemostasis occurs in two stages: (1) formation of a platelet plug followed by (2) production of fibrin, a protein that reinforces the platelet plug. In patients with hemophilia, platelet aggregation proceeds normally, but fibrin production does not. The underlying problem is a deficiency of clotting factors—specifically, factor VIII (in hemophilia A) and factor IX (in hemophilia B). As indicated in Figure 54-1, both fac-

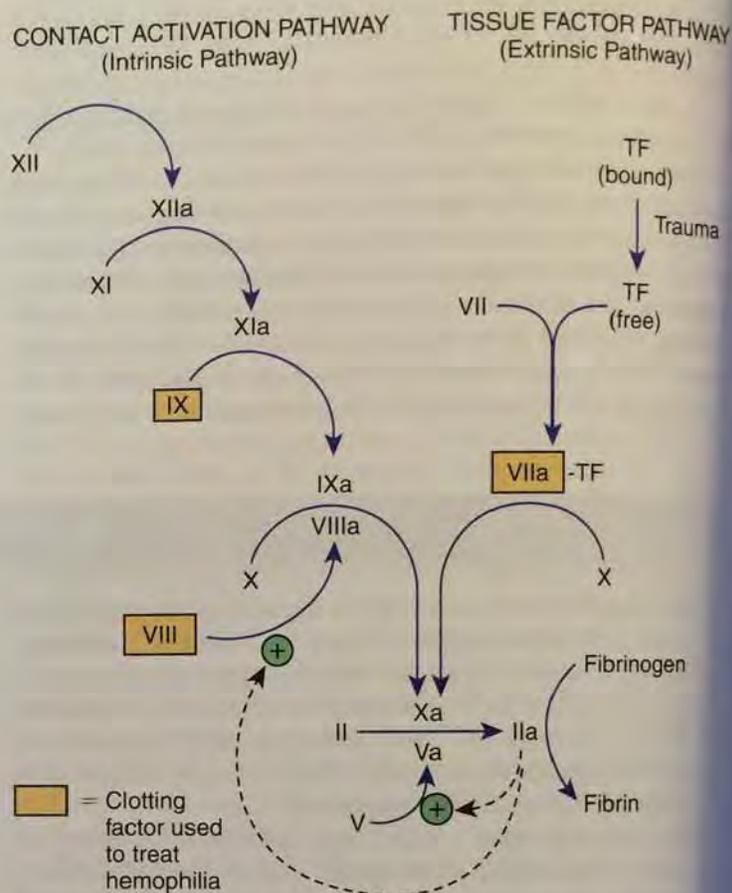


Figure 54-1 ■ Outline of the coagulation cascade showing clotting factors used to treat hemophilia.

TF = tissue factor. Common names for factors shown in roman numerals: II = prothrombin, IIa = thrombin, VII = proconvertin, VIII = antihemophilic factor, IX = Christmas factor, X = Stuart factor, XI = plasma thromboplastin antecedent, and XII = Hageman factor. The letter "a" after a factor's name (eg, factor VIIIa) indicates the active form of the factor. Note that factors VIII and IX, which are deficient in hemophilia A and B, respectively, are part of the contact activation (intrinsic) coagulation pathway. The symbol (+) indicates acceleration of the reaction.

tors are part of the contact activation (intrinsic) coagulation pathway, and both—in their activated forms—are needed to catalyze the conversion of factor X to its active form (factor Xa), which in turn catalyzes the conversion of prothrombin to thrombin, which catalyzes the formation of fibrin. If either factor VIII or factor IX is deficient, the contact activation pathway will not work properly, causing clot formation to be delayed. As a result, bleeding will continue longer than in the population at large.

It should be noted that the degree of factor deficiency—and hence the likelihood of serious bleeding—depends on the nature of the underlying gene mutation. In some patients, the

mutation produces a severe deficiency, resulting in a high probability of prolonged bleeding. In others, the mutation causes mild deficiency, and hence the tendency to bleed is low.

Inheritance Pattern

The genes for factors VIII and IX are *recessive*, and both are carried on the X chromosome. Because males have only one X chromosome, a male with a defective gene will have hemophilia. In contrast, a female with a defective gene on one X chromosome will usually be an asymptomatic carrier, since she still has a functioning gene on her other X chromosome. Be aware, however, that although females are usually asymptomatic carriers, there are two situations in which females *can* have hemophilia: (1) a female could be born with defective genes on *both* X chromosomes, which is rare; and (2) a female who was born with one defective gene could experience *inactivation* of the good gene. Boys whose mothers are carriers have a 1 in 2 chance of inheriting the disease. Girls whose mothers are carriers have a 1 in 2 chance of being carriers themselves. Males with hemophilia cannot pass the disease on to their sons, but all of their daughters will be carriers. The risk of acquiring hemophilia is shared by all races and ethnic groups.

Clinical Features

Hemophilia may be severe, moderate, or mild, depending on the degree of clotting factor deficiency. Patients with severe hemophilia may experience life-threatening hemorrhage in response to minor trauma, whereas those with mild hemophilia may experience little or no excessive bleeding. The defining characteristics of severe, moderate, and mild hemophilia are summarized in Table 54-1.

Severe Hemophilia. In patients with severe hemophilia, the concentration of clotting factor VIII or IX is very low—less than 1% of normal. As a result, these patients experience frequent bleeds within joints and soft tissues, especially muscle. Trauma or surgery can cause profuse hemorrhage. Joint bleeding occurs most often in the knee, followed in turn by the elbow, ankle, shoulder, and hip. Bleeding in these joints causes swelling and intense pain. With recurrent episodes, permanent injury to the joint develops. In addition to occurring in joints, bleeding may occur in muscles, mucous membranes (eg, nosebleeds), the GI and urinary tracts, near the

pharynx (which can cause life-threatening restriction of airflow), and within the skull (which carries a 30% risk of death). Among patients with hemophilia A, about 60% have severe disease. In contrast, among patients with hemophilia B, only 20% to 45% have severe disease. Although severe hemophilia can be devastating, most patients can live normal and productive lives, thanks to the availability of safe factor concentrates for replacement therapy.

Moderate Hemophilia. In patients with moderate hemophilia, the concentration of factor VIII or factor IX is between 1% and 5% of normal. Excessive bleeding in response to minor trauma is unlikely. However, serious bleeding *can* be induced by significant trauma, tooth extractions, and surgery. Joint bleeding may occur, but the frequency is much lower than with severe hemophilia.

Mild Hemophilia. In patients with mild hemophilia, the concentration of clotting factors is between 6% and 24% of normal. Joint bleeding is uncommon, but can be induced by severe injury or surgery.

Overview of Therapy

Whenever possible, treatment should be guided by a team of specialists at a hemophilia treatment center. Typically, the team consists of a hematologist, orthopedist, dietitian, psychologist, physical therapist, occupational therapist, genetics counselor, infectious disease specialist, social worker, and nurse coordinator.

The cornerstone of treatment is *replacement therapy* with factor VIII (hemophilia A) or factor IX (hemophilia B). In the past, factor replacement was performed only to terminate a bleeding episode. Today, however, there is increasing emphasis on primary prophylaxis, especially for young children. Why? Because, by minimizing bleeding episodes, prophylaxis can minimize long-term damage to joints.

For some patients with mild *hemophilia A*, bleeding can be stopped with *desmopressin*, a drug that promotes release of factor VIII from the vascular endothelium. Desmopressin has the advantage of being much cheaper than factor VIII, and can be administered by nasal spray as well as by IV infusion. Keep in mind, however, that repeated use of desmopressin can deplete stored factor VIII, making the drug ineffective until more factor VIII is made.

Antifibrinolytic drugs (ie, drugs that prevent the breakdown of fibrin) can be used as adjuncts to factors VIII and IX

TABLE 54-1 ■ Clinical Classification of Hemophilia Severity

Disease Parameter	Disease Severity		
	Severe	Moderate	Mild
Clotting factor level (VIII or IX)	Less than 1% of normal	Between 1% and 5% of normal	Between 6% and 24% of normal
Bleeding tendency	Can bleed with very mild injury	Can bleed with moderate injury	Can bleed with severe injury, surgery, or invasive procedures
Bleeding frequency	May bleed once or twice a week	May bleed once a month	May never have a bleeding episode
Occurrence of joint bleeding	Frequent	Less frequent	Infrequent, but can occur in response to severe injury

in special situations, such as tooth extractions. Two antifibrinolytic drugs are currently available: aminocaproic acid and tranexamic acid.

In some patients receiving factor VIII or factor IX, antibodies against the factor develop. These antibodies, referred to as *inhibitors*, prevent the factor from working. When inhibitors are present, bleeding can be stopped by infusing *activated factor VII*. Other treatments are also available, as discussed below under *Managing Patients Who Develop Inhibitors*.

Pain Management

How should we manage bleeding-related pain? For mild pain, *acetaminophen* [Tylenol, others] is the drug of choice. For severe pain, an *opioid analgesic* may be needed. Regardless of pain severity, *aspirin should be avoided!* Why? First, aspirin causes irreversible inhibition of platelet aggregation, and can thereby increase bleeding risk. Second, aspirin can induce GI ulceration and bleeding, an obvious problem.

Can we use nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin? As a rule, these agents should also be avoided. Why? First, like aspirin, most NSAIDs inhibit platelet aggregation (although the inhibition is reversible rather than irreversible). Second, like aspirin, most NSAIDs can promote GI ulceration and bleeding (although the risk is somewhat lower than with aspirin).

What about the second-generation NSAIDs, known as cyclooxygenase-2 (COX-2) inhibitors? As discussed in Chapter 71, the COX-2 inhibitors (eg, celecoxib) do not suppress platelet aggregation, and they cause less GI ulceration and bleeding than traditional NSAIDs. Accordingly, these agents are clearly preferred to traditional NSAIDs, although their safety in hemophilia has not been proved.

Immunization

Children with hemophilia should undergo the normal immunization schedule (see Chapter 68). Some clinicians inject vaccines subQ, rather than IM, to avoid muscle hemorrhage. However, since the efficacy of subQ vaccination is not certain, and since most patients tolerate IM injections without bleeding, IM vaccination is generally preferred. The risk of bleeding after IM injection can be reduced by prolonged application of pressure.

To minimize the risk of hepatitis (see below), all patients with newly diagnosed hemophilia should be vaccinated for hepatitis A and hepatitis B, as should all other patients with hemophilia who are not seropositive for hepatitis A or B. Family members who administer clotting factors at home should also be immunized, provided they test negative for hepatitis.

PREPARATIONS USED TO TREAT HEMOPHILIA

Factor VIII Concentrates

Factor VIII concentrates are the mainstay of hemophilia A treatment. What's a concentrate? It's simply a powdered formulation in which the amount of factor VIII is very high. When treatment is needed, the powder is dissolved in a sterile solution and administered IV.

TABLE 54-2 ■ Some Factor VIII and Factor IX Concentrates

Type of Preparation	Factor VIII	Factor IX
Recombinant		
Third generation	Advate Xyntha	BeneFix
Second generation	Helixate FS Kogenate FS ReFacto	
First generation	Recombinate	
Plasma-Derived		
Ultrapure	Hemofil-M Monoclate-P Wilate* [†]	AlphaNine SD Bebulin VH [‡] Mononine Profilnine SD [‡] Proplex T [‡]
Intermediate and high purity	Alphanate* Koate-DVI* Humate-P*	

*Contains von Willebrand factor in addition to factor VIII.

[†]Approved only for von Willebrand disease.

[‡]Contains factors II, VII, and X, in addition to factor IX.

All factor VIII concentrates available today are very safe. They carry essentially no risk of HIV/AIDS, and little or no risk of hepatitis.

Production Methods and Product Safety

Factor VIII concentrates are made in two basic ways: (1) purification from human plasma and (2) production in cell culture using recombinant DNA technology. Recombinant factor VIII is somewhat safer than plasma-derived factor VIII, but is also more expensive. All factor VIII products, whether recombinant or plasma derived, are equally effective. Available products are listed in Table 54-2.

Plasma-Derived Factor VIII. Prior to 1985, factor VIII produced from donor plasma often contained viral contaminants. As a result, nearly all people with hemophilia developed hepatitis and/or HIV/AIDS. Today, however, the risk of viral contamination is exceedingly low. Why? First, donated plasma is now screened for viral pathogens—specifically, human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and parvovirus B19. Second, techniques for inactivating *lipid-coated* viruses (HIV, HBV, and HCV) are now employed. Unfortunately, viruses that lack a lipid coat, such as HAV and parvovirus B19, are not eliminated. Nonetheless, no case of virus transmission has been reported with any of the products now used in the United States.

There is one additional concern: *prions*. These strange proteins, which are responsible for Creutzfeldt-Jakob disease (CJD, the human form of "mad cow disease"), are not susceptible to any known inactivation technique. Hence, the possibility of transmitting CJD remains.

As indicated in Table 54-2, plasma-derived factor VIII is available in varying degrees of purity. The ultrapure products (eg, Hemofil-M) are prepared using monoclonal antibodies.

Recombinant Factor VIII. Recombinant factor VIII is produced in culture, using hamster cells that have been ge-

netically transformed. All recombinant factor VIII products are very safe, and hence are considered the agents of choice for treating hemophilia A.

During the manufacturing process, most recombinant factor VIII products are exposed to bovine serum albumin (BSA), human serum albumin (HSA), or both. Because BSA or HSA could, in theory, be a source of viruses or prions, manufacturing processes that reduce the use of BSA and HSA have been developed. As a result, we now have three "generations" of recombinant products:

- *First-generation product*—Recombinate—is made using BSA in the cell culture, and contains HSA as a stabilizer in the vial.
- *Second-generation products*—Helixate FS, Kogenate FS, and ReFacto—are made using HSA in the cell culture, but they contain neither BSA nor HSA in the vial.
- *Third-generation products*—Advate and Xyntha—are not exposed to BSA or HSA during cell culture, and they contain neither BSA nor HSA in the vial.

Theoretically, the third-generation products—Advate and Xyntha—which are never exposed to any proteins of animal or human origin, are safer than the first- or second-generation products. However, there are no published data showing this is the case. With all three generations, the risk of human viral contamination is essentially zero. Transmission of HIV, HBV, or HCV has not been reported.

Adverse Effects: Allergic Reactions

Factor VIII concentrates can cause allergic reactions, which can range from mild to severe. Symptoms of a mild reaction include hives, rash, urticaria, stuffy nose, and fever. These can be managed with an antihistamine (eg, diphenhydramine [Benadryl]). Rarely, anaphylaxis may develop. Symptoms of this potentially fatal reaction include wheezing, tightness in the throat, shortness of breath, and swelling in the face. The treatment of choice is epinephrine, injected subQ.

Dosage and Administration

On-Demand Therapy. On-demand therapy is indicated for patients who are bleeding or about to undergo surgery. As a rule, administration is by slow IV push done over 5 to 10 minutes. Continuous infusion may also be done, but only by a clinician with special training.

Dosage depends primarily on the site and severity of the bleed. Table 54-3 indicates approximate dosages for a variety of bleeding situations. The dosing target is expressed as a percentage of normal factor VIII activity. For example, when treating a joint bleed, the dosing target is 40% of the normal activity level.

How can we calculate dosage? By knowing that, *for each unit of factor VIII we give per kilogram of body weight, we will raise factor VIII activity in plasma by 2%*. Hence, to calculate dosage, we simply multiply the patient's weight by the target activity level for factor VIII and then divide by 2, as in this example:

$$\frac{50 \text{ (kg body weight)} \times 40 \text{ (target \%)}}{2} = 1000 \text{ (units of factor VIII)}$$

To help guide dosing, we can measure factor VIII activity in plasma before and after treatment. However, although knowl-

edge of factor VIII activity is helpful, dosage is ultimately determined by the clinical response.

Prophylactic Therapy. For prophylaxis, factor VIII is administered on a regular schedule. The goal is to *prevent* bleeding, and thereby prevent life-threatening hemorrhage and long-term injury to joints. Children with severe hemophilia are the primary candidates for prophylaxis. Treatment is often done at home. The goal is to maintain factor VIII activity above 1% of normal. As a rule, this can be achieved by infusing factor VIII concentrate 3 times a week. However, dosing just once or twice a week may work for some patients. Recombinant factor VIII products are generally preferred, although plasma-derived products, which are just as effective and much less expensive, may also be used.

To facilitate frequent IV administration, a central venous access device can be installed. Options include an external catheter (eg, Hickman catheter) or an implanted venous port (eg, Port-A-Cath). Both types of device are intended for long-term use, and can remain in place several years. It should be noted, however, that although these devices make prophylaxis much easier, they do carry risks, especially infection and thrombosis.

Factor IX Concentrates

Therapeutic Use, Production, and Safety

Factor IX concentrates are the mainstay of treatment for hemophilia B. The pharmacology of these concentrates is nearly identical to that of the factor VIII concentrates. Like the factor VIII concentrates, the factor IX concentrates are made either by extraction from donor plasma or by recombinant DNA technology (see Table 54-2). None of the products in current use poses a risk of HIV/AIDS. However, the plasma-derived products may carry a very small risk of hepatitis A, parvovirus B19, or CJD—although there have been no reports of transmitting any of these infections with current products. Because recombinant factor IX [BeneFix] is, in theory, safer than plasma-derived factor IX [AlphaNine SD, Bebulin VH, Mononine, Profilnine SD, Proplex T], recombinant factor IX is considered the preparation of choice. Like factor VIII, factor IX can cause allergic reactions.

Dosage and Administration

On-Demand Therapy. On-demand therapy, administered by IV push, should be initiated at the earliest sign of bleeding. As with factor VIII, dosage is determined primarily by the site and severity of bleeding (see Table 54-3). However, factors VIII and IX differ in that, on a unit-per-kilogram (unit/kg) basis, we need twice as much factor IX to achieve an equivalent increase in plasma factor level. Hence, with factor IX, *for each unit we give per kilogram of body weight, we will raise the plasma activity level by 1%* (compared with 2% for each unit/kg of factor VIII). To calculate dosage, we simply multiply the patient's weight by the target factor IX activity level (expressed as a percentage of normal factor IX activity level), as in this example:

$$50 \text{ (kg body weight)} \times 40 \text{ (target \%)} = 2000 \text{ (units of factor IX)}$$

As with factor VIII therapy, we can measure plasma levels of factor IX activity to guide treatment—although the dose depends ultimately on the clinical response.

TABLE 54-3 ■ Estimated Dosages for Factor VIII and Factor IX

Type of Hemorrhage	Factor VIII (Hemophilia A)		Factor IX (Hemophilia B)	
	Target Activity Level*	Dose (units/kg)	Target Activity Level*	Dose (units/kg)
Joint	40%	20	40%	40
Muscle (except the iliopsoas muscle)	40%	20	40%	40
Iliopsoas muscle [†]				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50
CNS/Head				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50
Throat and neck				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50
Gastrointestinal				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50
Ophthalmic	80%–100%	40–50	80%–100%	80–100
Renal	50%	25	50%	50
Deep laceration	50%	25	50%	50
Surgical				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50

CNS = central nervous system.

*Target activity levels are expressed as a percentage of normal activity level.

[†]The iliopsoas is a compound muscle consisting of the iliacus and psoas major muscles, located in the groin region.

Data are from Hemophilia of Georgia: Protocols for the Treatment of Hemophilia and von Willebrand Disease. Atlanta: Hemophilia of Georgia (available online as of November 1, 2011, at www.hog.org/doc-Lib/20090820_HOGProtocol2009.pdf).

Prophylactic Therapy. As with factor VIII, prophylaxis is done to prevent bleeding, and thereby prevent injury to joints. The dosing goal is to maintain factor IX levels above 1% of normal. Because factor IX has a longer half-life than factor VIII (18 to 24 hours vs. 8 to 12 hours), prophylaxis can be done less often (twice a week rather than 3 times a week). The usual dose is 20 to 40 units/kg.

Desmopressin

Therapeutic Use. Desmopressin [DDAVP, Stimate], an analog of antidiuretic hormone, can stop or prevent bleeding in patients with *mild* hemophilia A. The drug works by releasing stored factor VIII from the vascular endothelium. Levels of factor VIII begin to rise within 30 minutes of dosing, and peak within 90 to 120 minutes. Desmopressin can be used to stop episodes of trauma-induced bleeding, and can be given preoperatively to maintain hemostasis during surgery. Desmopressin does not release factor IX, and hence cannot be used to treat hemophilia B. Principal adverse effects are fluid retention and hyponatremia. The basic pharmacology of desmo-

pressin, along with its use in hypothalamic diabetes insipidus, is discussed in Chapter 59 (Drugs Related to Hypothalamic and Pituitary Function).

Preparations, Dosage, and Administration. For treatment of hemophilia A, desmopressin may be administered IV or by intranasal spray. An oral formulation is available, but is not indicated for hemophilia.

For *intravenous therapy*, desmopressin [DDAVP] is formulated in a concentrated solution (4 mcg/mL) that must be diluted in physiologic saline. The usual dosage is 0.3 mcg/kg infused over 15 to 30 minutes.

For *intranasal therapy*, desmopressin is available under two trade names: *DDAVP*, which delivers 10 mcg/spray, and *Stimate*, which delivers 150 mcg/spray. Only *Stimate* is used for hemophilia. For patients who weigh 50 kg or more, the dosage is 150 mcg/nostril, for a total of 300 mcg. For patients who weigh less than 50 kg, the dosage is one spray (150 mcg) in just one nostril.

Antifibrinolytic Agents

Antifibrinolytic agents inhibit the normal process of fibrin breakdown. As discussed in Chapter 52, when a clot is no longer needed, an enzyme called *plasmin* dissolves the fibrin meshwork that holds the clot together, and thereby promotes clot removal. Unfortunately, in people with hemophilia, fibrin breakdown can lead to a resumption of bleeding. Accordingly, by preserving fibrin with an antifibrinolytic drug, we can help keep bleeding under control. Because of their mechanism, antifibrinolytic drugs are most useful

for preventing recurrent bleeding, and less useful for stopping an ongoing bleed.

Two antifibrinolytic drugs are currently available: *aminocaproic acid* and *tranexamic acid*. Both agents act primarily by preventing the formation of plasmin from its precursor (plasminogen). These drugs are most useful for controlling bleeding in mucous membranes (of the nose, mouth, and throat) as well as bleeding caused by dental extractions—presumably because fibrinolytic activity at all of these sites is especially high.

Aminocaproic Acid. Aminocaproic acid [Amicar] is available in solution (250 mg/mL) for IV use, and in tablets (500 and 1000 mg) and solution (250 mg/mL) for oral use. Dosages to prevent or treat serious bleeding are as follows:

- *Oral therapy, adults*—give 5 gm for the first hour, then 1 or 1.25 gm every hour
- *IV therapy, adults*—infuse 4 to 5 gm over the first hour, then infuse at a rate of 1 gm/hr
- *Oral therapy, children*—give 100 mg/kg for the first hour, then 33.3 mg/kg every hour
- *IV therapy, children*—infuse 100 mg/kg over the first hour, then infuse at a rate of 33.3 mg/kg/hr

In all cases, continue dosing for 8 hours or until bleeding stops.

Tranexamic Acid. For treatment of hemophilia, tranexamic acid [Cyklokapron] is available in solution (100 mg/mL) for IV dosing. To control bleeding associated with dental extractions, the recommended dosage is 10 mg/kg immediately before the extraction, followed by doses of 10 mg/kg 3 to 4 times a day for 2 to 8 days. Dosage should be decreased in patients with renal impairment.

As discussed in Chapter 64 (Drugs That Affect Uterine Function), an oral formulation of tranexamic acid, marketed as *Lysteda*, is used to treat heavy cyclic menstrual bleeding.

Managing Patients Who Develop Inhibitors

Patients receiving factor VIII or factor IX can develop antibodies against the factor. These antibodies, referred to as inhibitors, neutralize the clotting factor, and thereby render factor replacement ineffective. In most cases, the antibodies develop early, typically after only 9 to 12 courses of treatment.

Some patients are more likely to develop inhibitors than others. Among patients with *severe* hemophilia A, between 20% and 30% develop antibodies to factor VIII, compared with 3% to 13% of those with *mild* hemophilia A. Among patients with severe hemophilia B, between 2% and 12% develop antibodies to factor IX. The risk of inhibitor development among African American and Hispanic patients is unusually high (up to 50%).

The titer of inhibitors to factor VIII is measured using the Bethesda assay. In this procedure, serial dilutions of the Bethesda assay. In this procedure, serial dilutions of the Bethesda assay. In this procedure, serial dilutions of normal patient plasma are mixed with an equal volume of normal plasma, after which factor VIII activity in the mixture is measured. The dilution that inhibits 50% of factor VIII activity defines the inhibitor titer. For example, if the 1:40 dilution inhibits 50% of the factor VIII activity, the patient is said to have a titer of 40 *Bethesda units* (BU) of factor VIII inhibitor.

For some patients, *immune tolerance therapy* (ITT) can eliminate inhibitor production. The procedure involves repeated administration of factor replacement products over an extended time. The success rate is high (63% to 83%) for patients with hemophilia A, and very low for those with hemophilia B. A low antibody titer (less than 5 BU) increases the chances of success. If ITT fails to stop antibody production, then hemostasis must be achieved with drugs, as discussed immediately below.

Drugs for Patients with Factor VIII Inhibitors

To control bleeding in patients with inhibitors to factor VIII, the preferred treatments are (1) activated factor VII and (2) anti-inhibitor coagulant complex. Neither option is clearly superior to the other. Accordingly, selection between them is based on previous response and prescriber preference.

Activated Factor VII (Factor VIIa). Factor VIIa [NovoSeven RT], manufactured by recombinant DNA technology, can control bleeding in patients with inhibitors to factor VIII or factor IX. As indicated in Figure 54-1, factor VIIa has the same action as factors VIII and IX. That is, it catalyzes the conversion of factor X to its active form. Hence, by giving factor VIIa, we can bypass neutralization of factors VIII and IX, and thereby allow clotting to proceed normally.

Factor VIIa is generally well tolerated. No human proteins are used in making this agent, and hence there is no risk of transmitting a human virus. Rarely, thrombotic events have occurred—arterial thrombosis, cerebral sinus thrombosis, and myocardial infarction (MI). In most cases, these events were seen when NovoSeven RT was used off-label to stop bleeding in nonhemophiliacs, including patients with acute intracerebral hemorrhage.

Factor VIIa is supplied as a powder in single-use vials (1.2, 2.4, and 4.8 mg) and must be reconstituted in sterile water prior to use. Administration is by IV bolus. The usual dosage is 90 mcg/kg, repeated every 2 hours until bleeding stops. However, some patients require much higher doses (eg, 300 mcg/kg). Treatment is very expensive: A single 90-mcg/kg dose for a 70-kg patient costs about \$10,000. The drug should be stored under refrigeration.

Anti-inhibitor Coagulant Complex (AICC). AICC [Feiba VH Immuno*], made from pooled human plasma, contains variable amounts of clotting factors II, VII, IX, and X—in both their activated and nonactivated forms. AICC is indicated for patients with inhibitors to factor VIII or factor IX who are bleeding or about to undergo surgery. Benefits are believed to derive from factors VIIa and Xa, which bypass factors VIII and IX in the coagulation cascade (see Fig. 54-1).

Because AICC is made from human plasma, there is a theoretical risk of transmitting viral or prion disease. However, there have been no reports of transmitting CJD, HIV, or hepatitis A, B, or C with this product as currently formulated.

Because AICC contains multiple coagulation factors, it poses a risk of thrombotic complications, specifically, MI and disseminated intravascular coagulation (DIC). Fortunately, these events are very rare. The risk of MI or DIC is increased with repeated dosing and by liver disease.

Preparations of Feiba VH Immuno are standardized in *Immuno units*. The usual dosage is 50 to 100 Immuno units/kg, infused IV at a rate no faster than 2 Immuno units/kg/min. Dosing can be repeated every 6 hours, but the total daily dose must not exceed 200 Immuno units/kg.

Factor VIII Concentrate. If the inhibitor titer is very low (less than 5 BU), we may be able to overcome inhibition with high doses of factor VIII itself. However, if the inhibitor titer is high, then factor VIII will not work, and the agents discussed above must be employed.

Porcine Factor VIII. Porcine factor VIII (factor VIII from pigs) can

*FYI: Feiba stands for factor VIII inhibitor bypassing activity.

establish hemostasis in patients with hemophilia A who have developed antibodies to human factor VIII. Porcine factor VIII may be produced in two ways: by extraction from pig blood and by recombinant DNA technology. Recombinant porcine factor VIII is now in clinical trials. Factor VIII extracted from pig blood [Hyate:C] is no longer available.

Antibodies to human factor VIII can cross-react with porcine factor VIII. However, the degree of cross-reactivity is low. Accordingly, if the antibody titer is not too high (less than 50 BU/mL), porcine factor VIII is likely to work. If the titer exceeds 50 BU/mL, significant neutralization of the porcine factor can occur.

Drugs for Patients with Factor IX Inhibitors

Treatment options for patients with factor IX inhibitors are limited. In contrast to factor VIII inhibitors, which may be overcome with large doses of human factor VIII or porcine factor VIII, factor IX inhibitors are difficult to overcome with any preparation of factor IX available. Furthermore, elimination of factor IX inhibitors with ITT often fails. Currently, factor VIIa and AICC are the treatments of choice. Both options are effective because they bypass the blockade caused by the inhibitor.

KEY POINTS

- Hemophilia is a bleeding disorder seen almost exclusively in males. The underlying cause is a genetically based deficiency of clotting factors.
- Hemophilia has two forms: hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency).
- Hemophilia may be severe, moderate, or mild, depending on the degree of clotting factor deficiency.
- Patients with severe hemophilia may experience life-threatening hemorrhage in response to minor trauma, whereas those with mild hemophilia may experience little or no excessive bleeding.
- Repeated bleeding in the knee and other joints can cause permanent joint damage.
- The cornerstone of hemophilia treatment is replacement therapy with factor VIII (hemophilia A) or factor IX (hemophilia B).
- Replacement therapy may be done prophylactically (to prevent bleeding and thereby prevent joint injury) or on demand (to stop an ongoing bleed or prevent excessive bleeding during surgery).
- Clotting factor products are made in two basic ways: extraction from donor plasma and production in cell culture using recombinant DNA technology.
- All clotting factor concentrates, whether plasma derived or recombinant, are equally effective.
- All clotting factor concentrates in use today are very safe: They carry no risk of transmitting HIV/AIDS, and little or no risk of transmitting hepatitis or CJD. However, because recombinant factors are, in theory, slightly safer than plasma-derived factors, recombinant factors are considered the treatment of choice.
- As a rule, clotting factors are given by slow IV push. Continuous infusion may also be done, but only by a clinician with special training.
- Clotting factor dosage depends primarily on the site and severity of the bleed.
- A dose of 1 unit of factor VIII/kg will raise the plasma level of factor VIII activity by 2%, whereas 1 unit of factor IX/kg will raise the plasma level of factor IX activity by only 1%.
- Although we can monitor the activity of clotting factors in blood to help guide treatment, dosage is ultimately determined by the clinical response.
- For prophylaxis, clotting factor concentrates are administered on a regular schedule, usually 3 times a week for factor VIII and twice a week for factor IX. With both factors, the goal is to maintain plasma factor levels above 1% of normal.
- To facilitate frequent IV administration during prophylaxis, a central venous access device can be installed.
- Clotting factor concentrates can cause allergic reactions. Mild reactions can be managed with an antihistamine (eg, diphenhydramine [Benadryl]). The most severe reaction—anaphylaxis—is treated with subQ epinephrine.
- For some patients with mild hemophilia A, bleeding can be stopped with desmopressin, a drug that promotes release of stored factor VIII. Desmopressin does not release factor IX, and hence cannot treat hemophilia B.
- Two drugs—aminocaproic acid and tranexamic acid—can suppress fibrinolysis (by blocking production of plasmin) and can thereby promote hemostasis in hemophilia A and hemophilia B. These antifibrinolytic agents are more effective for preventing recurrent bleeding than for stopping an ongoing bleed.
- Development of inhibitors (antibodies that neutralize factor VIII or factor IX) is a serious complication of hemophilia therapy.
- Activated factor VII (factor VIIa) and AICC are preferred agents for controlling bleeding when inhibitors of factor VIII or factor IX are present.
- People with hemophilia should avoid aspirin and other traditional NSAIDs because these agents suppress platelet aggregation and promote GI ulceration and bleeding. Second-generation NSAIDs (COX-2 inhibitors) are probably safe.

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Summary of Major Nursing Implications*

FACTOR VIII AND FACTOR IX CONCENTRATES

Preadministration Assessment

Therapeutic Goal

Factor VIII is indicated for replacement therapy in patients with hemophilia A, and factor IX is indicated for replacement therapy in patients with hemophilia B.

Both factors may be given prophylactically (to prevent bleeding and subsequent joint injury) or "on demand" (to stop ongoing bleeding or prevent excessive bleeding during anticipated surgery).

Baseline Data

Obtain a baseline level for activity of factor VIII or factor IX.

Identifying High-Risk Patients

Use with *caution* in patients with a history of allergic reactions to the factor concentrate.

Implementation: Administration

Route

Intravenous.

Administration

Administer by slow IV push or continuous infusion.

Record the following each time you give a factor concentrate:

- Time and date
- Infusion site and rate
- Total dose
- Manufacturer, trade name, lot number, and expiration date of the factor concentrate

Teach home caregivers about

- The importance of having an assistant, who can give aid or call for help if complications arise
- The importance and proper method of hand washing

- Making dosage calculations
- Reconstituting the powdered factor concentrate
- Infusion technique
- Cleanup and waste disposal
- Recording the time, date, and other information listed above

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Success is indicated by preventing bleeding (during prophylactic therapy) or controlling bleeding (during on-demand therapy). With both forms of therapy, monitoring activity levels of factor VIII or factor IX can help guide treatment.

Minimizing Adverse Effects

Allergic Reactions. Clotting factor concentrates can cause allergic reactions, ranging from mild to severe. **Inform patients about symptoms of mild reactions (eg, hives, rash, urticaria, stuffy nose, fever), and advise them to take an antihistamine (eg, diphenhydramine) if these occur.** Inform patients about symptoms of anaphylaxis (wheezing, tightness in the throat, shortness of breath, swelling in the face), and instruct them to seek immediate emergency care if these develop. The treatment of choice is epinephrine, injected subQ.

Minimizing Adverse Interactions

Aspirin. Warn patients not to use aspirin, a drug that inhibits platelet aggregation and can cause GI ulceration and bleeding.

NSAIDs Other Than Aspirin. Advise patients that first-generation NSAIDs (eg, ibuprofen, naproxen) have actions similar to those of aspirin, and hence should be avoided.

Advise patients that second-generation NSAIDs (eg, celecoxib), which do not inhibit platelets and cause minimal GI effects, are *probably* safe.

*Patient education information is highlighted as blue text.

RED BLOOD CELL DEVELOPMENT**IRON DEFICIENCY**

Biochemistry and Physiology of Iron

Iron Deficiency: Causes, Consequences, and Diagnosis

Oral Iron Preparations

Ferrous Iron Salts

Carbonyl Iron

Parenteral Iron Preparations

Iron Dextran

Sodium–Ferric Gluconate Complex, Iron Sucrose, and Ferumoxytol

Guidelines for Treating Iron Deficiency

VITAMIN B₁₂ DEFICIENCYBiochemistry and Physiology of Vitamin B₁₂Vitamin B₁₂ Deficiency: Causes, Consequences, and DiagnosisVitamin B₁₂ Preparations: CyanocobalaminGuidelines for Treating Vitamin B₁₂ Deficiency**FOLIC ACID DEFICIENCY**

Physiology and Biochemistry of Folic Acid

Folic Acid Deficiency: Causes, Consequences, and Diagnosis

Folic Acid Preparations

Guidelines for Treating Folic Acid Deficiency

Anemia is defined as a decrease in the number, size, or hemoglobin content of erythrocytes (red blood cells [RBCs]). Causes include blood loss, hemolysis, bone marrow dysfunction, and deficiencies of substances essential for RBC formation and maturation. Most deficiency anemias result from deficiency of iron, vitamin B₁₂, or folic acid. Accordingly, this chapter focuses on anemias caused by these deficiencies. To facilitate discussion, we begin by reviewing RBC development.

RED BLOOD CELL DEVELOPMENT

RBCs begin developing in the bone marrow and then mature in the blood. As developing RBCs grow and divide, they evolve through four stages (Fig. 55–1). In their earliest stage, RBCs lack hemoglobin and are known as *proerythroblasts*. In the next stage, they gain hemoglobin and are called *erythroblasts*. Both the erythroblasts and the proerythroblasts reside in bone marrow. After the erythroblast stage, RBCs evolve into *reticulocytes* (immature erythrocytes) and enter the systemic circulation. Following the reticulocyte stage, circulating RBCs reach full maturity and are referred to as *erythrocytes*.

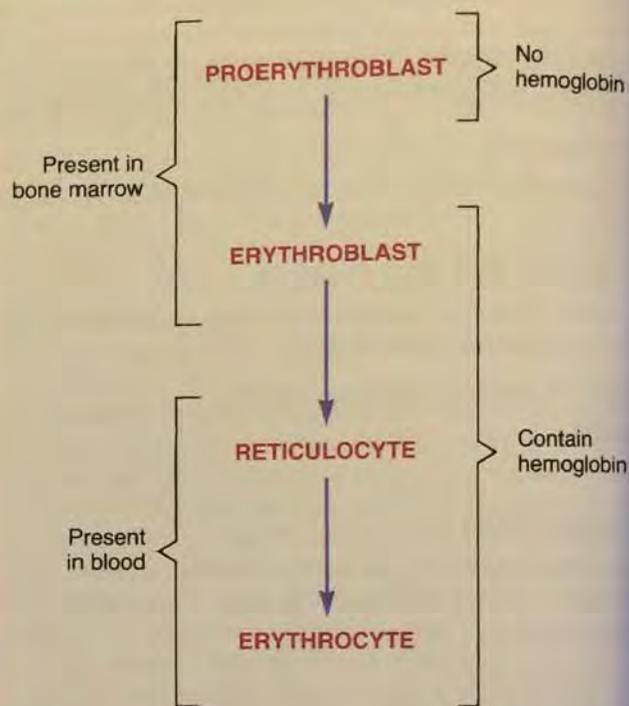


Figure 55–1 ■ Stages of red blood cell development.

Development of RBCs requires the cooperative interaction of several factors: bone marrow must be healthy; erythropoietin (a stimulant of RBC maturation) must be present; iron must be available for hemoglobin synthesis; and other factors, including vitamin B₁₂ and folic acid, must be available to support synthesis of DNA. If any of these is absent or amiss, anemia will result.

IRON DEFICIENCY

Iron deficiency is the most common nutritional deficiency, and the most common cause of nutrition-related anemia. Worldwide, people with iron deficiency number in the hundreds of millions. In the United States, about 5% of the population is iron deficient.

BIOCHEMISTRY AND PHYSIOLOGY OF IRON

In order to understand the consequences of iron deficiency as well as the rationale behind iron therapy, we must first understand the biochemistry and physiology of iron. This information is reviewed below.

Metabolic Functions

Iron is essential to the function of hemoglobin, myoglobin (the oxygen-storing molecule of muscle), and a variety of iron-containing enzymes. Most (70% to 80%) of the body's iron is present in hemoglobin. A much smaller amount (10%) is present in myoglobin and iron-containing enzymes.

Fate in the Body

The major pathways for iron movement and utilization are shown in Figure 55-2. In the discussion below, the numbers in parentheses refer to the circled numbers in the figure.

Uptake and Distribution. The life cycle of iron begins with (1) uptake of iron into mucosal cells of the small intestine. These cells absorb 5% to 20% of dietary iron. Their maximum absorptive capacity is 3 to 4 mg/day. Iron in the ferrous form (Fe^{++}) is absorbed more readily than iron in the ferric form (Fe^{+++}). Vitamin C enhances absorption, and food reduces absorption.

Following uptake, iron can either (2a) undergo storage within mucosal cells in the form of *ferritin* (a complex consisting of iron plus a protein used to store iron) or (2b) undergo binding to *transferrin* (the iron transport protein) for distribution throughout the body.

Utilization and Storage. Iron that is bound to transferrin can undergo one of three fates. The majority of transferrin-bound iron (3a) is taken up by cells of the bone marrow for incorporation into hemoglobin. Small amounts (3b) are taken up by the liver and other tissues for storage as ferritin. Lastly (3c), some of the iron in plasma is taken up by muscle (for production of myoglobin) and some is taken up by all other tissues (for production of iron-containing enzymes).

Recycling. As Figure 55-2 depicts, iron associated with hemoglobin undergoes continuous recycling. After hemoglobin is made in bone marrow, iron re-enters the circulation (4) as a component of hemoglobin in erythrocytes. (The iron in circulating erythrocytes accounts for about 70% of total body

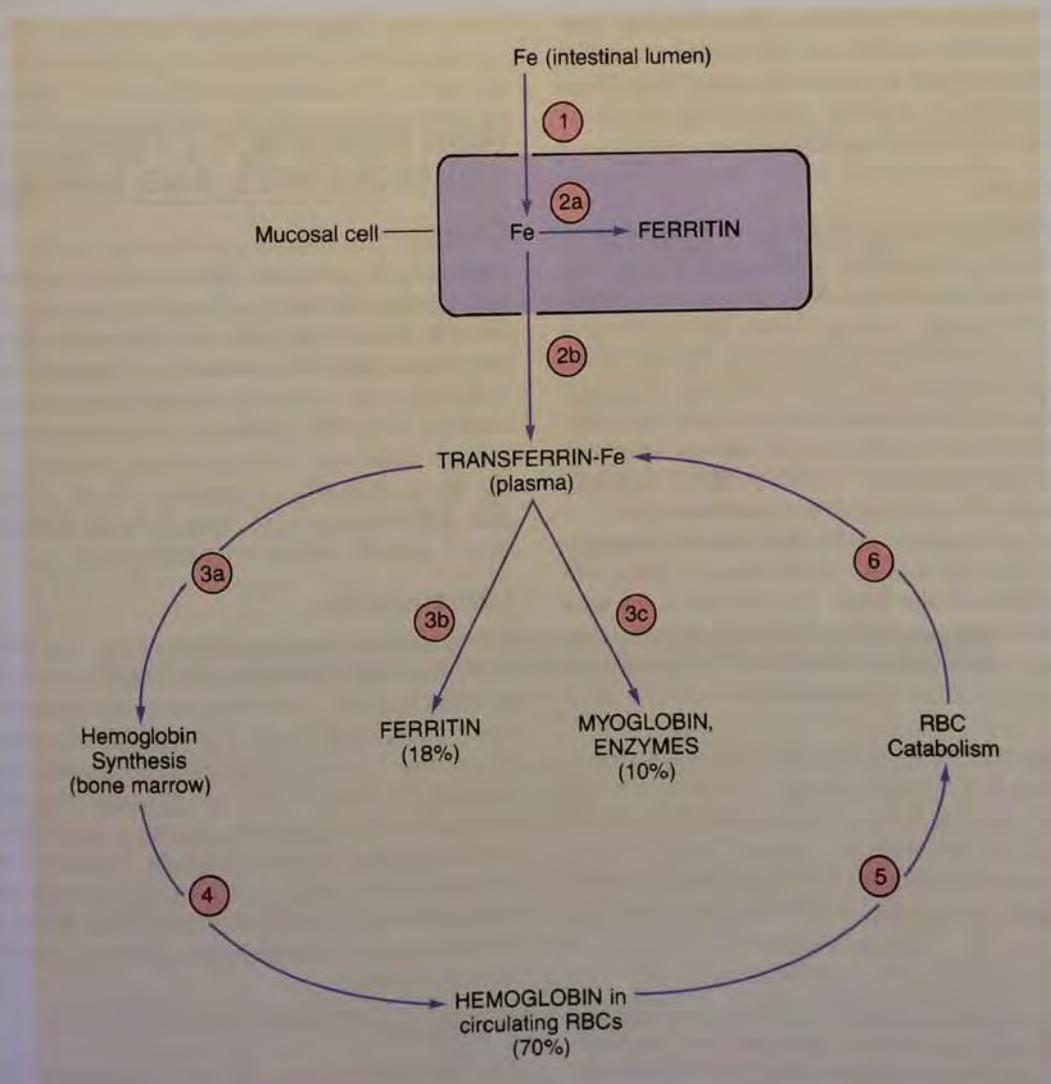


Figure 55-2 • Fate of iron in the body.

Pathways labeled with circled numbers are explained in the text. Values in parentheses indicate percentage of total body stores. Elimination of iron is not shown, because most iron is rigidly conserved. (Fe = iron, RBC = red blood cell.)

iron.) After 120 days of useful life, RBCs are catabolized (5). Iron released by this process re-enters the plasma bound to transferrin (6), and then the cycle begins anew.

Elimination. Excretion of iron is minimal. Under normal circumstances, only 1 mg of iron is excreted each day. At this rate, if none of the lost iron were replaced, body stores would decline by only 10% a year.

Iron leaves the body by several routes. Most excretion occurs via the bowel. Iron in ferritin is lost as mucosal cells slough off, and iron also enters the bowel in bile. Small amounts are excreted in urine and sweat.

Note that, although very little iron leaves the body as a result of excretion (ie, normal physiologic loss), substantial amounts can leave because of blood loss. Hence, menorrhagia (excessive menstrual flow), hemorrhage, and blood donations can all cause iron deficiency.

Regulation of Body Iron Content. The amount of iron in the body is regulated through control of intestinal absorption. As noted, most of the iron that enters the body stays in the body. Hence, if all dietary iron were readily absorbed, body iron content would rapidly accumulate to a toxic level. However, *excessive buildup is prevented through control of iron uptake: As body stores rise, uptake of iron declines; conversely, as body stores become depleted, uptake increases.* For example, when body stores of iron are high, only 2% to 3% of dietary iron is absorbed. In contrast, when body stores are depleted, as much as 20% may be absorbed.

Daily Requirements

Requirements for iron are determined largely by the rate of erythrocyte production. When RBC production is low, iron needs are low too. Conversely, when RBC production is high, iron needs rise. Accordingly, among infants and children—individuals whose rapid growth rate requires massive RBC synthesis—iron requirements are high (relative to body weight). In contrast, the daily iron needs of adults are relatively low. Adult males need only 8 mg of dietary iron each day. Adult females need considerably more (15 to 18 mg/day), in order to replace iron lost through menstruation.

During pregnancy, requirements for iron increase dramatically, owing to (1) expansion of maternal blood volume and (2) production of RBCs by the fetus. In most cases, the iron needs of pregnant women are too great to be met by diet alone. Consequently, iron supplements (about 27 mg/day) are recommended during pregnancy and for 2 to 3 months after parturition.

Table 55-1 summarizes the recommended dietary allowances (RDAs) of iron as a function of age. Of note, the RDA values in the table are about 10 times greater than actual physiologic need. Why? Because, on average, only 10% of dietary iron is absorbed. Hence, if physiologic requirements are to be met, the diet must contain 10 times more iron than we need.

Dietary Sources

Iron is available in foods of plant and animal origin. Foods especially rich in iron include liver, egg yolk, brewer's yeast, and wheat germ. Other foods with a high iron content include muscle meats, fish, fowl, cereal grains, beans, and green leafy vegetables. Foods that do not provide much iron include milk and most nongreen vegetables. Since iron can be extracted from cooking utensils, using iron pots and pans can augment dietary iron. Except for individuals who have very high iron requirements (infants, pregnant women, those undergoing chronic blood loss), the average diet is sufficient to meet iron needs.

TABLE 55-1 ■ Recommended Dietary Allowances (RDAs) for Iron

Life Stage	Age	RDA for Iron (mg/day)
Infants	7–12 mo	11
Children	1–3 yr	7
	4–8 yr	10
Males	9–13 yr	8
	14–18 yr	11
	≥19 yr	8
Females: nonpregnant, nonlactating	9–13 yr	8
	14–18 yr	15
	19–50 yr	18
	≥51 yr	8
Females: pregnant	14–50 yr	27*
Females: lactating	14–18 yr	10
	19–50 yr	9

*Iron requirements during pregnancy cannot be met through dietary sources alone, and hence supplements are recommended.

IRON DEFICIENCY: CAUSES, CONSEQUENCES, AND DIAGNOSIS

Causes

Iron deficiency results when there is an imbalance between iron uptake and iron demand. As a rule, the imbalance results from increased demand—not from reduced uptake. The most common causes of increased iron demand (and resulting iron deficiency) are (1) blood volume expansion during pregnancy coupled with RBC synthesis by the growing fetus; (2) blood volume expansion during infancy and early childhood; and (3) chronic blood loss, usually of GI or uterine origin. Rarely, iron deficiency results from reduced iron uptake; potential causes include gastrectomy and sprue.

Consequences

Iron deficiency has multiple effects, the most conspicuous being *iron deficiency anemia*. In the absence of iron for hemoglobin synthesis, red blood cells become *microcytic* (small) and *hypochromic* (pale). The reduced oxygen-carrying capacity of blood results in listlessness, fatigue, and pallor of the skin and mucous membranes. If tissue oxygenation is severely compromised, tachycardia, dyspnea, and angina may result. In addition to causing anemia, iron deficiency impairs myoglobin production and synthesis of iron-containing enzymes. In young children, iron deficiency can cause developmental problems, and in school-age children, iron deficiency may impair cognition.

Diagnosis

The hallmarks of iron deficiency anemia are (1) the presence of microcytic, hypochromic erythrocytes, and (2) the absence of hemosiderin (aggregated ferritin) in bone marrow. Additional laboratory data that can help confirm a diagnosis include reduced RBC count, reduced reticulocyte hemoglobin content, reduced hemoglobin and hematocrit values, reduced

serum iron content, and increased serum iron-binding capacity (IBC).*

When a diagnosis of iron deficiency anemia is made, it is imperative that the underlying cause be determined. This is especially true when the suspected cause is GI-related blood loss. Why? Because GI blood loss may be indicative of peptic ulcer disease or GI cancer, conditions that demand immediate treatment.

ORAL IRON PREPARATIONS

As shown in Table 55-2, iron for oral therapy is available in multiple forms. Of these, the ferrous salts (especially ferrous sulfate) and carbonyl iron are used most often. Accordingly, discussion below is limited to these iron preparations.

Ferrous Iron Salts

We have two basic types of iron salts: ferrous salts and ferric salts. Discussion here is limited to the ferrous iron salts. Why? Because the ferrous salts are absorbed 3 times more readily than the ferric salts, and hence are more widely used. Four ferrous iron salts are available: ferrous sulfate, ferrous gluconate, ferrous fumarate, and ferrous aspartate. All four are equally effective, and with all four, GI disturbances are the major adverse effect.

Ferrous Sulfate

Indications. Ferrous sulfate is the treatment of choice for iron deficiency anemia. It is also the preferred drug for preventing deficiency when iron needs cannot be met by diet alone (eg, during pregnancy or chronic blood loss). Ferrous sulfate costs less than ferrous gluconate or ferrous fumarate, but has equal efficacy and tolerability.

*Serum IBC measures iron binding by transferrin. An increase in IBC indicates an increase in the amount of transferrin that is not carrying any iron, and hence signals reduced iron availability.

Adverse Effects. GI Disturbances. The most significant adverse effects involve the GI tract. These effects, which are dose dependent, include nausea, pyrosis (heartburn), bloating, constipation, and diarrhea. Gastrointestinal reactions are most intense during initial therapy, and become less disturbing with continued drug use. Because of their GI effects, oral iron preparations can aggravate peptic ulcers, regional enteritis, and ulcerative colitis. Accordingly, patients with these disorders should not take iron by mouth. In addition to its other GI effects, oral iron may impart a dark green or black color to stools. This effect is harmless and should not be interpreted as a sign of GI bleeding.

Staining of Teeth. Liquid iron preparations can stain the teeth. This can be prevented by (1) diluting liquid preparations with juice or water, (2) administering the iron through a straw or with a dropper, and (3) rinsing the mouth after administration.

Toxicity. Iron in large amounts is toxic. Poisoning is almost always the result of accidental or intentional overdose, not from therapeutic doses. Death from iron ingestion is rare in adults. By contrast, *in young children, iron-containing products are the leading cause of poisoning fatalities.* For children, the lethal dose of elemental iron is 2 to 10 gm. To reduce the risk of pediatric poisoning, iron should be stored in childproof containers and kept out of reach.

Symptoms. The effects of iron poisoning are complex. Early reactions include nausea, vomiting, diarrhea, and shock. These are followed by acidosis, gastric necrosis, hepatic failure, pulmonary edema, and vasomotor collapse.

Diagnosis and Treatment. With rapid diagnosis and treatment, mortality from iron poisoning is low (about 1%). Serum iron should be measured and the intestine x-rayed to determine if unabsorbed tablets are present. Gastric lavage will remove iron from the stomach. Acidosis and shock should be treated as required.

If the plasma level of iron is high (above 350 to 500 mcg/dL), it should be lowered with parenteral *deferoxamine* [Desferal]. Another oral drug—*deferasirox* [Exjade]—is indicated for patients with chronic iron overload caused by blood transfusions. Both agents—deferoxamine and deferasirox—adsorb iron and thereby prevent toxic effects. The pharmacology of these drugs is discussed in Chapter 109 (Management of Poisoning).

Drug Interactions. Interaction of iron with other drugs can alter the absorption of iron, the other drug, or both. *Ant-*

TABLE 55-2 ■ Iron Preparations Available for Oral Therapy

Iron Preparation	Trade Names	Description
Ferrous iron salts:		
Ferrous sulfate	Feosol, FeroSul, Ferodan [◆] , Slow FE, others	All four compounds are salts of the ferrous form of iron
Ferrous gluconate	Fergon, Floradix, others	
Ferrous fumarate	Ferro-Sequels, Hemocyte, Palafer [◆] , others	
Ferrous aspartate	FE Aspartate	
Ferrous bisglycinate	Ferrochel, others	An iron–amino acid chelate
Ferric ammonium citrate	Iron Citrate	A ferric iron salt
Carbonyl iron	Feosol, Ireon, Icar, others	Microparticles of elemental iron
Heme-iron polypeptide	Proferrin	Hemoglobin extracted from porcine RBCs
Polysaccharide iron complex	Niferex-150 Forte, Ferrex 150, Triferex 150 [◆] , others	Ferric iron complexed to hydrolyzed starch

acids reduce the absorption of iron. Coadministration of iron with tetracyclines decreases absorption of both. *Ascorbic acid* (vitamin C) promotes iron absorption but also increases its adverse effects. Accordingly, attempts to enhance iron uptake by combining iron with ascorbic acid offer no advantage over a simple increase in iron dosage.

Preparations. Ferrous sulfate is available in standard tablets, and in enteric-coated and sustained-release formulations. The enteric-coated and sustained-release products are designed to reduce gastric disturbances. Unfortunately, although side effects may be lowered, these special formulations have disadvantages. First, iron may be released at variable rates, causing variable and unpredictable absorption. Second, these preparations are expensive. Standard tablets do not share these drawbacks.

Some iron products are formulated with vitamin C. The goal is to improve absorption. Unfortunately, the amount in most products is too low to help: More than 200 mg of vitamin C is needed to enhance the absorption of 30 mg of elemental iron.

Trade names for ferrous sulfate products include *Feosol*, *FeroSul*, *Slow FE*, and *Ferodan*.

Dosage and Administration. General Considerations. Dosing with oral iron can be complicated in that oral iron salts differ with regard to percentage of elemental iron (Table 55-3). Ferrous sulfate, for example, contains 20% iron by weight. In contrast, ferrous gluconate contains only 11.6% iron by weight. Consequently, in order to provide equivalent amounts of elemental iron, we must use different doses of these iron salts. For example, if we want to provide 100 mg of elemental iron using ferrous sulfate, we need to administer a 500-mg dose. To provide this same amount of elemental iron using ferrous fumarate, the dose would be only 300 mg. In the discussion below, dosage values refer to milligrams of elemental iron, and not to milligrams of any particular iron compound needed to provide that amount of elemental iron.

Food affects therapy in two ways. First, food helps protect against iron-induced GI distress. Second, food decreases iron absorption by 50% to 70%. Hence, we have a dilemma: *Absorption is best* when iron is taken *between* meals, but *GI distress is lowest* when iron is taken *with* meals. As a rule, iron should be administered between meals, thereby maximizing absorption. If necessary, the dosage can be lowered to render GI effects more acceptable.

For two reasons, it may be desirable to take iron *with* food during *initial* therapy. First, since the GI effects of iron are most intense when treatment commences, the salving effects of food can be especially beneficial early on. Second, by reducing GI discomfort during the early phase of therapy, dosing with food can help promote adherence.

Use in Iron Deficiency Anemia. Dosing with oral iron represents a compromise between a desire to replenish lost iron rapidly and a desire to keep GI effects to a minimum. For most adults, this compromise can best be achieved by giving 65 mg 3 times a day, yielding a total daily dose of about 200 mg. Since there is a ceiling to intestinal absorption of iron, doses above this amount provide only a modest increase in therapeutic effect. On the other hand, at dosages greater than 200 mg/day, GI disturbances become disproportionately high. Hence, elevation of the daily dose above 200 mg would augment adverse effects without offering a significant in-

TABLE 55-3 ■ Commonly Used Oral Iron Preparations

Iron Preparation	% Elemental Iron (by weight)	Dose Providing 100 mg Elemental Iron
Ferrous Iron Salts		
Ferrous sulfate	20	500 mg
Ferrous sulfate (dried)	30	330 mg
Ferrous fumarate	33	300 mg
Ferrous gluconate	11.6	860 mg
Ferrous aspartate	16	625 mg
Elemental Iron		
Carbonyl iron	100	100 mg

crease in benefits. When treating iron deficiency in infants and children, a typical dosage is 5 mg/kg/day administered in three or four divided doses.

Timing of administration is important: Doses should be spaced evenly throughout the day. This schedule gives the bone marrow a continuous iron supply, and thereby maximizes RBC production.

Duration of therapy is determined by the therapeutic objective. If correction of anemia is the sole objective, a few months of therapy is sufficient. However, if the objective also includes replenishing ferritin, treatment must continue another 4 to 6 months. It should be noted, however, that drugs are usually unnecessary for ferritin replenishment: In most cases, diet alone can do the job. Accordingly, once anemia has been corrected, pharmaceutical iron can usually be stopped.

Prophylactic Use. Pregnant women are the principal candidates for prophylactic therapy. A total daily dose of 27 mg, taken between meals, is recommended. Other candidates include infants, children, and women experiencing menorrhagia.

Ferrous Gluconate, Ferrous Fumarate, and Ferrous Aspartate

In addition to ferrous sulfate, three other oral ferrous salts are available: ferrous gluconate [Fergon], ferrous fumarate [Ferro-Sequels, Hemocyte, Palafer], and ferrous aspartate [FE Aspartate]. Except for differences in percentage of iron content (see Table 55-3), all of these preparations are equivalent. Hence, when dosage is adjusted to provide equal amounts of elemental iron, ferrous gluconate, ferrous fumarate, and ferrous aspartate produce pharmacologic effects identical to those of ferrous sulfate. All four agents produce equivalent therapeutic responses, and all four cause the same degree of GI distress. Patients who fail to respond to one will not respond to the others. Patients who cannot tolerate the GI effects of one will find the others intolerable too.

Carbonyl Iron

Carbonyl iron is pure, elemental iron in the form of microparticles, which confer good bioavailability. Therapeutic efficacy equals that of the ferrous salts. Because of the microparticles, iron is absorbed slowly, and hence the risk of toxicity is reduced. Compared with ferrous sulfate, carbonyl iron requires a much higher dosage to cause serious harm. Because of this increased margin of safety, carbonyl iron should pose a reduced risk to children in the event of accidental ingestion.

Carbonyl iron is available in several formulations, including (1) 45-mg tablets, marketed as *Feosol*; (2) 65-mg tablets, marketed as *Iron*; (3) 90-mg film-coated tablets marketed as *Ferralex 90*; (4) 15-mg chewable tablets, marketed as *Icar*; and (5) a suspension (15 mg/1.25 mL), also marketed as *Icar*. Because these products contain 100% iron, rather than an iron salt, there should be no confusion about dosage: 100 mg of any formulation provides 100 mg of elemental iron. The usual dosage is 50 mg, 3 times a day.

PARENTERAL IRON PREPARATIONS

Iron is available in four forms for parenteral therapy. However, only one of these forms—iron dextran—is approved for iron deficiency of all causes. Approval of the other three forms—iron sucrose, sodium–ferric gluconate complex, and ferumoxytol—is limited to treating iron deficiency anemia in patients with chronic kidney disease.

Iron Dextran

Iron dextran [INFeD, DexFerrum, Infufer[®], Dexiron[®]] is the most frequently used parenteral iron preparation. The drug is a complex consisting of ferric hydroxide and dextrans (polymers of glucose). The rate of response to parenteral iron is equal to that of oral iron. Iron dextran is dangerous—fatal anaphylactic reactions have occurred—and hence should be used only when circumstances demand.

Indications

Iron dextran is reserved for patients with a clear diagnosis of iron deficiency and for whom oral iron is either ineffective or intolerable. Primary candidates for parenteral iron are patients who, because of intestinal disease, are unable to absorb iron taken orally. Iron dextran is also indicated when blood loss is so great (500 to 1000 mL/wk) that oral iron cannot be absorbed fast enough to meet hematopoietic needs. Parenteral iron may also be employed when there is concern that oral iron might exacerbate pre-existing disease of the stomach or bowel. Lastly, parenteral iron can be given to the rare patient for whom the GI effects of oral iron are intolerable.

Adverse Effects

Anaphylactic Reactions. Potentially fatal anaphylaxis is the most serious adverse effect. These reactions are triggered by dextran in the product, not by the iron. Although anaphylactic reactions are rare, their possibility demands that iron dextran be used only when clearly required. Furthermore, whenever iron dextran is administered, injectable epinephrine and facilities for resuscitation should be at hand. To reduce risk, each full dose should be preceded by a small test dose. However, be aware that even the test dose can trigger a fatal reaction. In addition, even when the test dose is uneventful, patients can still die from the full dose.

Other Adverse Effects. Hypotension is common in patients receiving parenteral iron. In addition, iron dextran can cause headache, fever, urticaria, and arthralgia. More serious reactions—circulatory failure and cardiac arrest—may also occur. When administered IM, iron dextran can cause persistent pain and prolonged, localized discoloration. Very rarely, tumors develop at sites of IM injection. Intravenous administration may result in lymphadenopathy and phlebitis.

Preparations, Dosage, and Administration

Preparations. Iron dextran [INFeD, DexFerrum, Infufer[®], Dexiron[®]] is available in single-dose vials (1 and 2 mL) that contain 50 mg/mL of elemental iron.

Dosage. Dosage determination is complex. Dosage depends on the degree of anemia, the weight of the patient, and the presence of persistent bleeding. For patients with iron deficiency anemia who are not losing blood, the equation in Figure 55-3 provides a guideline for estimating total iron dosage.

Administration. Iron dextran may be administered IM or IV. Intravenous administration is preferred. This route is just as effective as IM administration but causes fewer anaphylactic reactions and other adverse effects.

Intravenous. To minimize anaphylactic reactions, intravenous iron dextran should be administered by the following protocol: (1) administer a small test dose (25 mg over 5 minutes) and observe the patient for at least 15 minutes; (2) if the test dose appears safe, slowly administer a larger dose (500 mg over a 10- to 15-minute interval); and (3) if the 500-mg dose is uneventful, additional doses may be given as needed.

Intramuscular. Intramuscular iron dextran has significant drawbacks and should be avoided. Disadvantages include persistent pain and discoloration at the injection site, possible development of tumors, and a greater risk of anaphylaxis. When IM administration must be performed, iron dextran should be injected deep into each buttock using the Z-track technique. (Z-track injection keeps the iron dextran deep in the muscle, thereby minimizing leakage and surface discoloration.) As with IV iron dextran, a small test dose should precede the full therapeutic dose.

Sodium–Ferric Gluconate Complex, Iron Sucrose, and Ferumoxytol

Iron sucrose, sodium–ferric gluconate complex (SFGC), and ferumoxytol represent alternatives to iron dextran for parenteral iron therapy. With all three drugs, the risk of anaphylaxis is very low, and hence there is little or no need for giving test doses. As a result, these drugs are more convenient than iron dextran. Unfortunately, indications for these drugs are limited to treatment of iron deficiency anemia in patients with chronic kidney disease (CKD). They are not approved for iron deficiency from other causes.

Sodium–Ferric Gluconate Complex

SFGC, sold under the trade name *Ferrlecit*, is a parenteral iron product indicated for iron deficiency anemia in patients with CKD who are undergoing chronic hemodialysis. The drug is always used in conjunction with erythropoietin, an agent that stimulates RBC production (see Chapter 56). SFGC can cause transient flushing and hypotension, associated with lightheadedness, malaise, fatigue, weakness, and severe pain in the chest, back, flanks, or groin. This reaction can be minimized by infusing the drug slowly. In contrast to iron dextran, SFGC poses little risk of anaphylaxis. Accordingly, repeated test doses are unnecessary—although a test dose is required the first time the drug is used. SFGC is supplied in 5-mL ampules that contain 62.5 mg of elemental iron. Dilution is not required (but may be done) before the infusion. For most patients, a single dose consists of 125 mg (contents of 2 ampules) infused slowly (over 10 minutes or more). The typical patient requires a cumulative dose of 1 gm (eight 125-mg infusions on separate days). A small test dose (25 mg infused over 60 minutes) should precede the first full dose. Every time the drug is administered, facilities for cardiopulmonary resuscitation should be immediately available.

Iron Sucrose

Like SFGC, iron sucrose [Venofer] is a parenteral form of iron indicated for iron deficiency anemia in patients with CKD. However, in contrast to SFGC, whose indications are limited to CKD patients undergoing hemodialysis in

$$\text{mg iron} = 0.66 \times \text{kg body weight} \times \left(100 - \frac{\text{hemoglobin value in g/dL}}{14.8} \right)$$

Figure 55-3 • Formula for estimating total dosage of parenteral iron dextran.

conjunction with erythropoietin therapy, iron sucrose is indicated for a broader range of CKD patients, specifically

- Non-dialysis-dependent (NDD) patients receiving erythropoietin
- NDD patients *not* receiving erythropoietin
- Hemodialysis-dependent (HDD) patients receiving erythropoietin
- Peritoneal dialysis-dependent (PDD) patients receiving erythropoietin

The most common adverse effects of iron sucrose are hypotension (36%) and cramps (23%). The drug has also been associated with heart failure, sepsis, and taste perversion. Life-threatening hypersensitivity reactions are very rare: No cases were observed during clinical trials, and only 27 cases (out of 450,000 patients) were reported during postmarketing surveillance. Nonetheless, facilities for cardiopulmonary resuscitation should be available during administration. However, in contrast to iron dextran and SFGC, no test dose is needed.

Iron sucrose is supplied in 5-mL single-dose vials that contain 100 mg of elemental iron. Administration is IV, either by (1) slow injection (1 mL/min) or (2) infusion (dilute iron sucrose in up to 100 mL of 0.9% saline and infuse over 15 minutes or longer). Iron sucrose should not be mixed with other drugs or with peripheral nutrition solutions. All patients should receive a *total* dose of 1000 mg, but the dosing schedule and administration technique depend on the patient as follows:

- HDD patients—Give ten 100-mg doses during each of 10 consecutive dialysis sessions. Administer by slow IV injection or IV infusion.
- NDD patients—Give five 200-mg doses on separate occasions over a 14-day span. Administer by slow IV injection.
- PDD patients—Give two 300-mg doses 14 days apart, then one 400-mg dose 14 days later. Administer by slow IV infusion.

Ferumoxytol

Ferumoxytol [Feraheme], approved in 2009, is a parenteral form of iron indicated for iron deficiency anemia in all patients with CKD, whether or not they are on dialysis or using erythropoietin. Compared with SFGC and iron sucrose, ferumoxytol is much more convenient. Why? Because ferumoxytol requires only 2 doses (given over 3 to 8 days), whereas SFGC and iron sucrose require 3 to 10 doses (given over several weeks).

Ferumoxytol is generally well tolerated. The most common adverse effects are nausea (3.1%), dizziness (2.6%), hypotension (1.9%), headache (1.8%), vomiting (1.5%), and edema (1.5%). In clinical trials, about 0.2% of patients experienced serious hypersensitivity reactions. Accordingly, facilities for cardiopulmonary resuscitation should be immediately available. However, in contrast to iron dextran and SFGC, no test dose is needed.

Because of its unique composition (ferumoxytol is a superparamagnetic form of iron oxide), the drug can interfere with magnetic resonance imaging (MRI) studies. This interference is most profound 1 to 2 days after dosing, but can persist for up to 3 months. Fortunately, ferumoxytol does not interfere with other forms of diagnostic imaging, including x-rays, computed tomography (CT), positron emission tomography (PET), ultrasound, or nuclear medicine imaging.

Ferumoxytol [Feraheme] is supplied in 17-mL single-dose vials (30 mg elemental iron/mL). Administration is by slow IV injection, defined here as 1 mL/sec (30 mg/sec). The usual dosage is 510 mg on day 1, followed by another 510 mg 3 to 8 days later. Additional doses may be given as needed. Following each injection, patients should be monitored for at least 30 minutes for hypotension and hypersensitivity reactions. For patients on dialysis, dosing should be done at least 1 hour after starting dialysis, and only after blood pressure has stabilized.

GUIDELINES FOR TREATING IRON DEFICIENCY

Assessment. Prior to starting therapy, the cause of iron deficiency must be determined. Without this information, appropriate treatment is impossible. Potential causes of deficiency include pregnancy, bleeding, inadequate diet, and, rarely, impaired intestinal absorption.

The objective is to increase production of hemoglobin and erythrocytes. When therapy is successful, reticulocytes will increase within 4 to 7 days; within 1 week, increases in hemoglobin and the hematocrit will be apparent; and within 1 month, hemoglobin levels will rise by at least 2 gm/dL. If these responses fail to occur, the patient should be evaluated

for (1) compliance, (2) continued bleeding, (3) inflammatory disease (which can interfere with hemoglobin production), and (4) malabsorption of oral iron.

Routes of Administration. Iron preparations are available for oral, IV, and IM administration. Oral iron is preferred. Why? Because oral iron is safer than parenteral iron and just as effective. Parenteral iron should be used only when oral iron is ineffective or intolerable. Of the two parenteral routes, IV is safer and preferred.

Duration of Therapy. Therapy with oral iron should be continued until hemoglobin levels become normal (about 15 gm/dL). This phase of treatment may require 1 to 2 months. After this, continued treatment can help replenish stores of ferritin. However, for most patients, dietary iron alone is sufficient.

Therapeutic Combinations. As a rule, combinations of antianemic agents should be avoided. Combining oral iron with parenteral iron can lead to iron toxicity. Accordingly, use of oral iron should cease prior to giving iron injections. Combinations of iron with vitamin B₁₂ or folic acid should be avoided; as discussed in the following sections, using these combinations can confuse interpretation of hematologic responses.

VITAMIN B₁₂ DEFICIENCY

The term *vitamin B₁₂* refers to a group of compounds with similar structures. These compounds are large molecules that contain an atom of cobalt. Because of the cobalt atom, members of the vitamin B₁₂ family are known as *cobalamins*.

The most prominent consequences of vitamin B₁₂ deficiency are *anemia* and *injury to the nervous system*. Anemia reverses rapidly following vitamin B₁₂ administration. Neurologic damage takes longer to repair and, in some cases, may never fully resolve. Additional effects of B₁₂ deficiency include GI disturbances and impaired production of white blood cells and platelets.

BIOCHEMISTRY AND PHYSIOLOGY OF VITAMIN B₁₂

In order to understand the consequences of vitamin B₁₂ deficiency and the rationale behind therapy, we must first understand the normal biochemistry and physiology of B₁₂. This information is reviewed below.

Metabolic Function

Vitamin B₁₂ is essential for synthesis of DNA, and hence is required for the growth and division of virtually all cells. The mechanism by which the vitamin influences DNA synthesis is depicted in Figure 55-4. As indicated, vitamin B₁₂ helps catalyze the conversion of folic acid to its active form. Active folic acid then participates in several reactions essential for DNA synthesis. Hence, *it is by permitting utilization of folic acid that vitamin B₁₂ influences cell growth and division*—and it is the absence of usable folic acid that underlies the blood cell abnormalities seen during B₁₂ deficiency.

Fate in the Body

Absorption. Efficient absorption of B₁₂ requires *intrinsic factor*, a compound secreted by parietal cells of the stomach. Following ingestion, vitamin B₁₂ forms a complex with intrinsic

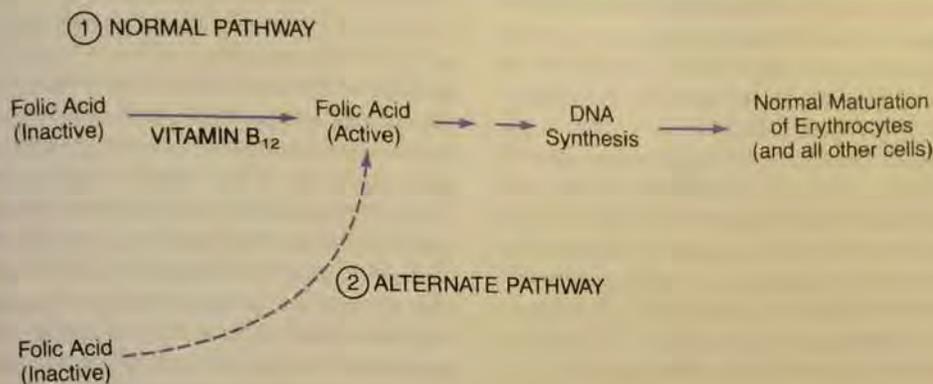


Figure 55-4 ■ Relationship of folic acid and vitamin B₁₂ to DNA synthesis and cell maturation. Folic acid requires activation to be of use. Normally, activation occurs via a vitamin B₁₂-dependent pathway. However, when folic acid is present in large amounts, activation can occur via an alternate pathway, thereby bypassing the need for B₁₂.

sis factor. Upon reaching the ileum, the B₁₂-intrinsic factor complex interacts with specific receptors on the intestinal wall, causing the complex to be absorbed. In the absence of intrinsic factor, absorption of vitamin B₁₂ is greatly reduced. However, about 1% of the amount present can still be absorbed by passive diffusion; no intrinsic factor is needed.

Distribution and Storage. Following absorption, the vitamin B₁₂-intrinsic factor complex dissociates. Free B₁₂ then binds to *transcobalamin II* for transport to tissues. Most vitamin B₁₂ goes to the liver and is stored. Total body stores of B₁₂ are tiny, ranging from 2 to 3 mg by most estimates.

Elimination. Excretion of vitamin B₁₂ takes place very slowly. Each day, about 0.1% of the total body store is lost. Because B₁₂ is excreted so slowly, years are required for B₁₂ deficiency to develop—even when none of the lost B₁₂ is replaced.

Daily Requirements

Because very little vitamin B₁₂ is excreted, and because body stores are small to begin with, daily requirements for this vitamin are minuscule. The average adult needs about 2.4 mcg of B₁₂ per day. Children need even less.

Dietary Sources

The ability to biosynthesize vitamin B₁₂ is limited to microorganisms; higher plants and animals can't make it. The microorganisms that make B₁₂ reside in the soil, sewage, and the intestines of humans and other animals. Unfortunately, the B₁₂ produced in the human GI tract is unavailable for absorption. Consequently, humans must obtain the majority of their B₁₂ by consuming animal products. Liver and dairy products are especially good sources. Between 10% and 30% of adults over age 50 are unable to absorb vitamin B₁₂ found naturally in foods. Accordingly, these people should meet their requirements by consuming B₁₂-fortified foods or a B₁₂-containing vitamin supplement.

VITAMIN B₁₂ DEFICIENCY: CAUSES, CONSEQUENCES, AND DIAGNOSIS

Causes

In the majority of cases, vitamin B₁₂ deficiency is the result of *impaired absorption*. Only rarely is insufficient B₁₂ in the diet the cause. Potential causes of poor absorption include (1) regional enteritis, (2) celiac disease (a malabsorption syndrome involving abnormalities in the intestinal villi), and (3) development of antibodies directed against the vitamin B₁₂-intrinsic factor complex. In addition, because stomach acid is required

to release vitamin B₁₂ from foods, the vitamin cannot be absorbed if acid secretion is significantly reduced, as often happens in the elderly and in those taking acid-suppressing drugs.

Most frequently, impaired absorption of vitamin B₁₂ occurs secondary to a lack of intrinsic factor. The usual causes are atrophy of gastric parietal cells and surgery of the stomach (total gastric resection).

When vitamin B₁₂ deficiency is caused by an absence of intrinsic factor, the resulting syndrome is called *pernicious anemia*—a term suggesting a highly destructive or fatal condition. Pernicious anemia is an old term that refers back to the days when, for most patients, vitamin B₁₂ deficiency had no effective therapy. Hence, the condition was uniformly fatal. Today, vitamin B₁₂ deficiency secondary to lack of intrinsic factor can be managed successfully. Hence, the label *pernicious* no longer bears its original ominous connotation.

Consequences

Many of the consequences of B₁₂ deficiency result from disruption of DNA synthesis. The tissues affected most are those with a high proportion of cells undergoing growth and division. Accordingly, B₁₂ deficiency has profound effects on the bone marrow (the site where blood cells are produced) and the epithelial cells lining the mouth and GI tract.

Megaloblastic Anemia. The most conspicuous consequence of B₁₂ deficiency is an anemia in which large numbers of *megaloblasts* (oversized erythroblasts) appear in the bone marrow, and in which *macrocytes* (oversized erythrocytes) appear in the blood. These strange cells are produced because of impaired DNA synthesis; lacking sufficient DNA, growing cells are unable to divide; hence, as erythroblasts mature and their division is prevented, oversized cells result. Most megaloblasts die within the bone marrow; only a few evolve into the macrocytes that can be seen in the blood. Because of these unusual cells, the anemia associated with vitamin B₁₂ deficiency is often referred to as either *megaloblastic* or *macrocytic* anemia.

Severe anemia is the principal cause of mortality from B₁₂ deficiency. Anemia produces peripheral and cerebral hypoxia. Heart failure and dysrhythmias are the usual cause of death.

It is important to note that the hematologic effects of vitamin B₁₂ deficiency can be reversed with large doses of *folic*

acid. As indicated in Figure 55-4, when folic acid is present in large amounts, some of it can be activated by an alternate pathway that is independent of vitamin B₁₂. This pathway bypasses the metabolic block caused by B₁₂ deficiency, thereby permitting DNA synthesis to proceed.

Neurologic Damage. Deficiency of vitamin B₁₂ causes demyelination of neurons, primarily in the spinal cord and brain. A variety of signs and symptoms can result. Early manifestations include paresthesias (tingling, numbness) of the hands and feet and a reduction in deep tendon reflexes. Late-developing responses include loss of memory, mood changes, hallucinations, and psychosis. If vitamin B₁₂ deficiency is prolonged, neurologic damage can become permanent.

The precise mechanism by which B₁₂ deficiency results in neuronal damage is unknown. We do know, however, that neuronal damage is not related to effects on folic acid or DNA. That is, the mechanism that underlies neuronal damage is different from the mechanism that underlies disruption of hematopoiesis. Consequently, although administering large doses of folic acid can correct the hematologic consequences of B₁₂ deficiency, folic acid will not improve the neurologic picture.

Other Effects. As noted, vitamin B₁₂ deficiency can adversely affect virtually all tissues in which a high proportion of cells are undergoing growth and division. Hence, in addition to disrupting the production of erythrocytes, lack of B₁₂ also prevents the bone marrow from making leukocytes (white blood cells) and thrombocytes (platelets). Loss of these blood elements can lead to infection and spontaneous bleeding. Disruption of DNA synthesis can also suppress division of the cells that form the epithelial lining of the mouth, stomach, and intestine, thereby causing oral ulceration and a variety of GI disturbances.

Diagnosis

When megaloblastic anemia occurs, it may be due to vitamin B₁₂ deficiency or other causes, especially a lack of folic acid. Hence, if therapy is to be appropriate, a definitive diagnosis must be made. Two tests are particularly helpful. The first is obvious: measurement of plasma B₁₂. The second procedure, known as the Schilling test, measures vitamin B₁₂ absorption. The combination of megaloblastic anemia plus low plasma vitamin B₁₂ plus evidence of B₁₂ malabsorption permits a clear diagnosis of vitamin B₁₂ deficiency.

VITAMIN B₁₂ PREPARATIONS: CYANOCOBALAMIN

Cyanocobalamin is a purified, crystalline form of vitamin B₁₂. This compound is the drug of choice for all forms of B₁₂ deficiency.

Adverse Effects

Cyanocobalamin is generally devoid of serious adverse effects. One potential response, *hypokalemia*, may occur as a natural consequence of increased erythrocyte production. Erythrocytes incorporate significant amounts of potassium. Hence, as large numbers of new erythrocytes are produced, levels of free potassium may fall.

Preparations, Dosage, and Administration

Cyanocobalamin can be given orally, intranasally, and by IM or subQ injection. Most pharmacology texts, including prior editions of this one, will tell you that oral therapy is appropriate only for people who absorb B₁₂ well; all other patients (ie, those with impaired absorption) should use intranasal or parenteral therapy. However, this statement is not correct. Although it is true that various conditions—including lack of intrinsic factor, low gastric acidity, and regional enteritis—severely impair B₁₂ absorption, these conditions do not prevent absorption entirely. Hence, even people with impaired absorption can still be treated orally; the only catch is that doses must be very high. Is there any advantage to oral therapy compared with parenteral therapy? Yes. First, oral therapy is more comfortable (injections sometimes hurt). Second, oral therapy is more convenient (because it avoids regular trips to the physician for shots).

Oral. Oral cyanocobalamin is appropriate for most people with mild to moderate B₁₂ deficiency, regardless of the cause. (The principal exception is patients with severe neurologic involvement.) If the B₁₂ deficiency is due to malabsorption, dosages must be high—typically 1000 to 10,000 mcg/day. To ensure that absorption has been adequate, B₁₂ levels should be measured periodically.

In addition to treating patients with B₁₂ deficiency, oral cyanocobalamin can be used as a dietary supplement. The usual dosage is 6 mcg/day.

Three oral formulations are available: standard tablets (100, 500, 1000, and 5000 mcg), sublingual tablets (1000 mcg), and lozenges (50, 100, 250, and 500 mcg).

Parenteral. Parenteral cyanocobalamin (generic only) can be administered by IM or deep subQ injection. Cyanocobalamin must NOT be given IV. Intramuscular and subQ injections are generally well tolerated, although they occasionally cause pain and other local reactions.

Parenteral administration is indicated for patients with impaired B₁₂ absorption—although most of these people can be treated with oral cyanocobalamin instead. If the cause of malabsorption is irreversible (eg, parietal cell atrophy, total gastrectomy), therapy must continue lifelong. A typical dosing schedule for megaloblastic anemia is 30 mcg/day for 5 to 10 days followed by 100 to 200 mcg monthly until remission is complete. After anemia has been corrected, doses of 100 mcg are administered monthly for life.

Intranasal. Intranasal cyanocobalamin [Nascobal, CaloMist] represents a convenient alternative to IM or subQ injection for people who cannot take cyanocobalamin by mouth. Efficacy of intranasal cyanocobalamin has not been determined for patients with nasal congestion, allergic rhinitis, or upper respiratory infections. Accordingly, until more is known, patients with these disorders should not use this formulation until symptoms subside. Hot foods or liquids can increase nasal secretions, which might flush cyanocobalamin gel from the nose. Accordingly, hot foods should not be eaten within 1 hour before or 1 hour after administering the drug.

Intranasal cyanocobalamin is available in two metered-dose formulations: Nascobal and CaloMist. Nascobal delivers 500 mcg/actuation; CaloMist delivers only 25 mcg/actuation. The dosing schedule with Nascobal is 500 mcg in one nostril once a week. The dosing schedule with CaloMist is 25 mcg in each nostril once a day; if needed, the dosage can be increased to 25 mcg in each nostril twice a day.

GUIDELINES FOR TREATING VITAMIN B₁₂ DEFICIENCY

Route of B₁₂ Administration. As discussed above, oral therapy can be used for most patients, including those with conditions that impair B₁₂ absorption. The major exception is patients with severe neurologic deficits caused by B₁₂ deficiency. For these people, parenteral cyanocobalamin is indicated.

Treatment of Moderate B₁₂ Deficiency. The primary manifestations of moderate B₁₂ deficiency are megaloblasts in the bone marrow and macrocytes in peripheral blood. Moderate deficiency does not cause leukopenia, thrombocytopenia, or neurologic complications. Moderate deficiency can be managed with vitamin B₁₂ alone; no other measures are required.

Treatment of Severe B₁₂ Deficiency. Severe deficiency produces multiple effects, all of which must be attended to. Unlike mild deficiency, in which erythrocytes are the only blood cells affected, severe deficiency disrupts production of all blood cells. Loss of erythrocytes leads to hypoxia, cerebrovascular insufficiency, and heart failure. Loss of leukocytes encourages infection, and loss of thrombocytes promotes bleeding. In addition to causing serious hematologic deficits, severe B₁₂ deficiency has adverse effects on the nervous system and GI tract.

Treatment of severe deficiency involves the following: (1) IM injection of vitamin B₁₂ and folic acid (the folic acid accelerates recovery of hematologic deficits); (2) administration of 2 to 3 units of packed RBCs (to correct anemia quickly); (3) transfusion of platelets (to suppress bleeding); and (4) therapy with antibiotics if infection has developed.

Following treatment with vitamin B₁₂ plus folic acid, recovery from anemia occurs quickly. Within 1 to 2 days, megaloblasts disappear from the bone marrow; within 3 to 5 days, reticulocyte counts become elevated; by day 10, the hematocrit begins to rise; and within 14 to 21 days, the hematocrit becomes normal.

Recovery from neurologic damage is slow and depends on how long the damage had been present. When deficits have been present for only 2 to 3 months, recovery is relatively fast. When deficits have been present for many months or for years, recovery is slow: Months may pass before any improvement is apparent, and complete recovery may never occur.

Long-Term Treatment. For patients who lack intrinsic factor or who suffer from some other permanent cause of vitamin B₁₂ malabsorption, lifelong treatment is required. Traditional therapy consists of monthly IM or subQ injections of

cyanocobalamin. However, *large* daily oral doses can be just as effective, as can intranasal doses (weekly with Nascobal or daily with CaloMist). During prolonged therapy, treatment should be periodically assessed: plasma levels of vitamin B₁₂ should be measured every 3 to 6 months, blood samples should be examined for the return of macrocytes, and blood counts should be performed.

Potential Hazard of Folic Acid. Treatment with folic acid can exacerbate the neurologic consequences of B₁₂ deficiency. Recall that folic acid, by itself, can reverse the *hematologic* effects of B₁₂ deficiency—but will not alleviate *neurologic* deficits. Hence, by correcting the most obvious manifestation of B₁₂ deficiency (anemia), folic acid can mask the fact that deficiency of B₁₂ still exists. As a result, *use of folic acid can lead to undertreatment with B₁₂ itself*, and can thereby permit neurologic damage to progress. Clearly, folic acid is not a substitute for vitamin B₁₂, and vitamin B₁₂ deficiency should never be treated with folic acid alone. Whenever folic acid is employed during treatment of vitamin B₁₂ deficiency, extra care must be taken to ensure that B₁₂ dosage is adequate.

FOLIC ACID DEFICIENCY

In one respect, folic acid deficiency is identical to vitamin B₁₂ deficiency: In both states, *megaloblastic anemia* is the most conspicuous pathology. However, in other important ways, folic acid deficiency and vitamin B₁₂ deficiency are dissimilar (Table 55-4 provides a summary). Consequently, when a patient presents with megaloblastic anemia, it is essential to determine whether the cause is deficiency of folic acid, vitamin B₁₂, or both.

PHYSIOLOGY AND BIOCHEMISTRY OF FOLIC ACID

Metabolic Function

As noted when we discussed vitamin B₁₂, folic acid (also known as *folate*) is an essential factor for DNA synthesis. Without folic acid, DNA replication and cell division cannot proceed.

In order to be usable, dietary folic acid must first be converted to an active form. Under normal conditions, activation occurs through a pathway that employs vitamin B₁₂ (see Fig. 55-4). However, when large amounts of folate are ingested, some can be activated through an alternate pathway—one that

TABLE 55-4 • Vitamin B₁₂ Deficiency Versus Folic Acid Deficiency

	Vitamin B ₁₂ Deficiency	Folic Acid Deficiency
Usual cause	Vitamin B ₁₂ malabsorption from lack of intrinsic factor	Low dietary folic acid
Primary hematologic effect	Megaloblastic anemia	Megaloblastic anemia
Neurologic effect	Damage to brain and spinal cord	None*
Diagnosis	Low plasma vitamin B ₁₂ ; low B ₁₂ absorption (Schilling test)	Low plasma folic acid
Treatment (usual route)	Cyanocobalamin (PO or IM)	Folic acid (PO)
Usual duration of therapy	Lifelong	Short term

*Folic acid deficiency early in pregnancy can cause neural tube defects in the fetus.

does not employ vitamin B₁₂. Hence, even in the absence of vitamin B₁₂, if sufficient amounts of folic acid are consumed, active folate will be available for DNA synthesis.

Fate in the Body

Folic acid is absorbed in the early segment of the small intestine, and then transported to the liver and other tissues, where it is either used or stored.

Folic acid in the liver undergoes extensive enterohepatic recirculation. That is, folate from the liver is excreted into the intestine, after which it is reabsorbed and then returned to the liver through the hepatic-portal circulation. This enterohepatic recirculation helps salvage up to 200 mcg of folate per day. Accordingly, the process is an important way to maintain folate stores.

In contrast to vitamin B₁₂, folic acid is not conserved rigidly: every day, significant amounts are excreted. As a result, if intake of folic acid were to cease, signs of deficiency would develop rapidly (within weeks if body stores were already low).

Daily Requirements

The RDA of folic acid, as set by the Food and Nutrition Board of the Institute of Medicine, is 400 mcg for adult males and for adult females who are neither pregnant nor lactating. RDAs during pregnancy and lactation increase, to 600 mcg and 500 mcg, respectively. Although the RDA for adult females is set at 400 mcg, women of child-bearing age should consume even more: 400 to 800 mcg of *supplemental* folate, in addition to the folate in food (see below). Individuals with malabsorption syndromes (eg, tropical sprue) may require as much as 2000 mcg (2 mg) per day; at these high doses, folate will be taken up in sufficient quantity despite impaired absorption.

Dietary Sources

Folic acid is present in all foods. Good sources include liver, peas, lentils, oranges, whole-wheat products, asparagus, beets, broccoli, and spinach. Also, many grain products (eg, cereals, bread, pasta, rice, flour) are now fortified with folic acid.

FOLIC ACID DEFICIENCY: CAUSES, CONSEQUENCES, AND DIAGNOSIS

Causes

Folic acid deficiency has two principal causes: (1) poor diet (especially in alcoholics), and (2) malabsorption secondary to intestinal disease. Rarely, certain drugs may cause folate deficiency.

Alcoholism. Alcoholism, either acute or chronic, may be the most common cause of folate deficiency. Deficiency results for two reasons: (1) insufficient folic acid in the diet and (2) derangement of enterohepatic recirculation secondary to alcohol-induced injury to the liver. Fortunately, with improved diet and reduced alcohol consumption, alcohol-related folate deficiency will often reverse.

Sprue. Sprue is an intestinal malabsorption syndrome that decreases folic acid uptake. Since sprue does not block folate absorption entirely, deficiency can be corrected by giving large doses of folic acid orally.

Consequences

All People. With the important exception that folic acid deficiency does not injure the nervous system, the effects of folate deficiency are identical to those of vitamin B₁₂ deficiency. Hence, as with B₁₂ deficiency, the most

prominent consequence of folate deficiency is *megaloblastic anemia*. In addition, like B₁₂ deficiency, lack of folic acid may result in leukopenia, thrombocytopenia, and injury to the oral and GI mucosa. Since we already noted that many of the consequences of vitamin B₁₂ deficiency result from depriving cells of active folic acid, the similarities between folate deficiency and vitamin B₁₂ deficiency should be no surprise.

The Developing Fetus. Folic acid deficiency *very early* in pregnancy can cause neural tube defects (eg, spina bifida, anencephaly). Accordingly, it is imperative that all women of reproductive age ensure adequate folate levels *before* pregnancy occurs. To accomplish this, the U.S. Preventive Services Task Force (USPSTF) now recommends that *all women who may become pregnant consume 400 to 800 mcg of supplemental folic acid each day—in addition to the folate they get from food.*

Other Consequences. As discussed in Chapter 81 (Vitamins), folic acid deficiency may increase the risk of colorectal cancer and atherosclerosis.

Diagnosis

When patients present with megaloblastic anemia, it is essential to distinguish between folate deficiency and vitamin B₁₂ deficiency as the cause. How? By comparing plasma levels of folate and vitamin B₁₂. If folic acid levels are low and vitamin B₁₂ levels are normal, a diagnosis of folate deficiency is suggested. Conversely, if folate levels are normal and B₁₂ is low, B₁₂ deficiency would be the likely diagnosis. A decision against folic acid deficiency would be strengthened if neurologic deficits were observed.

FOLIC ACID PREPARATIONS

Nomenclature

Nomenclature regarding folic acid preparations can be confusing and deserves comment. Two forms of folic acid are available. One form is inactive as administered (but undergoes activation after being absorbed). The second form is active to start with. Both forms have several generic names: the *inactive* form is referred to as *folacin*, *folate*, *pteroylglutamic acid*, or *folic acid*; the *active* form is referred to as *leucovorin calcium*, *folinic acid*, or *citrovorum factor*. The inactive form is by far the most commonly used.

Folic Acid (Pteroylglutamic Acid)

Chemistry. Folic acid is inactive as administered and cannot support DNA synthesis. Activation takes place rapidly following absorption.

Indications. Folic acid has three uses: (1) treatment of megaloblastic anemia resulting from folic acid deficiency; (2) prophylaxis of folate deficiency, especially during pregnancy and lactation; and (3) initial treatment of severe megaloblastic anemia resulting from vitamin B₁₂ deficiency.

Adverse Effects. Oral folic acid is nontoxic when used *short term*. Massive dosages (eg, as much as 15 mg) have been taken with no ill effects. However, as noted in Chapter 81 (Vitamins), even moderately large doses (1000 mcg/day), when taken *long term*, may increase the risk of some cancers, including colorectal cancer and cancer of the prostate.

Warning. If taken in sufficiently large doses, folic acid can correct the hematologic consequences of vitamin B₁₂ deficiency, thereby masking the fact that a deficiency in vitamin B₁₂ still exists. Since folic acid will not prevent the neurologic consequences of B₁₂ deficiency (despite correcting the hematologic picture), this masking effect may allow the development of irreversible damage to the nervous system. To reduce the chances of this problem, folate should not be used indiscriminately: Unless specifically indicated, consumption of folic acid should not exceed 1000 mcg/day. Furthermore, whenever folic acid is given to patients known to have a deficiency in vitamin B₁₂, special care must be taken to ensure that the vitamin B₁₂ dosage is adequate.

Formulations and Routes of Administration. Folic acid is available in tablets (0.4, 0.8, and 1 mg) for oral use and in a 5-mg/mL solution (Folvite) for IM, IV, or subQ injection. As a rule, injections are reserved for patients with severely impaired GI absorption.

Dosage. For treatment of folate-deficient megaloblastic anemia in adults, the usual oral dosage is 1000 to 2000 mcg/day. Once symptoms have resolved, the maintenance dosage is 400 mcg/day. For prophylaxis during pregnancy and lactation, doses up to 1000 mcg/day may be used.

Leucovorin Calcium (Folinic Acid)

Leucovorin calcium is an active form of folic acid used primarily as an adjunct to cancer chemotherapy (see Chapter 102). Leucovorin is not used routinely to correct folic acid deficiency. Why? Because folic acid is just as effective and cheaper.

GUIDELINES FOR TREATING FOLIC ACID DEFICIENCY

Choice of Treatment Modality. The modality for treating folic acid deficiency should be matched with the cause. If the deficiency is due to poor diet, it should be corrected by

dietary measures—not with supplements (except for women who may become pregnant). Ingestion of one serving of a fresh vegetable or one glass of fruit juice a day will often suffice. In contrast, when folate deficiency is the result of malabsorption, diet alone cannot correct the deficiency, and hence supplemental folate will be needed.

Route of Administration. Oral administration is preferred for most patients. Unlike vitamin B₁₂, folic acid is rarely administered by injection. Even in the presence of intestinal disease, oral folic acid can be effective, providing the dosage is high enough.

Prophylactic Use of Folic Acid. Folic acid should be taken prophylactically only when clearly appropriate. The principal candidates for prophylactic folate are women who might become pregnant, and women who are pregnant or lactating. Since folic acid may mask vitamin B₁₂ deficiency, indiscriminate use of folate should be avoided.

Treatment of Severe Deficiency. Folic acid deficiency can produce severe megaloblastic anemia. To ensure a rapid response, therapy should be initiated with an IM injection of folic acid and vitamin B₁₂. (Because of the metabolic interrelationship between folic acid and vitamin B₁₂, combining these agents accelerates recovery.) After the initial injection, treatment should be continued with folic acid alone. Folic acid should be given orally in a dosage of 1000 to 2000 mcg/day for 1 to 2 weeks. After this, maintenance doses of 400 mcg/day may be required.

Therapy is evaluated by monitoring the hematologic picture. When treatment has been effective, megaloblasts will disappear from the bone marrow within 48 hours; the reticulocyte count will increase measurably within 2 to 3 days; and the hematocrit will begin to rise in the second week.

KEY POINTS

- The principal cause of iron deficiency is increased iron demand secondary to (1) maternal and fetal blood volume expansion during pregnancy; (2) blood volume expansion during infancy and early childhood; or (3) chronic blood loss, usually of GI or uterine origin.
- The major consequence of iron deficiency is microcytic, hypochromic anemia.
- Ferrous sulfate, given PO, is the drug of choice for iron deficiency.
- Iron-deficient patients who cannot tolerate or absorb oral ferrous salts are treated with parenteral iron—usually iron dextran administered IV.
- The major adverse effects of ferrous sulfate are GI disturbances. These are best managed by reducing the dosage (rather than by administering the drug with food, which would greatly reduce absorption).
- Parenteral iron dextran carries a significant risk of fatal anaphylactic reactions. The risk is much lower with other parenteral iron products (eg, iron sucrose).
- When iron dextran is used, a small test dose is required before each full dose. Be aware, however, that patients can die from the test dose, and patients who did not react to the test dose may still die from the full dose.
- The principal cause of vitamin B₁₂ deficiency is impaired absorption secondary to lack of intrinsic factor.
- The principal consequences of B₁₂ deficiency are megaloblastic (macrocytic) anemia and neurologic injury.
- Vitamin B₁₂ deficiency caused by malabsorption is treated lifelong with cyanocobalamin. Traditional treatment consists of IM injections administered monthly. However, large oral doses administered daily are also effective, as are intranasal doses (administered weekly with Nascobal or daily with CaloMist).
- For initial therapy of severe vitamin B₁₂ deficiency, parenteral folic acid is given along with cyanocobalamin.
- When folic acid is combined with vitamin B₁₂ to treat B₁₂ deficiency, it is essential that the dosage of B₁₂ be adequate. Why? Because folic acid can mask continued B₁₂ deficiency.

(by improving the hematologic picture), while allowing the neurologic consequences of B₁₂ deficiency to progress.

- The principal causes of folic acid deficiency are poor diet (usually in alcoholics) and malabsorption secondary to intestinal disease.
- The principal consequences of folic acid deficiency are megaloblastic anemia and neural tube defects in the developing fetus.

- To prevent neural tube defects, all women who may become pregnant should ingest 400 to 800 mcg of supplemental folate daily, in addition to the folate they get in food.

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Summary of Major Nursing Implications*

IRON PREPARATIONS

Carbonyl iron
 Ferric ammonium citrate
 Ferrous aspartate
 Ferrous bisglycinate
 Ferrous fumarate
 Ferrous gluconate
 Ferrous sulfate
 Ferumoxytol
 Heme-iron polypeptide
 Iron dextran
 Iron sucrose
 Polysaccharide iron complex
 Sodium–ferric gluconate complex (SFGC)

Except where indicated, the implications summarized below apply to all iron preparations.

Preadministration Assessment

Therapeutic Goal

Prevention or treatment of iron deficiency anemias.

Baseline Data

Prior to treatment, assess the degree of anemia. Fatigue, listlessness, and pallor indicate mild anemia; dyspnea, tachycardia, and angina suggest severe anemia. Laboratory findings indicative of anemia are subnormal hemoglobin levels, subnormal hematocrit, subnormal hemosiderin in bone marrow, and the presence of microcytic, hypochromic erythrocytes.

The cause of iron deficiency (eg, pregnancy, occult bleeding, menorrhagia, inadequate diet, malabsorption) must be determined.

Identifying High-Risk Patients

All iron preparations are *contraindicated* for patients with anemias other than iron deficiency anemia.

Parenteral preparations are *contraindicated* for patients who have had a severe allergic reaction to them in the past.

Use *oral* preparations with *caution* in patients with peptic ulcer disease, regional enteritis, and ulcerative colitis.

Implementation: Administration

Routes

Oral. Ferrous sulfate, ferrous fumarate, ferrous gluconate, ferrous aspartate, ferrous bisglycinate, ferric ammonium citrate, carbonyl iron, heme-iron polypeptide, polysaccharide iron complex, sodium ferric gluconate complex (SFGC).

Parenteral. Iron dextran, SFGC, iron sucrose, ferumoxytol.

Oral Administration

Food reduces GI distress from oral iron but also greatly reduces absorption. **Instruct patients to administer oral iron between meals to maximize uptake.** If GI distress is intolerable, the dosage may be reduced. If absolutely necessary, oral iron may be administered with meals.

Liquid preparations can stain the teeth. **Instruct patients to dilute liquid preparations with juice or water, administer them through a straw, and rinse the mouth after.**

Warn patients not to crush or chew sustained-release preparations.

Warn patients against ingesting iron salts together with antacids or tetracyclines.

Inform patients that oral iron preparations differ and warn them against switching from one to another.

Parenteral Administration: Iron Dextran

Iron dextran may be given IV or IM. Intravenous administration is safer and preferred.

Intravenous. To minimize anaphylactic reactions, follow this protocol: (1) Infuse 25 mg as a test dose and observe the patient for at least 15 minutes. (2) If the test dose appears safe, infuse 500 mg over 10 to 15 minutes. (3) If the 500-mg dose proves uneventful, give additional doses as needed.

Intramuscular. Intramuscular injection can cause significant adverse reactions (anaphylaxis, persistent pain, localized discoloration, promotion of tumors) and is generally avoided. Make injections deep into each buttock using the Z-track technique. Give a 25-mg test dose and wait 1 hour before giving the full therapeutic dose.

Parenteral Administration: SFGC

To minimize adverse reactions, precede the first full dose with a test dose (25 mg infused IV over 60 minutes). Administer therapeutic doses by slow IV infusion (no faster than 12.5 mg/min).

Parenteral Administration: Iron Sucrose

Hemodialysis-Dependent Patients. Administer iron sucrose directly into the dialysis line. Do not mix with other drugs or with parenteral nutrition solutions. Administer by either (1) slow injection (1 mL/min) or (2) infusion (dilute iron sucrose in up to 100 mL of 0.9% saline and infuse over 15 minutes or longer).

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Peritoneal Dialysis-Dependent Patients. Administer by slow infusion.

Non-Dialysis-Dependent Patients. Administer by slow injection.

Parenteral Administration: Ferumoxytol

Give 510 mg by slow IV injection, defined here as 1 mL/sec (30 mg/sec), taking about 17 seconds for the total 510-mg dose. Repeat 3 to 8 days later.

Implementation: Measures to Enhance Therapeutic Effects

If the diet is poor in iron, advise the patient to increase consumption of iron-rich foods (eg, liver, egg yolks, brewer's yeast, wheat germ, muscle meats, fish, fowl).

Ongoing Evaluation and Interventions

Evaluating Therapeutic Responses

Evaluate treatment by monitoring hematologic status. Reticulocyte counts should increase within 4 to 7 days, hemoglobin content and the hematocrit should begin to rise within 1 week, and hemoglobin levels should rise by at least 2 gm/dL within 1 month. If these responses do not occur, evaluate the patient for adherence, persistent bleeding, inflammatory disease, and malabsorption.

Minimizing Adverse Effects

GI Disturbances. Forewarn patients about possible GI reactions (nausea, vomiting, constipation, diarrhea) and inform them these will diminish over time. If GI distress is severe, the dosage may be reduced, or, if absolutely necessary, iron may be administered with food.

Inform patients that iron will impart a harmless dark green or black color to stools.

Anaphylactic Reactions. Parenteral iron dextran (and, rarely, SFGC, iron sucrose, and ferumoxytol) can cause potentially fatal anaphylaxis. Before giving parenteral iron, ensure that injectable epinephrine and facilities for resuscitation are immediately available. After administration, observe the patient for 60 minutes. Give test doses as described above. Precede all doses of iron dextran and the first dose of SFGC with a test dose; test doses are unnecessary with iron sucrose and ferumoxytol.

Managing Acute Toxicity. Iron poisoning can be fatal to young children. Instruct parents to store iron out of reach and in childproof containers. If poisoning occurs, rapid treatment is imperative. Use gastric lavage to remove iron from the stomach. Administer deferoxamine if plasma levels of iron exceed 500 mcg/mL. Manage acidosis and shock as required.

CYANOCOBALAMIN (VITAMIN B₁₂)

Preadministration Assessment

Therapeutic Goal

Correction of megaloblastic anemia and other sequelae of vitamin B₁₂ deficiency.

Baseline Data

Assess the extent of vitamin B₁₂ deficiency. Record signs and symptoms of anemia (eg, pallor, dyspnea, palpitations, fatigue). Determine the extent of neurologic damage. Assess GI involvement.

Baseline laboratory data include plasma vitamin B₁₂ levels, erythrocyte and reticulocyte counts, and hemoglobin and hematocrit values. Bone marrow may be examined for megaloblasts. A Schilling test may be ordered to assess vitamin B₁₂ absorption.

Identifying High-Risk Patients

Use with *caution* in patients receiving folic acid.

Implementation: Administration

Routes and Administration

Administration may be IM, subQ, oral, or intranasal. For most patients, lifelong treatment is required. Traditional therapy consists of IM or subQ injections administered monthly. However, treatment can be just as effective with large daily oral doses or with intranasal doses (administered weekly with Nascobal or daily with CaloMist). **Inform patients that intranasal doses should not be administered within 1 hour before or 1 hour after consuming hot foods or hot liquids.**

Implementation: Measures to Enhance Therapeutic Effects

Promoting Adherence

Patients with permanent impairment of B₁₂ absorption require lifelong B₁₂ therapy. To promote adherence, **educate patients about the nature of their condition and impress upon them the need for monthly injections, daily oral therapy, or daily or weekly intranasal therapy.** Schedule appointments for injections at convenient times.

Improving Diet

When B₁₂ deficiency is not due to impaired absorption, a change in diet may accelerate recovery. **Advise the patient to increase consumption of B₁₂-rich foods (eg, muscle meats, dairy products).**

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Assess for improvements in hematologic and neurologic status. Over a period of 2 to 3 weeks, megaloblasts should disappear, reticulocyte counts should rise, and the hematocrit should normalize. Neurologic damage may take months to improve; in some cases, full recovery may never occur.

For patients receiving long-term therapy, vitamin B₁₂ levels should be measured every 3 to 6 months, and blood counts should be performed.

Minimizing Adverse Effects

Hypokalemia may develop during the first days of therapy. Monitor serum potassium levels and observe the patient for signs of potassium insufficiency. **Teach patients the**

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

signs and symptoms of hypokalemia (eg, muscle weakness, irregular heartbeat) and instruct them to report these immediately.

Minimizing Adverse Interactions

Folic acid can correct hematologic effects of vitamin B₁₂ deficiency, but not the neurologic effects. By improving the hematologic picture, folic acid can mask ongoing B₁₂ deficiency, resulting in undertreatment and progression of neurologic injury. Accordingly, when folic acid and cyanocobalamin are used concurrently, special care must be taken to ensure that the cyanocobalamin dosage is adequate.

FOLIC ACID (FOLACIN, FOLATE, PTEROYLGLUTAMIC ACID)

Preadministration Assessment

Therapeutic Goal

Folic acid is used for (1) treatment of megaloblastic anemia resulting from folic acid deficiency; (2) initial treatment of severe megaloblastic anemia resulting from vitamin B₁₂ deficiency; and (3) prevention of folic acid deficiency, especially in women who might become pregnant, and in women who are pregnant or lactating.

Baseline Data

Assess the extent of folate deficiency. Record signs and symptoms of anemia (eg, pallor, dyspnea, palpitations, fatigue). Determine the extent of GI damage.

Baseline laboratory data include serum folate levels, erythrocyte and reticulocyte counts, and hemoglobin and hematocrit values. In addition, bone marrow may be evaluated for megaloblasts. To rule out vitamin B₁₂ deficiency, vitamin B₁₂ determinations and a Schilling test may be ordered.

Identifying High-Risk Patients

Folic acid is *contraindicated* for patients with pernicious anemia (except during the acute phase of treatment). Inappropriate use of folic acid by these patients can mask signs of vitamin B₁₂ deficiency, thereby allowing further neurologic deterioration.

Implementation: Dosage and Administration

Routes

Oral, subQ, IV, and IM. Oral administration is most common and preferred. Injections are employed only when intestinal absorption is severely impaired.

Dosage

Prevention of Neural Tube Defects. To reduce the risk of neural tube defects, women who might become pregnant should consume 400 to 800 mcg of supplemental folate daily—in addition to the folate they get from food.

Treatment of Folate-Deficient Megaloblastic Anemia. The initial oral dosage is 1000 to 2000 mcg/day. Once symptoms have resolved, the maintenance dosage is 400 mcg/day.

Implementation: Measures to Enhance Therapeutic Effects

Improving Diet

If the diet is deficient in folic acid, advise the patient to increase consumption of folate-rich foods (eg, green vegetables, liver). If alcoholism underlies dietary deficiency, offer counseling for alcoholism as well as dietary advice.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor hematologic status. Within 2 weeks, megaloblasts should disappear, reticulocyte counts should increase, and the hematocrit should begin to rise.

*Patient education information is highlighted as blue text.

Hematopoietic Agents

HEMATOPOIETIC GROWTH FACTORS

Erythropoietic Growth Factors

Epoetin Alfa (Erythropoietin)

Darbepoetin Alfa (Erythropoietin, Long Acting)

Methoxy Polyethylene Glycol-Epoetin Beta (Erythropoietin, Very Long Acting)

Leukopoietic Growth Factors

Filgrastim (Granulocyte Colony-Stimulating Factor)

Pegfilgrastim (Granulocyte Colony-Stimulating Factor, Long Acting)

Sargramostim (Granulocyte-Macrophage Colony-Stimulating Factor)

Thrombopoietic Growth Factor

Oprelvekin (Interleukin-11)

DRUGS THAT MIMIC HEMATOPOIETIC GROWTH FACTORS OR ENHANCE THEIR ACTIONS

Thrombopoietin Receptor Agonists

Romiplostim

Eltrombopag

Plerixafor

HEMATOPOIETIC GROWTH FACTORS

Hematopoiesis is the process by which our bodies make red blood cells, white blood cells, and platelets. The process is regulated in part by hematopoietic growth factors—naturally occurring hormones that stimulate the proliferation and differ-

entiation of hematopoietic stem cells, and enhance function in the mature forms of those cells. In a laboratory setting, hematopoietic growth factors can cause stem cells to form colonies of mature blood cells. Because of this action, some hematopoietic growth factors are also known as *colony-stimulating factors*. Therapeutic applications of hematopoietic growth factors include (1) acceleration of neutrophil and platelet repopulation after cancer chemotherapy, (2) acceleration of bone marrow recovery after an autologous bone marrow transplantation (BMT), and (3) stimulation of erythrocyte production in patients with chronic renal failure (CRF).

The names used for the hematopoietic growth factors are a potential source of confusion. Why? Because each product has a biologic name, a generic name, and one or more proprietary (trade) names. The biologic, generic, and proprietary names for available products are listed in Table 56-1.

ERYTHROPOIETIC GROWTH FACTORS

Erythropoietic growth factors—also known as *erythropoiesis stimulating agents* or ESAs—stimulate production of erythrocytes (red blood cells, RBCs). Because they increase RBC production, ESAs represent an alternative to infusions for patients with low RBC counts, including patients with CRF and cancer patients undergoing myelosuppressive chemotherapy. Unfortunately, although these drugs can be beneficial, postmarketing surveillance has shown clear evidence of harm. In all patients, ESAs may increase the risk of stroke, heart failure, blood clots, myocardial infarction (MI), and death. In patients with cancer, ESAs may shorten time to tumor progression and reduce overall survival. Because of this

TABLE 56-1 ■ Nomenclature for Hematopoietic Growth Factors

Biologic Name	Pharmacologic Names	
	Generic Name	Trade Name
Erythropoietic Growth Factors		
Erythropoietin	Darbepoetin alfa Epoetin alfa MPEG-epoetin beta*	Aranesp Epogen, Procrit, Eprex ♣ Mircera
Leukopoietic Growth Factors		
Granulocyte colony-stimulating factor (G-CSF)	Filgrastim Pegfilgrastim	Neupogen Neulasta
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Sargramostim	Leukine
Thrombopoietic Growth Factor		
Interleukin-11	Oprelvekin	Neumega

*MPEG-epoetin beta = methoxy polyethylene glycol-epoetin beta.

potential for harm, use of ESAs has dropped sharply, especially among patients with cancer.

In the United States, two ESAs are available: epoetin alfa (erythropoietin) and darbepoetin alfa (a long-acting form of erythropoietin). A third ESA—methoxy polyethylene glycol-epoetin beta (a very-long-acting form of erythropoietin)—is available in other countries, but not in the United States.

Epoetin Alfa (Erythropoietin)

Epoetin alfa [Epogen, Procrit, Eprex[®]] is a growth factor produced by recombinant DNA technology. Chemically, the compound is a glycoprotein containing 165 amino acids. The protein portion of epoetin alfa is identical to that of human erythropoietin, a naturally occurring hormone. Epoetin alfa is used to maintain erythrocyte counts in (1) patients with CRF, (2) patients with nonmyeloid malignancies who have anemia secondary to chemotherapy, and (3) HIV-infected patients taking zidovudine. In addition, the drug can be used to elevate erythrocyte counts in anemic patients prior to elective surgery.

Physiology

Erythropoietin is a glycoprotein hormone that stimulates production of red blood cells in the bone marrow. The hormone is produced by peritubular cells in the proximal tubules of the kidney. In response to anemia or hypoxia, circulating levels of erythropoietin rise dramatically, triggering an increase in erythrocyte synthesis. However, because production of erythrocytes requires iron, folic acid, and vitamin B₁₂, the response to erythropoietin is minimal if any of these is deficient.

Erythropoietin has significant physiologic effects outside the hematopoietic system. Animal studies indicate that erythropoietin is secreted by cells of many organs, including the brain, bone marrow, liver, heart, kidney, uterus, testes, and blood vessels—and that receptors for erythropoietin are present at most of these sites. Actions of the hormone include modulation of angiogenesis (blood vessel formation) and maintenance of cellular integrity (by inhibiting apoptotic mechanisms of cell injury). In the future, these actions may be exploited to treat a variety of disorders, including stroke, diabetic nephropathy, multiple sclerosis, myocardial infarction (MI), and heart failure (HF).

Therapeutic Uses

Anemia of Chronic Renal Failure. Epoetin alfa can partially reverse anemia associated with CRF, thereby reducing—but not eliminating—the need for transfusions. Benefits accrue to patients on dialysis as well as those who do not yet require dialysis. Initial effects can be seen within 1 to 2 weeks. Hemoglobin reaches maximal acceptable levels (10 to 11 gm/dL) in 2 to 3 months. Unfortunately, although treatment reduces the need for transfusions, it does *not* improve quality of life, decrease fatigue, or prevent progressive renal deterioration.

For therapy to be effective, iron stores must be adequate. Transferrin saturation should be at least 20%, and ferritin concentration should be at least 100 ng/mL. If pretreatment assessment indicates these values are low, they must be restored with iron supplements.

Chemotherapy-Induced Anemia. Epoetin alfa is used to treat chemotherapy-induced anemia in patients with *nonmyeloid malignancies*, thereby reducing the need for periodic

transfusions. Since transfusions require hospitalization, whereas epoetin can be self-administered at home, epoetin therapy can spare patients considerable inconvenience. Because epoetin works slowly (the hematocrit may take 2 to 4 weeks to recover), transfusions are still indicated when rapid replenishment of red blood cells is required. Please note that epoetin is not approved for patients with *leukemias* and *other myeloid malignancies*. Why? Because the drug may stimulate proliferation of these cancers. Furthermore, since ESAs can shorten survival time in *all* cancer patients (see below), epoetin is indicated only when the goal of cancer therapy is *palliation*. When the goal is *cure*, ESAs should not be used. (It makes no sense to give a potentially lethal drug to a patient who might be cured.) A new clinical guideline—*American Society of Hematology/American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer*—issued in 2010, provides detailed information on using ESAs in patients with cancer.

HIV-Infected Patients Taking Zidovudine. Epoetin alfa is approved for treating anemia caused by therapy with zidovudine (AZT) in patients with AIDS. For these patients, treatment can maintain or elevate erythrocyte counts and reduce the need for transfusions. However, if endogenous levels of erythropoietin are at or above 500 milliunits/mL, raising them further with epoetin is unlikely to help.

Anemia in Patients Facing Surgery. Epoetin may be given to increase erythrocyte levels in anemic patients scheduled for elective surgery. The drug should be used only when significant blood loss is anticipated—but should not be used prior to cardiac or vascular surgery. For surgical patients, epoetin offers two benefits: (1) it decreases the need for transfusions, and (2) by increasing erythrocyte synthesis, it allows patients to predeposit more blood in anticipation of transfusion needs.

Pharmacokinetics

Epoetin alfa is administered parenterally (IV or subQ). The drug cannot be given orally because, being a glycoprotein, it would be degraded in the GI tract. The plasma half-life is highly variable and unchanged by dialysis.

Adverse Effects and Interactions

Epoetin alfa is generally well tolerated. Although the drug is a protein, no serious allergic reactions have been reported. The most significant adverse effect is hypertension. There are no significant drug interactions. As discussed below under *Warnings*, improper use of epoetin alfa has been associated with serious cardiovascular events, tumor progression, and deaths.

Hypertension. In patients with CRF, epoetin is frequently associated with an increase in blood pressure. The extent of hypertension is directly related to the rate of rise in the hematocrit. To minimize risk, blood pressure should be monitored and, if necessary, controlled with antihypertensive drugs. If hypertension cannot be controlled, epoetin dosage should be reduced. In patients with pre-existing hypertension (a common complication of CRF), it is imperative that blood pressure be under control prior to epoetin use. About 30% of dialysis patients receiving epoetin require an adjustment in their antihypertensive therapy once the hematocrit has been normalized.

Cardiovascular Events. Epoetin has been associated with an increase in serious cardiovascular events. Among these are cardiac arrest, hypertension, HF, and thrombotic events, including stroke and MI. Risk is greatest when (1) the hemoglobin level exceeds 11 gm/dL or (2) the rate of rise in hemoglobin exceeds 1 gm/dL in any 2-week interval. Accordingly, dosage should be reduced when hemoglobin approaches 11 gm/dL or when the rate of rise exceeds 1 gm/dL in 2 weeks—and, in most patients, dosing should be temporarily stopped if hemoglobin rises to 11 gm/dL or more. To prevent clotting in the artificial kidney, CRF patients on dialysis may need increased anticoagulation with heparin.

Autoimmune Pure Red-Cell Aplasia. Very, very rarely, treatment with epoetin leads to pure red-cell aplasia (PRCA), a condition characterized by severe anemia and a complete absence of erythrocyte precursor cells in bone marrow. The cause is production of neutralizing antibodies directed against epoetin itself as well as any native erythropoietin the body is still able to produce. In the absence of epoetin and erythropoietin, production of red blood cells ceases. Because patients can no longer make erythrocytes, transfusions are required for survival. If evidence of PRCA develops, epoetin should be discontinued and blood should be assessed for neutralizing antibodies.

Warnings

Excessive Dosage. To minimize the risk of serious adverse events, the dosage of epoetin alfa and all other ESAs should be the lowest needed to gradually raise hemoglobin content to the lowest level sufficient to reduce the need for RBC transfusions. In most cases, hemoglobin level should not exceed 11 gm/dL. Why? Because when ESAs are administered in doses sufficient to raise hemoglobin above this level, there is an increased risk of serious cardiovascular events and death.

Cancer Patients. Postmarketing reports indicate that ESAs can accelerate tumor progression and shorten life in certain cancer patients—especially when hemoglobin has been driven above 12 gm/dL. In patients with advanced head and neck cancer who are undergoing radiation therapy, ESAs have shortened the time to tumor progression. In patients with metastatic breast cancer who are receiving chemotherapy, ESAs have shortened overall survival and increased deaths from tumor progression. Also, ESAs have increased the risk of death in patients with active malignant disease who are not receiving either radiation or chemotherapy, and hence ESAs are contraindicated for this group.

Renal Failure Patients. In patients with anemia of chronic renal failure, ESAs can increase the risk of serious cardiovascular events and death if hemoglobin levels are driven too high. Accordingly, dosage should be individualized to produce hemoglobin levels no higher than 10 to 11 gm/dL.

Preoperative Patients. When given to preoperative patients to reduce the need for RBC transfusion, ESAs have increased the risk of deep vein thrombosis—but only in patients who were not given an anticoagulant. Accordingly, anticoagulant therapy should be considered for all preoperative patients receiving an ESA.

Risk Evaluation and Mitigation Strategy

All Patients. Because ESAs can cause serious adverse effects, these drugs must be prescribed and used under a new Risk Evaluation and Mitigation Strategy (REMS), mandated by the Food and Drug Administration in 2010. Under the REMS, all patients must receive a *Medication Guide* that explains the risks and benefits of ESAs. The goal is to help pa-

tients make an informed decision when use of an ESA is under consideration. The guide also informs patients about what they can do to minimize risk.

Cancer Patients. The *ESA APPRISE Oncology Program** sets additional requirements for using ESAs in cancer patients. Prescribers must enroll in ESA APPRISE, complete a brief training module, discuss the risks and benefits of ESAs with the patient, and sign a form acknowledging that the discussion took place. Hospitals that dispense ESAs must be enrolled in ESA APPRISE, and must ensure that all ESA prescribers are enrolled as well. Prescribers who use ESAs for patients who do not have cancer are not required to enroll in ESA APPRISE.

Monitoring

Hemoglobin level should be measured at baseline and twice weekly thereafter until the target level has been reached and a maintenance dose established. Complete blood counts with a differential should be done routinely. Blood chemistry—blood urea nitrogen (BUN), uric acid, creatinine, phosphorus, and potassium—should be monitored. Iron should be measured periodically and maintained at an adequate level.

Preparations, Dosage, and Administration

Preparations. Epoetin alfa [Epogen, Procrit, Eprex[®]] is supplied in 1-mL single-dose vials (2000, 3000, 4000, 10,000, 20,000, and 40,000 units) and in 1- and 2-mL multidose vials (20,000 units). Vials should not be shaken (because epoetin is a protein that can be denatured by agitation). Don't mix epoetin with other drugs. Store at 2°C to 8°C (36°F to 46°F); don't freeze.

General Dosing Guidelines. Use the lowest dosage needed to gradually increase the hemoglobin concentration to the lowest level sufficient to reduce the need for RBC transfusion. For most patients, the target hemoglobin level is 10 to 11 gm/dL. Regimens that raise hemoglobin above 11 gm/dL are associated with an increased risk of serious cardiovascular events and death. Accordingly, dosage should be reduced when hemoglobin approaches 11 gm/dL, or when hemoglobin increases by more than 1 gm/dL in any 2-week interval. For most patients, if hemoglobin rises above 11 gm/dL, withhold treatment until hemoglobin drops below 11 gm/dL. When treatment resumes, decrease the dose by 25%, and then titrate upward as needed.

Dosing in Patients with Chronic Renal Failure. Route. Administration may be IV or subQ. When epoetin alfa first came into use, IV administration was preferred, in part because subQ administration was reputedly painful, and in part because bioavailability following subQ injection is reduced—although the half-life is prolonged. In 1998, a study comparing IV therapy with subQ therapy indicated that both methods produce equivalent effects. Furthermore, with subQ administration, 30% less epoetin is required, and reported discomfort at the injection site is minimal. Because epoetin is expensive, and because subQ therapy is equivalent to IV therapy and cheaper, it seems likely that subQ therapy will become the new standard.

Dosage. The initial dosage is 50 to 100 units/kg 3 times a week. Administration is by IV bolus for dialysis patients and by IV bolus or subQ injection for nondialysis patients. Once hemoglobin has risen high enough to avoid transfusions, an individualized maintenance dosage should be established: For dialysis patients, the median maintenance dosage is 75 units/kg 3 times a week; for nondialysis patients, the median maintenance dosage is 75 to 100 units/kg once a week. If hemoglobin rises above 11 gm/dL (for patients on dialysis) or 10 gm/dL (for patients not on dialysis), epoetin should be temporarily withheld.

Dosing in Patients Receiving Cancer Chemotherapy. Two dosing schedules may be used: once weekly or thrice weekly.

Once-Weekly Dosing. The initial dosage is 40,000 units subQ each week. If, after 4 weeks of therapy, hemoglobin has not increased by at least 1 gm/dL, the dosage should be increased to 60,000 units once weekly. If hemoglobin has not increased by 1 gm/dL after 4 weeks, treatment should stop, since further increases are not likely to succeed. When treatment *does* work, dosing should cease when chemotherapy stops.

*ESA (erythropoiesis stimulating agent) APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs) Oncology Program.

Thrice-Weekly Dosing. The initial dosage is 150 units/kg subQ 3 times a week. If the response is inadequate by 8 weeks, the dosage may be increased to 300 units/kg 3 times a week. Dosing should cease when chemotherapy stops.

Dosing in HIV-Infected Patients Taking Zidovudine. Prior to treatment, measure the endogenous erythropoietin level. If this level is already at or above 500 milliu/ml, epoetin alfa is unlikely to help.

The initial dosage is 100 units/kg (IV or subQ injection) 3 times a week for 8 weeks. If the response is insufficient, the dosage may be increased by increments of 50 to 100 units/kg until a maximum of 300 units/kg 3 times a week has been reached. If hemoglobin rises above 12 gm/dL, epoetin should be temporarily withheld.

Dosing in Anemic Patients Scheduled for Surgery. The recommended dosage is 300 units/kg/day subQ for 15 days starting 10 days before surgery.

Darbepoetin Alfa (Erythropoietin, Long Acting)

Actions and Therapeutic Use

Darbepoetin alfa [Aranesp] is a long-acting analog of epoetin alfa. Both drugs act on erythroid progenitor cells to stimulate production of erythrocytes. Darbepoetin differs structurally from epoetin in that it has two additional carbohydrate chains. Because of these chains, darbepoetin is cleared more slowly than epoetin, and hence has a longer half-life (49 hours vs. 18 to 24 hours). As a result, darbepoetin can be administered less frequently.

Darbepoetin is indicated for (1) anemia associated with CRF and (2) anemia associated with cancer chemotherapy. In patients with CRF, darbepoetin can reduce the need for erythrocyte infusions—but it does not reduce the incidence of renal events, cardiovascular events, or death—nor does it decrease fatigue or improve quality of life. In patients with cancer, treatment is limited to those with nonmyeloid malignancies whose anemia is caused by chemotherapy, and not by the cancer itself. Furthermore, since darbepoetin may increase the risk of cancer-related death, it should be used only when the objective of cancer therapy is palliation, not when the objective is cure.

Adverse Effects and Warnings

Darbepoetin is generally well tolerated. As with epoetin, the most common problem is hypertension. The risk can be minimized by ensuring that the rate of rise in hemoglobin does not exceed 1 gm/dL every 2 weeks. If hypertension develops, it should be controlled with antihypertensive drugs. Patients already taking antihypertensive drugs may need to increase their dosage.

Like epoetin alfa, darbepoetin increases the risk of PRCA, MI, HF, stroke, cardiac arrest, and other cardiovascular events, especially when the hemoglobin level exceeds 11 gm/dL or when the rate of rise in hemoglobin exceeds 1 gm/dL in 2 weeks.

Like epoetin alfa, darbepoetin can promote tumor progression and shorten survival in some cancer patients, and hence should not be used when the objective of chemotherapy is cure.

Monitoring

When initiating darbepoetin or changing dosage, the hemoglobin level should be measured weekly until it stabilizes. Thereafter, hemoglobin should be measured at least once a month.

Preparations, Dosage, Administration, and Monitoring

Preparations and Storage. Darbepoetin alfa [Aranesp] is available in 1-mL single-dose vials (25, 40, 60, 100, 200, 300, and 500 mcg/mL) and pre-filled single-dose syringes and auto-injectors (25 mcg/0.42 mL to 500 mcg/mL). Administration is by subQ and IV injection. Don't dilute darbepoetin or

mix it with other drugs. Because darbepoetin is a protein that can be denatured by agitation, do not shake the drug. Discard preparations that are discolored or contain particles. Store at 2°C to 8°C (36°F to 46°F); don't freeze.

General Dosing Guidelines. The treatment goal is to reduce the need for transfusions. Dosage should be reduced when hemoglobin approaches 11 gm/dL, or when hemoglobin increases by more than 1 gm/dL in any 2-week interval. If hemoglobin rises to 11 gm/dL or higher, withhold treatment until hemoglobin drops below 11 gm/dL. When treatment resumes, decrease the dose by 25%, and then titrate upward as needed.

Dosing in Patients with Chronic Renal Failure. The initial dosage is 0.45 mcg/kg, given either IV or subQ once a week. If hemoglobin rises above 11 gm/dL (for patients on dialysis) or 10 gm/dL (for patients not on dialysis), treatment should be temporarily withheld. Because responses develop gradually, dosage should be adjusted no more than once every 4 weeks. Quite often, the maintenance dosage is less than the initial dosage.

When switching from epoetin to darbepoetin, the new dosage and dosing frequency are based on the existing epoetin usage. For example, patients receiving 5000 to 11,000 units of epoetin each week should receive 25 mcg of darbepoetin each week. If the epoetin dosing frequency was 2 to 3 times a week, darbepoetin should be given once a week; if epoetin was given once a week, darbepoetin should be given once every 2 weeks.

Dosing in Patients Undergoing Cancer Chemotherapy. The initial dosage is 2.25 mcg/kg subQ once a week or 500 mcg subQ every 3 weeks. If the increase in hemoglobin is less than 1 gm/dL after 6 weeks, dosage should be increased to 4.5 mcg once a week. If the increase in hemoglobin exceeds 1 gm/dL in 2 weeks, or if hemoglobin rises high enough to avoid transfusions, dosage should be reduced by 40%. Dosing should cease when chemotherapy stops.

Methoxy Polyethylene Glycol-Epoetin Beta (Erythropoietin, Very Long Acting)

Description and Therapeutic Use

Methoxy polyethylene glycol (MPEG)-epoetin beta [Mircera], approved in 2007, is a long-acting derivative of erythropoietin. Like the natural hormone, MPEG-epoetin beta acts on erythroid progenitor cells to stimulate production of red blood cells.

MPEG-epoetin beta has a unique structure, created by conjugating one molecule of epoetin beta (a recombinant form of erythropoietin) to one molecule of methoxy propylene glycol. Because of this structure, MPEG-epoetin beta has a very long half-life (about 135 hours)—about 6 times that of darbepoetin alfa and 27 times that of epoetin alfa. Because it stays in the body so long, MPEG-epoetin beta can be dosed less frequently than the other two ESAs, making treatment more convenient.

MPEG-epoetin beta is indicated only for anemia associated with CRF. The drug is not approved for use by cancer patients. Why? Because in clinical trials, there were more deaths among patients taking MPEG-epoetin beta than among patients taking a comparator ESA.

As of this writing, MPEG-epoetin beta cannot be marketed in the United States. Why? Because there is an ongoing patent dispute between Hoffman LaRoche, the company that makes Mircera, and Amgen, the company that makes two other ESAs: Aranesp and Epogen.

Adverse Effects and Warnings

Adverse effects are like those of other ESAs. Hypertension is the most common (11%). The risk can be minimized by keeping the rate of rise in hemoglobin below 1 gm/dL every 2 weeks. If hypertension develops, it should be controlled with antihypertensive drugs.

Like other ESAs, MPEG-epoetin beta increases the risk of serious cardiovascular events, including PRCA, MI, HF, stroke, and cardiac arrest. Risk is greatest when the hemoglobin level exceeds 11 gm/dL or when the rate of rise in hemoglobin exceeds 1 gm/dL in 2 weeks.

More than other ESAs, MPEG-epoetin beta can promote tumor progression and shorten survival in some cancer patients. Accordingly, MPEG-epoetin beta is contraindicated for patients with cancer.

Monitoring

When initiating MPEG-epoetin beta or when changing the dosage, the hemoglobin level should be measured every 2 weeks until it stabilizes. Thereafter, hemoglobin should be measured every 2 to 4 weeks.

Preparations, Dosage, Administration, and Monitoring

Preparations and Storage. MPEG-epoetin beta [Mircera] is available in single-use vials (50, 100, 200, 300, 400, 600, and 1000 mcg/mL) and in two sizes of single-use pre-filled syringes: 0.3 mL (containing 50, 75, 100, 150, 200, 250, or 300 mcg) and 0.6 mL (containing 400, 600, or 800 mcg)

The syringes and vials should be stored cold (2°C to 8°C [36°F to 46°F]) and protected from light.

Administration. Administration is by IV injection or subQ injection (into the abdomen, arm, or thigh).

Dosage. Dosage differs for patients currently stabilized on another ESA versus patients not currently using an ESA.

Patients Not Currently Using an ESA. The initial dosage is 0.6 mcg/kg once every 2 weeks. When the hemoglobin target is reached, dosing should be done every 4 weeks, using twice the dose that had been given every 2 weeks.

Patients Already Stabilized on Epoetin Alfa or Darbepoetin Alfa. The dosage of MPEG-epoetin beta is based on the total weekly dosage of the current ESA as follows:

- Less than 8000 units epoetin alfa or less than 40 mcg darbepoetin alfa—give 60 mcg every 2 weeks or 120 mcg every month
- 8000 to 16,000 units epoetin alfa or 40 to 80 mcg darbepoetin alfa—give 100 mcg every 2 weeks or 200 mcg every month
- More than 16,000 units epoetin alfa or more than 80 mcg darbepoetin alfa—give 180 mcg every 2 weeks or 360 mcg every month

LEUKOPOIETIC GROWTH FACTORS

The leukopoietic growth factors stimulate production of leukocytes (white blood cells). Three preparations are available: filgrastim, pegfilgrastim, and sargramostim.

Filgrastim (Granulocyte Colony-Stimulating Factor)

Filgrastim [Neupogen] is a leukopoietic growth factor produced by recombinant DNA technology. The drug is essentially identical in structure and actions to human granulocyte colony-stimulating factor (G-CSF), a naturally occurring hormone. Filgrastim has two principal uses: elevation of neutrophil counts in cancer patients and treatment of severe chronic neutropenia.

Physiology

G-CSF acts on cells in bone marrow to increase production of neutrophils (granulocytes). In addition, it enhances phagocytic and cytotoxic actions of mature neutrophils. The hormone is produced by monocytes, fibroblasts, and endothelial cells in response to inflammation and allergic challenge, suggesting that its natural role is to help fight infection and cancer.

Therapeutic Uses

Cancer. Patients Undergoing Myelosuppressive Chemotherapy. Filgrastim is given to reduce the risk of infection in patients undergoing cancer chemotherapy. Many anticancer drugs act on the bone marrow to suppress production of neutrophils, thereby greatly increasing the risk of infection. By stimulating neutrophil production, filgrastim can decrease infection risk. Clinical trials have shown that treatment (1) reduces the incidence of severe neutropenia, (2) produces a dose-dependent increase in circulating neutrophils, (3) reduces the incidence of infection, (4) reduces the need for hospitalization, and (5) reduces the need for intravenous antibiotics. Unfortunately, this useful drug is very expensive: The cost for a single course of treatment is over \$3500. Because filgrastim stimulates proliferation of bone marrow cells, it should be used with great caution in patients with cancers that originated in the marrow.

Patients Undergoing Bone Marrow Transplantation. Filgrastim is given to shorten the duration of neutropenia in patients who have undergone high-dose chemotherapy fol-

lowed by BMT. As noted, the drug is not used when the cancer is of myeloid origin.

Harvesting of Hematopoietic Stem Cells. Hematopoietic stem cells (HSCs) are harvested prior to bone marrow ablation with high-dose chemotherapy. Following chemotherapy, the HSCs are infused back into the patient to accelerate repopulation of the bone marrow. Treatment with filgrastim prior to harvesting increases the number of circulating HSCs, and therefore facilitates collection. If treatment with filgrastim alone is inadequate, a drug called *plerixafor* (discussed at the end of the chapter) can be added to increase the HSC yield.

Severe Chronic Neutropenia. Filgrastim provides effective treatment for *congenital neutropenia* (Kostmann's syndrome), a condition characterized by pronounced neutropenia and frequent, severe infections. Therapy helps resolve existing infections and decreases the incidence of subsequent infections. Because treatment is chronic, the cost is very high. In addition to congenital neutropenia, filgrastim is used in patients with *idiopathic neutropenia* and *cyclic neutropenia*.

Investigational Uses. Filgrastim can reverse *zidovudine-induced neutropenia* in HIV-infected patients. However, the drug does not reduce the incidence of opportunistic infections. In patients with *acute myelogenous leukemia*, filgrastim has been given to stimulate division of cancer cells, thereby making them more sensitive to chemotherapeutic agents. Filgrastim has also been employed in patients with *aplastic anemia* and *myelodysplasia*.

Pharmacokinetics

Administration is parenteral (IV or subQ). Filgrastim cannot be used orally because, being a protein, it would be destroyed in the GI tract. The drug is eliminated by renal excretion. Its serum half-life is about 3.5 hours.

Adverse Effects and Interactions

When used short term, filgrastim is generally devoid of serious adverse effects. There are no drug interactions of note.

Bone Pain. Filgrastim causes bone pain in about 25% of patients. Pain is dose related and usually mild to moderate. In most cases, relief can be achieved with a nonopioid analgesic (eg, acetaminophen). If not, an opioid may be tried.

Leukocytosis. When administered in doses greater than 5 mcg/kg/day, filgrastim has caused white blood cell counts to rise above 100,000/mm³ in 2% of patients. Although no adverse effects were associated with this degree of leukocytosis, avoiding leukocytosis would nonetheless be prudent. Excessive white cell counts can be avoided by obtaining complete blood counts twice weekly during treatment and by reducing filgrastim dosage if leukocytosis develops.

Other Adverse Effects. Treatment frequently causes elevation of plasma uric acid, lactate dehydrogenase, and alkaline phosphatase. Increases are usually moderate and reverse spontaneously. Long-term therapy has caused splenomegaly.

Preparations, Dosage, and Administration

Preparations and Storage. Filgrastim [Neupogen] solution for injection is supplied in two concentrations: (1) 300 mcg/mL in 1-mL and 1.6-mL single-dose vials, and (2) 600 mcg/mL in 0.5-mL and 0.8-mL pre-filled syringes. The drug is stored at 2°C to 8°C (36°F to 46°F)—not frozen.

Dosage and Administration. General Considerations. Prior to administration, filgrastim can be kept at room temperature for up to 24 hours. Each vial or syringe should be used only once, and should not be agitated.

Cancer Chemotherapy. The usual dosage is 5 mcg/kg once daily, given IV or subQ. Therapy should start no sooner than 24 hours after termination of chemotherapy, and should continue up to 2 weeks after the expected

chemotherapy-induced nadir, or until the absolute neutrophil count has reached 10,000/mm³. Administer by subQ bolus, short IV infusion, or continuous IV or subQ infusion. A complete blood count and platelet count should be obtained prior to treatment and twice weekly during treatment.

Bone Marrow Transplant. The initial dosage is 10 mcg/kg/day, administered by slow IV or subQ infusion. During the period of neutrophil recovery, dosage is titrated against the neutrophil count.

Harvesting of Hematopoietic Stem Cells. The usual dosage is 10 mcg/kg/day IV (by bolus or infusion), starting at least 4 days before the first leukapheresis procedure, and continuing until the last leukapheresis.

Severe Chronic Neutropenia. For congenital neutropenia, the initial dosage is 6 mcg/kg subQ twice a day. The maintenance dosage is 6 mcg/kg/day.

Pegfilgrastim (Granulocyte Colony-Stimulating Factor, Long Acting)

Pegfilgrastim [Neulasta] is a long-acting derivative of filgrastim [Neupogen]. Both drugs stimulate myeloid cells to increase production of neutrophils. Pegfilgrastim is made by conjugating filgrastim with polyethylene glycol (PEG), in a process known as pegylation. Pegylation increases the size of filgrastim, and thereby delays its excretion by the kidneys. As a result, the drug's half-life is greatly increased—from 3.5 hours (for native filgrastim) up to about 17 hours. Because pegfilgrastim has a longer half-life than filgrastim, the drug is easier to use: A course of treatment consists of just one dose, rather than one dose every day for 2 weeks. At this time, pegfilgrastim has only one approved application: to decrease the incidence of infection, as indicated by febrile neutropenia, in patients undergoing chemotherapy of nonmyeloid malignancies. As discussed above, filgrastim has additional uses.

Adverse effects are much like those of filgrastim. Bone pain is the most common, occurring in 26% of patients. About 6% require an opioid analgesic for relief. Other side effects include reversible elevations of lactate dehydrogenase, alkaline phosphatase, and uric acid.

Preparations, Dosage, and Administration. Pegfilgrastim [Neulasta] is available in solution (10 mg/mL) in pre-filled, single-dose syringes. For all patients, treatment consists of one 6-mg subQ dose, injected 24 hours after each round of chemotherapy. Because stimulated myeloid cells are highly vulnerable to anticancer drugs, and because pegfilgrastim has a prolonged duration of action, at least 14 days must elapse between injecting pegfilgrastim and the next round of chemotherapy. Accordingly, if the scheduled interval between rounds of chemotherapy is less than 15 days (24 hours plus 14 days), pegfilgrastim cannot be used. Instead, filgrastim, with its shorter duration of action, should be employed. Pegfilgrastim has not been evaluated in infants, children, or adolescents who weigh less than 45 kg. Accordingly, the drug should not be used in these patients. Pegfilgrastim is expensive, costing over \$3000 per dose. A comparable course of filgrastim costs about the same.

Sargramostim (Granulocyte-Macrophage Colony-Stimulating Factor)

Sargramostim [Leukine] is a hematopoietic growth factor produced by recombinant DNA technology. The drug is nearly identical in structure and actions to human granulocyte-macrophage colony-stimulating factor (GM-CSF), a naturally occurring hormone. Sargramostim is given to accelerate bone marrow recovery following bone marrow transplantation (BMT).

Physiology

GM-CSF acts on cells in bone marrow to increase production of neutrophils, monocytes, macrophages, and eosinophils. In addition, the hormone acts on the mature forms of these cells

to enhance their function. For example, GM-CSF acts on neutrophils and macrophages to increase their chemotactic, antifungal, and antiparasitic actions. Also, the hormone acts on monocytes and polymorphonuclear leukocytes to enhance their actions against cancer cells. GM-CSF is synthesized by T lymphocytes, monocytes, fibroblasts, and endothelial cells. Like G-CSF, GM-CSF is produced in response to inflammation and allergic challenge, suggesting that its natural role is to help fight infection and cancer.

Therapeutic Uses

Adjunct to Autologous Bone Marrow Transplantation. Sargramostim can accelerate myeloid recovery in cancer patients who have undergone autologous BMT following high-dose chemotherapy (with or without concurrent irradiation). The drug is approved for promoting myeloid recovery following BMT in patients with acute lymphoblastic leukemia, non-Hodgkin's lymphoma, and Hodgkin's disease. In these patients, sargramostim can (1) accelerate neutrophil engraftment, (2) reduce the duration of antibiotic use, (3) reduce the duration of infectious episodes, and (4) reduce the duration of hospitalization. Therapy is expensive: The cost for a 21-day course of sargramostim is more than \$5000.

Treatment of Failed Bone Marrow Transplants. Sargramostim is approved for patients in whom an autologous or allogenic bone marrow transplant has failed to take. For these patients, the drug can produce a significant increase in survival time.

Patients with Acute Myelogenous Leukemia (AML). Sargramostim is given following induction chemotherapy in older patients with AML. The goal is to accelerate neutrophil recovery and reduce the incidence of life-threatening infections.

Investigational Uses. In HIV-infected patients, sargramostim can reverse neutropenia caused by zidovudine (a drug that inhibits HIV replication) and by ganciclovir (a drug for cytomegalovirus retinitis).

In patients with aplastic anemia (a syndrome characterized by pancytopenia and high mortality from infection and bleeding), sargramostim can increase neutrophil counts and reduce the incidence and severity of infections.

Sargramostim is beneficial for patients with myelodysplastic syndrome (MDS), a chronic disorder characterized by greatly reduced hematopoiesis. Patients with MDS are neutropenic, thrombocytopenic, and anemic, putting them at high risk for serious infections and bleeding. The syndrome has a mortality rate of 66%—and those who survive often develop leukemia. Treatment with sargramostim can increase counts of neutrophils, eosinophils, and monocytes. However, the premalignant clone still exists and may eventually cause leukemia.

Pharmacokinetics

Sargramostim is administered by IV infusion. Since the drug is a protein and hence would be degraded in the digestive tract, it cannot be administered by mouth. Other aspects of its kinetics are unremarkable.

Adverse Effects and Interactions

Sargramostim is generally well tolerated. A variety of acute reactions have been observed, including diarrhea, weakness, rash, malaise, and bone pain that can be managed with non-opioid analgesics (eg, acetaminophen). Pleural and pericardial effusions have occurred, but only when sargramostim dosage was massive (16 times the recommended dosage). There are no drug interactions of note.

Leukocytosis and Thrombocytosis. Stimulation of the bone marrow can cause excessive production of white blood

cells and platelets. Complete blood counts should be done twice weekly during therapy. If the white cell count rises above $50,000/\text{mm}^3$, if the absolute neutrophil count rises above $20,000/\text{mm}^3$, or if the platelet count rises above $500,000/\text{mm}^3$, sargramostim should be interrupted or the dosage reduced.

Preparations, Dosage, and Administration

Preparations. Sargramostim [Leukine] is available in concentrated solution (500 mcg/mL) and as a powder (250 mcg) to be reconstituted for IV infusion. To reconstitute the powder, add 1 mL of sterile water and gently swirl; don't shake.

Dilution. To prepare the final infusion solution, dilute the concentrated solution in either (1) 0.9% sodium chloride (if the final concentration of sargramostim is to be 10 mcg/mL or more) or (2) 0.9% sodium chloride plus 0.1% albumin (if the final concentration is to be less than 10 mcg/mL). Since the solution contains no antibacterial preservatives, it should be used as soon as possible—and no later than 6 hours after preparation.

Storage. All sargramostim preparations should be stored at 2°C to 8°C (36°F to 46°F)—never frozen.

Dosage and Administration. To accelerate myeloid recovery after autologous BMT, the recommended dosage is $250\text{ mcg}/\text{m}^2$ (as a 2-hour IV infusion) administered once daily for 21 days beginning 2 to 4 hours after the bone marrow infusion.

For patients in whom an autologous or allogenic bone marrow transplant has failed or in whom engraftment has been delayed, the recommended dosage is $250\text{ mcg}/\text{m}^2$ (as a 2-hour IV infusion) administered once daily for 14 days. After a 7-day hiatus, the 14-day series of infusions can be repeated, if needed. After another 7-day hiatus, the 14-day series can be repeated once more, if needed. If the graft still has not taken, further treatment is unlikely to help.

To accelerate neutrophil recovery following chemotherapy for AML, the recommended dosage is $250\text{ mcg}/\text{m}^2/\text{day}$ (as a 4-hour IV infusion), starting on day 11 (or 4 days after completing the course of chemotherapy). Continue daily infusions for 42 days, or until the absolute neutrophil count exceeds $1500\text{ cells}/\text{mm}^3$ on 3 consecutive days, whichever is less.

THROMBOPOIETIC GROWTH FACTOR

Thrombopoietic growth factors are endogenous compounds that stimulate production of thrombocytes (platelets). At this time, oprelvekin is the only thrombopoietic growth factor available. Two drugs with similar actions—romiplostim and eltrombopag—are discussed in the section that follows.

Oprelvekin (Interleukin-11)

Oprelvekin [Neumega] is a thrombopoietic growth factor produced by recombinant DNA technology. The drug is a protein nearly identical in structure and actions to human *interleukin-11*, a cytokine produced in bone marrow. Oprelvekin is given to stimulate platelet production in patients undergoing myelosuppressive chemotherapy for nonmyeloid cancers.

Actions

Oprelvekin acts on platelet progenitor cells to increase platelet production. Specifically, it stimulates proliferation of hematopoietic stem cells and megakaryocyte progenitor cells, and thereby increases synthesis of megakaryocytes, the cells that fragment into large numbers of platelets. In addition to promoting megakaryocyte *synthesis*, oprelvekin induces megakaryocyte *maturation*. The net result is increased platelet production. In patients treated with oprelvekin daily for 14 days, platelet counts begin to increase 5 to 9 days after the first injection, peak about 7 days after the last injection, and return to baseline 14 days after that.

Therapeutic Use

Oprelvekin is administered to patients undergoing myelosuppressive chemotherapy to minimize thrombocytopenia (platelet deficiency) and to decrease the need for platelet transfusions. Because it stimulates the bone marrow, oprelvekin should *not* be given to patients with cancers of myeloid origin.

In clinical trials, oprelvekin was effective for some patients but not for others. To assess its benefits, oprelvekin was given to patients who had required platelet transfusions following earlier rounds of chemotherapy. Some patients were on moderately myelosuppressive regimens and some were on highly suppressive regimens. Among those on moderately suppressive regimens, 30% were spared the need for platelet transfusions by combining oprelvekin with chemotherapy. Among those on highly suppressive regimens, only 13% were spared the need for platelet transfusions. Hence, although oprelvekin can increase platelet counts and decrease the need for platelet transfusions, not all patients benefit equally. As these data indicate, the more myelosuppressive the regimen, the less helpful oprelvekin is likely to be.

Pharmacokinetics

Oprelvekin is administered by subQ injection. (The drug is a protein and hence cannot be administered by mouth.) Serum levels peak about 3 hours after administration. Elimination is by hepatic and renal tubular metabolism, followed by excretion of the metabolites in urine. Children eliminate the drug faster than adults.

Adverse Effects

Fluid Retention. Oprelvekin causes retention of sodium and water by the kidney. The result is *peripheral edema* and a 10% to 15% *expansion of plasma volume*. Expansion of plasma volume decreases both the hematocrit and hemoglobin concentration, thereby causing anemia. As a result, about 48% of patients experience dyspnea (shortness of breath on exertion). Because of fluid retention, oprelvekin should be used with caution in patients with a history of heart failure or pleural effusion. Fluid balance should be monitored throughout treatment. Following oprelvekin withdrawal, fluid balance normalizes within days.

Cardiac Dysrhythmias. Tachycardia, atrial fibrillation, and atrial flutter are common. The incidence of tachycardia is higher in children (46%) than in adults. Conversely, atrial flutter and fibrillation are more likely in older adults. The cause of cardiac effects is unclear, although expansion of plasma volume is suspected. Oprelvekin does not affect the heart directly.

Severe Allergic Reactions. Oprelvekin has been associated with severe allergic reactions, including anaphylaxis. Signs of oprelvekin-induced allergy include rash, urticaria, flushing, fever, hypotension, joint pain, chest pain, wheezing, shortness of breath, and edema of the face, tongue, and larynx. Patients and healthcare providers should be alert for these reactions and, if allergy is diagnosed, oprelvekin should be withdrawn and never used again.

Effects on the Eye. Conjunctival injection (red eye) is common. The incidence is 50% in children and 19% in adults. Other ophthalmic effects are transient visual blurring and papilledema (edema of the optic disk).

Sudden Death. Two patients have died. Both had severe hypokalemia, and both had been treated with a diuretic and high doses of ifosfamide (an anticancer drug). Although oprelvekin is suspected, its precise role in these deaths is unknown.

Preparations, Dosage, and Administration

Preparation. Oprelvekin [Neumega] is supplied as a powder in 5-mg single-dose vials. To reconstitute, add 1 mL of Sterile Water for Injection (supplied with the drug) and gently swirl; don't shake. Neither the powder nor the diluent contains preservatives, and hence the solution must be used within 3 hours to avoid infection. Oprelvekin and its diluent should be refrigerated at 2°C to 8°C (36°F to 46°F).

Dosage and Administration. Oprelvekin is administered by subQ injection into the abdomen, thigh, hip, or upper arm. The recommended adult dosage is 50 mcg/kg once daily; the pediatric dosage is 75 to 100 mcg/kg once daily. Dosing should begin 4 to 6 hours after chemotherapy and should continue until the platelet count rises above 50,000/mm³—but should not continue beyond 21 days. Treatment should cease 2 days before the next round of chemotherapy.

DRUGS THAT MIMIC HEMATOPOIETIC GROWTH FACTORS OR ENHANCE THEIR ACTIONS

In this section we consider three drugs—romiplostim, eltrombopag, and plerixafor—that are not structurally related to any endogenous hematopoietic growth factor. Nonetheless, two of these drugs—romiplostim and eltrombopag—have effects similar to those of an endogenous growth factor. And the third drug—plerixafor—is used to enhance the effects of an endogenous growth factor.

THROMBOPOIETIN RECEPTOR AGONISTS

Like oprelvekin, the thrombopoietin receptor agonists (TRAs) stimulate production of platelets. However, TRAs and oprelvekin do so by different mechanisms. Currently, two TRAs are available: romiplostim and eltrombopag. Both are used to increase platelet production in patients with *idiopathic thrombocytopenic purpura* (ITP), also known as *immune thrombocytopenic purpura*. In contrast, oprelvekin is used to increase platelet production in patients undergoing cancer chemotherapy.

Romiplostim

Therapeutic Use: Idiopathic Thrombocytopenic Purpura.

Romiplostim [Nplate] is indicated for subQ treatment of ITP, a disorder characterized by *low platelet counts* secondary to (1) immune-mediated platelet destruction and (2) impaired platelet production. Symptoms include easy bruising, superficial bleeding, prolonged bleeding from cuts, spontaneous bleeding from the gums or nose, blood in the urine or stools, heavy menstrual bleeding, and profuse bleeding during surgery. Traditional treatments—glucocorticoids, IV immunoglobulins, and splenectomy—are designed to *reduce platelet destruction*. How? Glucocorticoids and IV immunoglobulins inhibit production of antiplatelet antibodies. Removal of the spleen removes the main source of antibody production. Romiplostim is indicated only after one or more of these traditional measures have failed. In patients who have not already undergone splenectomy, treatment with romiplostim may render splenectomy unnecessary.

Mechanism of Action. In contrast to traditional treatments, which reduce platelet destruction, romiplostim *increases platelet production*. How? Romiplostim is a unique kind of molecule known as a *peptibody* (a combination of a peptide and an antibody). Benefits derive from mimicking the actions of *thrombopoietin*, an endogenous compound that stimulates the proliferation and differentiation of megakaryocytes, the cells that fragment into platelets. Romiplostim stimulates megakaryocytes by binding to the same receptor used by thrombopoietin. Platelet counts begin rising 4 to 9 days after a single subQ dose, peak between days 12 and 16, and then decline to pretreatment levels by day 28.

Pharmacokinetics. The pharmacokinetics of romiplostim are highly variable. Plasma levels peak between 7 and 50 hours after subQ dosing. Serum concentrations vary between patients, and do not correlate well with dosage. The half-life ranges from 1 to 34 days.

Adverse Effects. The most common adverse effects are arthralgia (26% vs. 20% with placebo), dizziness (17% vs. 0%), insomnia (16% vs. 7%), pain in the extremities (13% vs. 5%), abdominal pain (11% vs. 0%), myalgia (14% vs. 2%), shoulder pain (8% vs. 0%), dyspepsia (7% vs. 0%), and paresthesias (6% vs. 0%). When romiplostim is discontinued, platelet counts may drop below pretreatment levels, thereby increasing the risk of bleeding. Uncommon but serious effects are *bone marrow fibrosis* (replacement of blood-forming cells with fibrotic tissue), *hematologic malignancy*

(from stimulation of bone marrow cells), and *thrombotic/thromboembolic complications* (from excessive production of platelets). Because of these serious adverse effects, romiplostim is available only through a restricted distribution program, known as the romiplostim NEXUS program. Only persons registered with the program can prescribe, administer, or receive the drug.

Preparations, Dosage, and Administration. Romiplostim [Nplate] is supplied as a powder (250 and 500 mcg in single-use vials) for reconstitution in sterile water to a final concentration of 500 mcg/mL. Treatment consists of a weekly subQ injection, which must be given by a healthcare provider registered in the romiplostim NEXUS program. The initial dose is 1 mcg/kg, and the maximum dose is 10 mcg/kg. After the initial dose, dosage is increased or decreased by 1 mcg/kg/wk to achieve and maintain platelet counts equal to or above 50 × 10⁹/L. If platelet counts rise above 400 × 10⁹/L, romiplostim should be discontinued.

Eltrombopag

Actions and Therapeutic Use. Eltrombopag [Promacta] is indicated for oral therapy of ITP in patients who have not responded adequately to at least one traditional intervention (ie, glucocorticoids, IV immunoglobulins, or splenectomy). Like romiplostim, eltrombopag increases platelet production by activating the thrombopoietin receptor on megakaryocytes, causing these cells to proliferate and differentiate. Unlike romiplostim, which is a complex peptide-antibody hybrid, eltrombopag is a relatively simple small molecule, with a molecular weight of 442.

Pharmacokinetics. Eltrombopag is administered by mouth. Food reduces absorption by 60%, and polycations (eg, calcium, aluminum, magnesium) reduce absorption by 70%. The drug undergoes extensive hepatic metabolism, followed by excretion in the feces (59%) and urine (31%). In patients with hepatic impairment, drug exposure is increased by 41% (with mild impairment) and by 80% to 93% (with moderate to severe impairment). Drug exposure is also affected by race: Among patients of black ancestry, total exposure is increased by 40%, and among patients of East Asian ancestry, total exposure is increased by 70%.

Adverse Effects. Eltrombopag is generally well tolerated, but nonetheless can cause serious adverse effects. Like romiplostim, eltrombopag may cause *bone marrow fibrosis*, *hematologic malignancy*, and *thrombotic/thromboembolic events*, and may pose a risk of *bleeding* from a rapid drop in platelet counts when treatment is stopped. In addition, the drug may cause *liver injury*. Accordingly, liver function tests—alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin—should be performed at baseline, every 2 weeks during the dosage adjustment phase, and every month thereafter. Eltrombopag should be discontinued if ALT levels exceed 3 times the upper limit of normal, or if there are clinical symptoms of liver injury. Owing to the risk of liver damage and other serious adverse effects, eltrombopag is available only through a restricted distribution program, known as PROMACTA CARES. Only persons registered with the program can prescribe, dispense, or receive the drug.

Drug Interactions. Absorption of eltrombopag can be greatly reduced by polycations (ie, calcium, magnesium, aluminum, selenium, zinc). Accordingly, at least 4 hours should separate administration of eltrombopag and drugs (eg, antacids) or supplements that contain these elements.

Preparations, Dosage, and Administration. Eltrombopag [Promacta] is supplied in 25- and 50-mg tablets for once-daily oral dosing on an empty stomach (ie, at least 1 hour before a meal or 2 hours after). Do not administer within 4 hours of drugs and supplements that contain calcium, magnesium, or other polycations. The usual initial dosage is 50 mg once daily. The maximum dosage is 75 mg once daily. After the initial dose, dosage is increased or decreased by 25 mg/day to achieve and maintain platelet counts equal to or above 50 × 10⁹/L. If platelet counts rise above 400 × 10⁹/L, eltrombopag should be discontinued. The initial dosage should be reduced to 25 mg/day in patients with liver impairment, and in those of East Asian ancestry (ie, Chinese, Japanese, Korean, Taiwanese).

PLERIXAFOR

Plerixafor [Mozobil], approved in 2009, is a CXCR4 antagonist used in conjunction with G-CSF to increase the harvest of HSCs prior to bone marrow ablation with high-dose chemotherapy in patients with multiple myeloma or non-Hodgkin's lymphoma. Once chemotherapy is completed, the harvested HSCs are infused back into the patient to accelerate repopulation of the bone marrow. In many patients, treatment with G-CSF alone can mobilize sufficient HSCs for bone marrow rescue. When G-CSF alone is inadequate,

plerixafor is added to increase the yield. How does plerixafor work? It blocks a receptor known as CXCR4, which plays an important role in holding HSCs in bone marrow. Hence, by blocking CXCR4, plerixafor promotes the release of HSCs from the bone marrow to peripheral blood, where these cells can be harvested for subsequent bone marrow rescue.

Plerixafor is administered by subQ injection, and plasma levels peak 30 to 60 minutes after dosing. The drug is eliminated intact in the urine. In patients with normal renal function, the half-life is 3 to 5 hours. In patients with significant renal impairment, the half-life is prolonged.

Plerixafor is generally well tolerated. The incidence of most side effects is the same as with placebo. Side effects that do occur more often with plerixafor include injection-site reactions (34% vs. 10% with placebo), diar-

rhea (37% vs. 17%), nausea (34% vs. 22%), and dizziness (11% vs. 6%).

Plerixafor is supplied in 24-mg single-use vials for subQ dosing. Treatment is done in conjunction with G-CSF as follows: (1) patients receive once-daily doses of G-CSF, starting at least 4 days before the first HSC collection, and continuing until the last HSC collection, and (2) after at least 4 days of pretreatment with G-CSF, patients receive up to 4 once-daily doses of plerixafor, each dose beginning 11 hours before an HSC collection. For patients with normal renal function, a single dose of plerixafor is 0.24 mg/kg (but no more than 40 mg total). For patients with reduced renal function (creatinine clearance below 50 mL/min), the dosage is 0.16 mg/kg (but no more than 27 mg total). Treatment is expensive: A single plerixafor vial (one dose) costs about \$6250.

KEY POINTS

- Epoetin is given to increase red blood cell counts, and thereby decrease the need for transfusions. Specific indications include anemia associated with (1) chronic renal failure, (2) myelosuppressive cancer chemotherapy, and (3) zidovudine therapy in patients with HIV/AIDS.
- By increasing the hematocrit, epoetin can cause or exacerbate hypertension.
- Epoetin increases the risk of cardiovascular events (eg, cardiac arrest, stroke, HF, MI), especially when the hemoglobin level exceeds 11 gm/dL or the rate of rise in hemoglobin exceeds 1 gm/dL in 2 weeks.
- In some cancer patients, epoetin can accelerate tumor progression and shorten life.
- Owing to the risk of serious toxicity, epoetin must be prescribed and used under a new Risk Evaluation and Mitigation Strategy (REMS).
- Filgrastim is given to elevate neutrophil counts, and thereby reduce the risk of infection. Specific indications are chronic severe neutropenia and neutropenia associated with cancer chemotherapy or BMT.
- The principal adverse effects of filgrastim are bone pain and leukocytosis.
- Sargramostim is used to accelerate recovery from BMT, treat patients in whom a bone marrow transplant has failed, and accelerate neutrophil recovery in patients undergoing chemotherapy for AML.
- The principal adverse effect of sargramostim is leukocytosis.
- Oprelvekin is given to stimulate platelet production in patients undergoing myelosuppressive chemotherapy for nonmyeloid cancers. The goal is to minimize thrombocytopenia and platelet transfusions.
- The principal adverse effects of oprelvekin are fluid retention (which causes edema and anemia), cardiac dysrhythmias (tachycardia, atrial fibrillation, and atrial flutter), and severe allergic reactions, including anaphylaxis.
- Since epoetin alfa, filgrastim, sargramostim, and oprelvekin stimulate proliferation of bone marrow cells, these drugs should be used with great caution, if at all, in patients with cancers of bone marrow origin.

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Summary of Major Nursing Implications

EPOETIN ALFA (ERYTHROPOIETIN)

Preadministration Assessment

Therapeutic Goal

Epoetin is used to restore and maintain erythrocyte counts, and thereby decrease the need for transfusions, in patients with chronic renal failure, HIV-infected patients receiving zidovudine, anemic patients facing elective surgery, and cancer patients receiving myelosuppressive chemotherapy, but only if the goal of chemotherapy is palliation, not cure. For most patients, the hemoglobin level should not exceed 10 or 11 mg/dL.

Baseline Data

All Patients. Obtain blood pressure; blood chemistry (BUN, uric acid, creatinine, phosphorus, potassium); complete blood counts with differential and platelet count; he-

moglobin level; degree of transferrin saturation (should be at least 20%); and ferritin concentration (should be at least 100 ng/mL).

HIV-Infected Patients. Obtain an erythropoietin level. If the level is above 500 milliunits/mL, epoetin is unlikely to help.

Identifying High-Risk Patients

Avoid epoetin alfa in patients with uncontrolled hypertension, hypersensitivity to mammalian cell-derived products or albumin, or cancer of myeloid origin.

Implementation: Administration

Routes

IV and subQ.

Summary of Major Nursing Implications*—cont'd

Handling and Storage

Epoetin alfa is supplied in single-use and multi-use vials; don't re-enter the single-use vials. Don't agitate. Don't mix with other drugs. Store at 2°C to 8°C (36°F to 46°F); don't freeze.

Administration

Chronic Renal Failure. Administer by IV bolus or subQ injection.

Chemotherapy-Induced Anemia. Administer by subQ injection.

Zidovudine-Induced Anemia. Administer by IV or subQ injection.

Surgery Patients. Administer by subQ injection.

Ongoing Evaluation and Interventions

Monitoring Summary

Measure hemoglobin level twice weekly until the maximum acceptable level has been achieved (10 or 11 mg/dL for most patients) and a maintenance dosage established. Measure hemoglobin periodically thereafter. Obtain complete blood counts with a differential and platelet counts routinely. Monitor blood chemistry, including BUN, uric acid, creatinine, phosphorus, and potassium. Monitor iron stores and maintain at an adequate level. Monitor blood pressure.

Minimizing Adverse Effects

Hypertension. Monitor blood pressure and, if necessary, control with antihypertensive drugs. If hypertension cannot be controlled, reduce epoetin dosage. In patients with pre-existing hypertension (a common complication of CRF), make certain that blood pressure is controlled prior to epoetin use.

Cardiovascular Events. Epoetin has been associated with an increase in cardiovascular events (eg, cardiac arrest, stroke, HF, and MI). Risk is greatest when the hemoglobin level exceeds 11 gm/dL or the rate of rise in hemoglobin exceeds 1 gm/dL in 2 weeks. To minimize risk, reduce dosage when hemoglobin approaches 11 gm/dL or when the rate of rise exceeds 1 gm/dL in 2 weeks, and temporarily stop dosing if hemoglobin rises to 11 gm/dL or more. CRF patients on dialysis may need a higher dosage of heparin to prevent clotting in the artificial kidney.

For patients taking the drug prior to elective surgery, anticoagulant treatment can reduce the risk of deep vein thrombosis.

Cancer Patients: Tumor Progression and Shortened Survival. Epoetin can accelerate tumor progression and shorten survival in some cancer patients. To reduce risk, dosage should be no higher than needed to bring hemoglobin gradually up to 12 gm/dL. Also, epoetin should be used only in cancer patients who are undergoing chemotherapy or radiation therapy. Those who are not receiving chemotherapy or radiation therapy should not get this drug.

Autoimmune Pure Red-Cell Aplasia. Epoetin use may lead to pure red-cell aplasia (PRCA), owing to production of neutralizing antibodies directed against epoetin and

native erythropoietin. If evidence of PRCA develops, epoetin should be discontinued and blood assessed for neutralizing antibodies. If PRCA is diagnosed, transfusions will be needed for life.

Patient Education. Give all patients a Medication Guide that explains the risks and benefits of epoetin, so that they can make an informed decision on whether or not to use this drug.

FILGRASTIM (GRANULOCYTE COLONY-STIMULATING FACTOR)

Preadministration Assessment

Therapeutic Goal

Filgrastim is given to promote neutrophil recovery in cancer patients following myelosuppressive chemotherapy or BMT. The drug is also used to treat severe chronic neutropenia.

Baseline Data

Obtain complete blood counts and platelet counts.

Identifying High-Risk Patients

Filgrastim is *contraindicated* for patients with hypersensitivity to *Escherichia coli*-derived proteins.

Use with *caution* in patients with cancers of bone marrow origin.

Implementation: Administration

Routes

IV, subQ.

Handling and Storage

Filgrastim is supplied in single-use vials. Don't re-enter the vial; discard the unused portion. Don't agitate. Store at 2°C to 8°C (36°F to 46°F); don't freeze. Prior to administration, filgrastim may be kept at room temperature for up to 24 hours.

Administration

Cancer Chemotherapy. Administer by subQ bolus, short IV infusion, or continuous IV or subQ infusion.

Bone Marrow Transplantation. Administer by slow IV or subQ infusion.

Chronic Severe Neutropenia. Inject subQ daily.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Obtain complete blood counts twice weekly. Discontinue treatment when the absolute neutrophil count reaches 10,000/mm³.

Minimizing Adverse Effects

Bone Pain. Evaluate for bone pain and treat with a nonopioid analgesic (eg, acetaminophen). Consider an opioid analgesic if the nonopioid is insufficient.

Leukocytosis. Massive doses can cause leukocytosis (white blood cell counts above 100,000/mm³). If leukocytosis develops, reduce filgrastim dosage.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

SARGRAMOSTIM (GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR)

Preadministration Assessment

Therapeutic Goal

Acceleration of myeloid recovery in cancer patients who have undergone autologous BMT following high-dose chemotherapy (with or without concurrent irradiation).

Treatment of patients for whom an autologous or allogenic bone marrow transplant has failed to take.

Acceleration of neutrophil recovery in older patients receiving induction chemotherapy for AML.

Baseline Data

Obtain complete blood counts with differential and platelet count.

Identifying High-Risk Patients

Sargramostim is *contraindicated* in the presence of hypersensitivity to yeast-derived products and excessive leukemic myeloid blasts in bone marrow or peripheral blood.

Exercise *caution* in patients with cardiac disease, hypoxia, peripheral edema, pleural or pericardial effusion, or cancers of bone marrow origin.

Implementation: Administration

Route

IV (by infusion).

Handling and Storage

Sargramostim is supplied in concentrated solution and as a powder, which must be reconstituted for IV infusion. To reconstitute the powder, add 1 mL of sterile water and gently swirl. Before infusing, dilute the concentrated solution or reconstituted powder. Administer as soon as possible after diluting—and no later than 6 hours after reconstitution. Store sargramostim (powder, reconstituted powder, final IV solution) at 2°C to 8°C (36°F to 46°F) until used.

Administration

Administer by 2-hour or 4-hour IV infusion.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Leukocytosis and Thrombocytosis. Obtain complete blood counts with a differential and platelet counts twice weekly. If the white blood cell count rises above 50,000/mm³, if the absolute neutrophil count rises above 20,000/mm³, or if

the platelet count rises above 500,000/mm³, temporarily interrupt sargramostim or reduce the dosage.

OPRELVEKIN (INTERLEUKIN-11)

Preadministration Assessment

Therapeutic Goal

Oprelvekin is given to minimize thrombocytopenia and the need for platelet transfusions in patients undergoing myelosuppressive therapy for nonmyeloid cancers.

Baseline Data

Determine baseline blood cell counts and platelet count, hematocrit, and fluid and electrolyte status.

Identifying High-Risk Patients

Use with *caution* in patients with cancers of myeloid origin; patients taking diuretics or ifosfamide; and patients with a history of atrial dysrhythmias, heart failure, pleural effusion, or papilledema.

Implementation: Administration

Route

SubQ.

Handling and Storage

Oprelvekin is supplied in single-use vials; don't re-enter the vial. Don't agitate. Don't mix with other drugs. Store at 2°C to 8°C (36°F to 46°F); don't freeze.

Administration

Administer once daily beginning 4 to 6 hours after chemotherapy. Continue for 21 days or until platelet counts exceed 50,000/mm³—whichever comes first.

Ongoing Evaluation and Interventions

Monitoring Summary

Monitor platelet counts from the time of the expected nadir until the count exceeds 50,000/mm³. Monitor blood cell counts, fluid status, and electrolyte status.

Minimizing Adverse Effects

Fluid Retention. Fluid retention can result in edema, expanded plasma volume, anemia, and dyspnea. **Instruct patients with a history of congestive heart failure or pleural effusion to contact the prescriber if dyspnea worsens.**

Cardiac Dysrhythmias. Oprelvekin can cause tachycardia, atrial flutter, and atrial fibrillation. Use caution in patients with a history of these disorders.

*Patient education information is highlighted as blue text.

Marshal Schlafer
and Rich Lehne

DIABETES MELLITUS: BASIC CONSIDERATIONS

- Types of Diabetes Mellitus
- Short-Term Complications of Diabetes
- Long-Term Complications of Diabetes
- Diabetes and Pregnancy
- Diagnosis
- Prediabetes
- Overview of Treatment
- Tight Glycemic Control
- Monitoring Treatment

INSULIN

Physiology

Preparations and Administration

- Sources of Insulin
- Types of Insulin
- Appearance
- Concentration
- Mixing Insulins
- Administration
- Storage

Therapeutic Use

- Indications
- Insulin Therapy of Diabetes
- Complications of Insulin Treatment
- Drug Interactions

DRUGS FOR TYPE 2 DIABETES

Oral Drugs

- Biguanides: Metformin
- Sulfonylureas
- Thiazolidinediones (Glitazones)
- Meglitinides (Glinides)
- Alpha-Glucosidase Inhibitors
- Gliptins (DPP-4 Inhibitors)
- Colesevelam
- Bromocriptine
- Dapagliflozin
- Combination Products

Injected Drugs (Other than Insulin)

- Exenatide
- Liraglutide
- Pramlintide

ACUTE COMPLICATIONS OF POOR GLYCEMIC CONTROL

Diabetic Ketoacidosis

Hyperglycemic Hyperosmolar Nonketotic Syndrome

GLUCAGON FOR INSULIN OVERDOSE

DIABETES MELLITUS: BASIC CONSIDERATIONS

The term *diabetes mellitus* is derived from the Greek word for *fountain* and the Latin word for *honey*. Hence, the term describes one of the prominent symptoms of untreated diabetes: production of large volumes of glucose-rich urine. Indeed, long ago, the disease we now call diabetes was “diagnosed” by the sweet smell of urine—and, yes, by its sweet taste, too. In this chapter we use the terms *diabetes mellitus* and *diabetes* interchangeably.

Diabetes is primarily a disorder of carbohydrate metabolism. Symptoms mainly result from a deficiency of insulin or from cellular resistance to insulin’s actions. The principal sign of diabetes is *sustained hyperglycemia*, which results from impaired glucose uptake by cells and from increased glucose production. When hyperglycemia develops, it can quickly lead to polyuria, polydipsia, ketonuria, and weight loss. Over time, hyperglycemia can lead to hypertension, heart disease, renal failure, blindness, neuropathy, amputations, impotence, and stroke. There is an often-overlooked point about diabetes: In addition to affecting carbohydrate metabolism, insulin deficiency disrupts metabolism of proteins and lipids as well. We refer to regulation of blood glucose levels as *glycemic control*.

Diabetes is a major public health concern. In the United States, diabetes is the most common endocrine disorder, and the sixth leading cause of death by disease. According to the 2011 National Diabetes Fact Sheet, compiled by the Centers for Disease Control and Prevention, about 26 million Americans have diabetes, and nearly one-quarter of them have not been diagnosed. Another 79 million or so Americans are prediabetic, and hence are at increased risk of developing diabetes in the future. In 2007, diabetes cost the U.S. economy an estimated \$174 billion (\$116 billion in direct medical expenditures and \$58 billion in lost productivity). These costs represent a 32% increase over the estimated costs for 2002. Put another way, the total cost of diabetes is going up by roughly \$8.4 billion every year.

We need to do a better job of diagnosing diabetes and treating it—and we need to do what we can to reduce the risk of

TABLE 57-1 ■ Characteristics of Type 1 and Type 2 Diabetes Mellitus

Characteristics	Type of Diabetes Mellitus	
	Type 1	Type 2
Alternative names	Insulin-dependent diabetes mellitus, juvenile-onset diabetes mellitus, ketosis-prone diabetes mellitus	Non-insulin-dependent diabetes mellitus, adult-onset diabetes mellitus
Age of onset	Usually childhood or adolescence	Usually over 40
Speed of onset	Abrupt	Gradual
Family history	Usually negative	Frequently positive
Prevalence	5–10% of diabetic patients have type 1 diabetes	90–95% of diabetic patients have type 2 diabetes
Etiology	Autoimmune process	Unknown—but there is a strong familial association, suggesting heredity is a risk factor
Primary defect	Loss of pancreatic beta cells	Insulin resistance and inappropriate insulin secretion
Insulin levels	Reduced early in the disease and completely absent later	Levels may be low (indicating deficiency), normal, or high (indicating resistance)
Treatment	Insulin replacement is mandatory, along with strict dietary control; oral antidiabetic drugs are <i>not</i> effective	Treat with an oral antidiabetic agent and/or insulin, but always in combination with a reduced-calorie diet and appropriate exercise
Blood glucose	Levels fluctuate widely in response to infection, exercise, and changes in caloric intake and insulin dose	Levels are more stable than in type 1 diabetes
Symptoms	Polyuria, polydipsia, polyphagia, weight loss	May be asymptomatic
Body composition	Usually thin and undernourished	Frequently obese
Ketosis	Common, especially if insulin dosage is insufficient	Uncommon

developing the disease in the first place. Unfortunately, the risk of developing diabetes is largely genetic, a factor that can't be modified. Nonetheless, we can still reduce risk significantly by adopting a healthy lifestyle, centered on getting more exercise and establishing a healthy diet.

Types of Diabetes Mellitus

There are two main forms of diabetes mellitus: type 1 diabetes mellitus and type 2 diabetes mellitus. Both forms have similar signs and symptoms. Major differences concern etiology, prevalence, treatments, and outcomes (illness severity and deaths). The distinguishing characteristics of type 1 and type 2 diabetes are summarized in Table 57-1 and discussed immediately below. Another important form—gestational diabetes—is discussed later under *Diabetes and Pregnancy*.

Type 1 Diabetes

Type 1 diabetes accounts for about 5% to 10% of all diabetes cases. Between 1.2 million and 2.4 million Americans have this disorder. In the past, type 1 diabetes was called *juvenile-onset diabetes mellitus* or *insulin-dependent diabetes mellitus* (IDDM). As a rule, type 1 diabetes develops during childhood or adolescence, and symptom onset is relatively abrupt.

The primary defect in type 1 diabetes is destruction of pancreatic beta cells—the cells responsible for insulin synthesis and release into the bloodstream. Insulin levels are reduced early in the disease and usually fall to zero later. Beta cell destruction is the result of an autoimmune process (ie, development of antibodies against the patient's own beta cells). The trigger for this immune response is unknown, but genetic factors almost certainly play a role.

Type 2 Diabetes

Type 2 diabetes is the most prevalent form of diabetes. Approximately 22 million Americans have this disease. In the past, type 2 diabetes was called *non-insulin-dependent diabetes mellitus* (NIDDM) or *adult-onset diabetes mellitus*. The disease usually begins in middle age and progresses gradually. Obesity is usually present, although people of normal weight can also develop the disease. In contrast to type 1 diabetes, type 2 diabetes carries little risk of ketoacidosis. However, type 2 diabetes does carry the same long-term risks as type 1 diabetes (see below).

Symptoms of type 2 diabetes usually result from a combination of *insulin resistance* and *impaired insulin secretion*. In contrast to patients with type 1 diabetes, those with type 2 diabetes are capable of insulin synthesis. In fact, early in

the disease, insulin levels tend to be normal or slightly elevated, a state known as *hyperinsulinemia*. However, although insulin is still produced, its secretion is no longer tightly coupled to plasma glucose content: release of insulin is delayed and peak output is subnormal. More importantly, the target tissues of insulin (liver, muscle, adipose tissue) exhibit insulin resistance: For a given blood insulin level, cells in these tissues are less able to take up and metabolize the glucose available to them. Insulin resistance appears to result from three causes: reduced binding of insulin to its receptors, reduced receptor numbers, and reduced receptor responsiveness. Over time, hyperglycemia leads to destruction of pancreatic beta cells, and hence insulin production and secretion eventually decline.

Although the underlying causes of type 2 diabetes are unknown, there is a strong familial association, suggesting that genetics play a role. This possibility was reinforced by a study that implicated the gene for *insulin receptor substrate-2* (IRS-2), a compound that helps mediate intracellular responses to insulin.

Short-Term Complications of Diabetes

Acute complications are seen mainly in patients with type 1 diabetes. Principal concerns are *hyperglycemia* and *hypoglycemia*. Hyperglycemia results when insulin dosage is insufficient. Conversely, hypoglycemia results when the insulin dosage is excessive compared with the body's metabolic needs. *Ketoacidosis*, a potentially fatal acute complication, develops when hypoglycemia becomes severe and is allowed to persist. As noted above, ketoacidosis is rare with type 2 diabetes, and relatively common in patients with type 1 diabetes. All three complications are discussed below.

Long-Term Complications of Diabetes

The long-term consequences of type 1 and type 2 diabetes usually take years to develop. More than 90% of diabetic deaths result from long-term complications, not from acute episodes of hyperglycemia, hypoglycemia, or ketoacidosis. Ironically, among patients with type 1 diabetes, insulin therapy can be viewed as having made long-term complications possible: Prior to the discovery of insulin, people with type 1 diabetes usually died long before chronic complications could arise.

Most long-term complications occur secondary to disruption of blood flow, owing to either macrovascular or microvascular damage. There is strong evidence that tight control of blood glucose can reduce *microvascular* injury. Tight glycemic control may also reduce *macrovascular* injury, although other measures (eg, exercise, healthy diet, control of blood pressure and blood lipids) are probably more important.

Macrovascular Damage

Cardiovascular disease (CVD) is the leading cause of death among diabetic patients. Diabetes carries an increased risk of heart disease, hypertension, and stroke. Much of this pathology is due to atherosclerosis, which develops earlier in diabetics than in nondiabetics and progresses faster too. Macrovascular complications result from a combination of hyperglycemia and altered lipid metabolism.

Microvascular Damage

Damage to small blood vessels and capillaries (the microvasculature) is common in diabetes. The basement membrane of capillaries thickens, causing blood flow in these narrow vessels to fall. Destruction of small blood vessels contributes to kidney damage, blindness, and various neuropathies. Microvascular injury is directly related to the degree and duration of hyperglycemia.

Retinopathy. Diabetes is the major cause of blindness among American adults. Every year, about 24,000 diabetic patients lose their sight. Visual losses result most commonly from damage to retinal capillaries. Microaneurysms may occur, followed by scarring and proliferation of new vessels; the overgrowth of new retinal capillaries reduces visual acuity. Capillary damage may also impair vision by causing local ischemia (reductions of local blood flow), which can kill retinal cells. Retinopathy is accelerated by hyperglycemia, hypertension, and smoking. Accordingly, these risk factors should be controlled or eliminated. All patients with diabetes, whether type 1 or type 2, should have a comprehensive eye exam at least once a year.

Nephropathy. Diabetic damage to the kidneys—diabetic nephropathy—is characterized by proteinuria, reduced glomerular filtration, and increased blood pressure. Diabetic nephropathy is the most common cause of end-stage renal disease, a condition that requires dialysis or a kidney transplant for survival. Between 10% and 20% of people with diabetes have or will develop kidney disease. The risk of nephropathy among patients with type 1 diabetes is 12 times higher than among patients with type 2 diabetes. Nephropathy is the primary cause of morbidity and mortality in patients with type 1 diabetes. If the injured kidney is replaced with a transplant, the new kidney is likely to fail within a few years unless tight glycemic control is established.

We can screen for kidney damage by testing for *microalbuminuria* (the presence of small amounts of albumin in the urine). Recall that albumin is the blood's major protein. When the kidney is healthy, the urine contains no albumin. Why? Because albumin is so large it cannot be filtered by the glomerulus. However, when the glomerulus is damaged, even slightly, some albumin gets filtered and enters the urine. If renal function undergoes further decline, larger amounts of albumin will enter the urine, causing *albuminuria*. After that! Eventually, renal failure.

Treatment of diabetes can delay the onset of nephropathy and reduce its severity. The Diabetes Control and Complications Trial (DCCT) revealed that tight glucose control decreases the risk of nephropathy by 35% to 57%. As discussed in Chapter 44, treatment with an *angiotensin-converting enzyme* (ACE) *inhibitor* or an *angiotensin II receptor blocker* (ARB) can slow progression of mild-to-moderate nephropathy that is already present. However, these drugs are not effective for primary prevention. Of note, ACE inhibitors and ARBs have an additional benefit: they can help control hypertension, a common complication of diabetes.

Sensory and Motor Neuropathy. Nerve degeneration often begins early in the course of diabetes, but symptoms are usually absent for years. Sensory and motor nerves may be affected. Symptoms of diabetic neuropathy—which are usually bilateral and symmetric—include tingling sensations of the fingers and toes (paresthesias), increased pain or decreased ability to feel pain, suppression of reflexes, and loss

of other sensations (especially vibratory sensation). These changes are one of the reasons why a complete foot exam for diabetic patients includes not only an examination for sores and possible infections, but also for sensory responses. The clinician will use a small needle or other stiff or sharp object to prod the bottoms of the feet, without the patient looking. Failure to detect the stimuli gives a good indication that neuropathies are developing.

Nerve damage is directly related to sustained hyperglycemia, which may cause metabolic disturbances in nerves or may injure the capillaries that supply nerves. In the DCCT, tight glycemic control reduced the incidence of peripheral neuropathy by 60%.

Autonomic Neuropathy: Gastroparesis. Diabetic gastroparesis (delayed stomach emptying) affects 20% to 30% of patients with long-standing diabetes. Manifestations include nausea, vomiting, delayed gastric emptying, and gastric or intestinal distention. Injury to the autonomic nerves that control GI motility seems to be the underlying cause. Symptoms can be reduced with *metoclopramide* [Reglan], a dopamine antagonist that promotes gastric emptying (see Chapter 80). In addition to affecting autonomic nerves that innervate the GI tract, diabetes can affect autonomic nerves that innervate other structures.

Amputations Secondary to Infection. Diabetes is responsible for more than half of lower limb amputations in the United States. Each year about 54,000 diabetic patients lose a foot or leg. The underlying cause is severe infection, which can develop following local trauma, be it major or minor. There are three reasons why serious infection can occur. First, hyperglycemia provides a glucose-rich environment for bacteria to grow. Second, diabetes can suppress immune function, and thereby compromise host defenses against infection. And third, diabetic neuropathy can prevent the patient from feeling discomfort and other sensations that would signal that a serious infection is developing. Because of these factors, an infection that would be inconsequential and self-limiting in nondiabetics can become very serious in a diabetic. If the infection spreads and becomes gangrenous, the only realistic and effective solution is amputation. Because of these possibilities, regular *foot exams* and *foot care* are an important part of diabetes management.

Erectile Dysfunction. The combination of blood vessel injury and neuropathy can cause erectile dysfunction (ED). Among men with diabetes, the estimated incidence of ED is 35% to 75%. Treatment with sildenafil [Viagra] and related drugs can often help.

Diabetes and Pregnancy

Before the discovery of insulin, virtually all babies born to mothers with severe diabetes died during infancy. Although insulin therapy has greatly improved outcomes, successful management of the diabetic pregnancy remains a challenge. Three factors contribute to the problem. First, the placenta produces hormones that antagonize insulin's actions. Second, production of cortisol, a hormone that promotes hyperglycemia, increases threefold during pregnancy. Both factors increase the body's need for insulin. And third, because glucose can pass freely from the maternal circulation to the fetal circulation, hyperglycemia in the mother will stimulate exces-

TABLE 57-2 • Criteria for the Diagnosis of Diabetes Mellitus

Fasting plasma glucose ≥ 126 mg/dL*
or
Casual plasma glucose ≥ 200 mg/dL plus symptoms of diabetes [†]
or
Oral glucose tolerance test (OGTT): 2-hr plasma glucose ≥ 200 mg/dL [‡]
or
Hemoglobin A1c 6.5% or higher

*Fasting is defined as no caloric intake for at least 8 hours.

[†]Casual is defined as any time of day without regard to meals. Classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

[‡]In this OGTT, plasma glucose content is measured 2 hours after ingesting the equivalent of 75 gm of anhydrous glucose dissolved in water. The OGTT is not recommended or needed for routine clinical use. Adapted from Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 26(Suppl 1):S5–S24, 2003.

sive secretion of insulin in the fetus. The resultant hyperinsulinism can have multiple adverse effects on the fetus.

Successful management of diabetes during pregnancy demands that proper glucose levels be maintained in both the fetus and mother; failure to do so may be teratogenic or may otherwise harm the fetus. Achieving glucose control requires diligence on the part of the mother and her prescriber. Some experts on diabetes in pregnancy advise that blood glucose levels must be monitored 6 to 7 times a day. Insulin dosage and food intake must be adjusted accordingly.

Because fetal death frequently occurs near term, it is desirable that delivery take place as soon as fetal development will permit. Hence, when tests indicate sufficient fetal maturation, it is common practice to deliver the infant early—either by cesarean section or by inducing labor with drugs.

Gestational diabetes is defined as diabetes that appears during pregnancy and then subsides rapidly after delivery. Gestational diabetes is managed in much the same manner as any other diabetic pregnancy: Blood glucose should be monitored and then controlled with diet and insulin. In most cases, the diabetic state disappears almost immediately after delivery, permitting discontinuation of insulin. However, if the diabetic state persists beyond parturition, it is no longer considered gestational and should be rediagnosed and treated accordingly.

In women taking an oral drug for type 2 diabetes, current practice is to discontinue the oral drug and switch to insulin. The only exception is the oral agent metformin, which is often satisfactory for managing type 2 diabetes in pregnancy. Women who discontinue oral medications can resume oral therapy after delivery.

Diagnosis

Until recently, diagnosis of diabetes was made solely on measuring blood levels of glucose. However, in 2010, the American Diabetes Association (ADA) recommended an alternative test, based on measuring blood levels of a compound known as hemoglobin A1c. For all of these tests, values diagnostic of diabetes are summarized in Table 57-2.

Tests Based on Blood Levels of Glucose

Excessive plasma glucose is diagnostic of diabetes. Several tests may be employed: a fasting plasma glucose (FPG) test, a casual plasma glucose test, and an oral glucose tolerance test (OGTT). To make a definitive diagnosis, the patient must be tested on two separate days, and both tests must be positive. Any combination of two tests (eg, two FPG tests; one FPG test and one OGTT) may be used.

Fasting Plasma Glucose Test. To determine FPG levels, blood is drawn at least 8 hours after the last meal. In normoglycemic individuals, FPG levels are less than 100 mg/dL. If FPG glucose levels are 126 mg/dL or higher, diabetes is indicated. Of the glucose-based tests employed to diagnose diabetes, the FPG test is preferred. In fact, if an initial casual plasma glucose test suggests diabetes, a follow-up FPG test is almost always used for confirmation.

Casual Plasma Glucose Test. For this test, blood can be drawn at any time, without regard to meals. Fasting is not required. Of note, the test can be performed in the office, using a finger-stick blood sample and the same type of test device employed by patients at home. A plasma glucose level that is 200 mg/dL or higher suggests diabetes. However, to make a definitive diagnosis, the patient must also display classic signs of diabetes: polyuria, polydipsia, and rapid weight loss. Ketonuria may also be present, but only if blood glucose is extremely high.

Oral Glucose Tolerance Test. This test, often abbreviated as OGTT, is used when diabetes is suspected but could not be definitively diagnosed by measuring fasting or casual plasma glucose levels. The OGTT is performed by giving an oral glucose load (equivalent to 75 gm of anhydrous glucose), and measuring plasma glucose levels 2 hours later. In individuals who do not have diabetes, 2-hour glucose levels will be below 140 mg/dL. Diabetes is suggested if 2-hour plasma glucose levels are 200 mg/dL or higher. The OGTT test is more expensive and time consuming than the alternatives, and is not used routinely.

Test Based on Blood Levels of Hemoglobin A1c

As described below under *Monitoring Treatment*, levels of hemoglobin A1c, or simply A1c, reflect average blood glucose levels over the previous 2 to 3 months. Accordingly, if a patient's A1c is high, we know that his or her glucose levels have been high for a long time. In other words, we know that he or she has diabetes. An A1c value of 6.5% or higher is considered diagnostic.

It is important to note that the A1c test is not appropriate for everyone. Why? Because some people have conditions that can skew the results. Among these are pregnancy, chronic kidney or liver disease, recent severe bleeding or blood transfusion, and certain blood disorders, including thalassemia, iron deficiency anemia, and anemia related to vitamin B₁₂ deficiency.

Prediabetes

Prediabetes is a state defined by *impaired fasting plasma glucose* (FPG between 100 and 125 mg/dL), or *impaired glucose tolerance* (2-hour OGTT result of 140 to 199 mg/dL). These values are below those that define diabetes, but are too high to be considered normal. People with prediabetes are at increased risk of developing type 2 diabetes and CVD—but not

TABLE 57-3 • General Treatment Targets for Patients with Diabetes*

Glycemic Control	
Premeal plasma glucose	70–130 mg/dL
Peak postmeal plasma glucose	<180 mg/dL
A1c	<7%
Blood Pressure	
Systolic	<130 mm Hg
Diastolic	<80 mm Hg
Blood Lipids	
LDL cholesterol	<100 mg/dL
Triglycerides	<150 mg/dL
HDL cholesterol	Men: >40 mg/dL Women: >50 mg/dL
Kidney Integrity	
Albumin/creatinine ratio	<30 mcg/mg ¹

*Treatment targets for certain subgroups of patients may differ from the targets in this table.

¹An albumin/creatinine ratio above 30 mcg albumin/1 mg creatinine indicates too much albumin in urine owing to glomerular injury.

the microvascular complications associated with diabetes (ie, retinopathy, nephropathy, neuropathy). The risk of CVD can be reduced by diet, exercise, and, if indicated, use of appropriate drugs to control blood lipids and blood pressure. The risk of progression to diabetes may be reduced by diet and exercise, and possibly by certain oral antidiabetic drugs.

It is important to note that many people who meet the criteria for “prediabetes” never go on to develop diabetes—even if they *don't* modify their lifestyle, and even if they *don't* take antidiabetic drugs. Hence, although “prediabetes” indicates an increased *risk* of diabetes, it by no means guarantees that diabetes will occur.

Overview of Treatment

The primary goal of treating type 1 or type 2 diabetes is prevention of long-term complications, especially CVD, retinopathy, kidney disease, and amputations. To minimize these complications, treatment must keep glucose levels as low as safely possible. In addition, treatment must keep blood pressure and blood lipids within an acceptable range. In both type 1 and type 2 diabetes, proper diet and adequate exercise are central components of management. Major treatment targets are summarized in Table 57-3.

Type 1 Diabetes

Preventing complications of diabetes requires a comprehensive plan directed at glycemic control and reduction of cardiovascular risk factors. Glycemic control is accomplished with an integrated program of diet, self-monitoring of blood glucose (SMBG), exercise, and insulin replacement. Of importance, glycemic control must be achieved *safely*; that is, without causing hypoglycemia. An essential component of treatment—education of the patient and his or her caregivers about diet, exercise, and drugs—is usually left to the nurse and a dietitian or nutritionist.

Dietary Measures. *Proper diet, balanced by insulin replacement, is the cornerstone of treatment.* Because patients

with type 1 diabetes are usually thin, the dietary goal is to maintain weight—not lose it. Dietary recommendations from the ADA include the following:

- Carbohydrates and monounsaturated fats, together, should provide 60% to 70% of daily energy intake.
- Protein should provide 15% to 20% of daily energy intake.
- Polyunsaturated fat should provide about 10% of daily energy intake.
- Saturated fats should provide less than 10% of daily energy intake.
- Cholesterol intake should be limited to 300 mcg/day.
- Total caloric intake should be spread evenly throughout the day, with meals spaced 4 to 5 hours apart.

Unfortunately, although following these guidelines is clearly beneficial, many patients find long-term adherence difficult to achieve.

For people who like sweets, the ADA recommendations have good news: You can eat foods that contain sucrose (table sugar)—provided you reduce intake of other carbohydrates. What matters most is the total amount of carbohydrate ingested—not the type of carbohydrate or its source.

What's the glycemic index and why is it important? The glycemic index is an indicator of how a particular carbohydrate will affect blood glucose levels. Specifically, eating foods that have a *high* glycemic index (eg, white bread, unprocessed white rice) will raise glucose levels *more rapidly* and to a *higher peak* than will eating foods that have a *low* glycemic index (eg, rolled oats, 100% whole wheat bread, lentils and legumes, most fruits and nonstarchy vegetables). In theory, foods with a low glycemic index should permit better glycemic control. Why? Because, when glucose levels rise slowly after eating, the body has more time to process the glucose load. Importantly, this advantage is lost if total intake of low-index foods is excessive. Put another way, we may be able to achieve better glycemic control by consuming high-glycemic-index foods in moderate amounts rather than by consuming low-index foods in enormous amounts. But the best control would be achieved by consuming low-index foods in moderate amounts—and minimizing consumption of high-index foods.

Exercise. Unless specifically contraindicated, regular exercise should be part of the management program. Exercise increases cellular responsiveness to insulin, and may also increase glucose tolerance. Accordingly, the ADA recommends that patients perform at least 150 min/wk of moderate-intensity aerobic activity. Because strenuous exercise can produce hypoglycemia, patient and provider must work to establish a safe balance between exercise, caloric intake, and insulin dosage. Unfortunately, although the benefits of exercise are well established, long-term adherence to a program is often difficult to maintain.

Insulin Replacement. *Among patients with type 1 diabetes, survival requires daily dosing with insulin.* Before insulin replacement became available, people with type 1 diabetes invariably died within a few years after disease onset. The cause of death was ketoacidosis. It is essential to coordinate insulin dosage with caloric intake. If caloric intake is too great or too small with respect to insulin dosage, hyperglycemia or hypoglycemia will result.

Note that *oral* antidiabetic agents, which can help patients with type 2 diabetes, are not effective for patients with type 1

diabetes. Why? Because the oral agents cannot substitute for the insulin that type 1 patients lack.

Managing Hypertension and Dyslipidemia. As noted earlier, an ACE inhibitor (eg, captopril) or an ARB (eg, losartan) can reduce the risk of diabetic nephropathy, a long-term consequence of poor glycemic control. These same drugs are preferred agents for managing diabetic hypertension. As indicated in Table 57-3, the goal is to keep blood pressure at or below 130/80 mm Hg.

To reduce high levels of LDL cholesterol, statins (eg, atorvastatin) are preferred drugs. Not only do statins reduce cardiovascular events in patients with high cholesterol, they reduce cardiovascular events in patients with normal or low cholesterol. Another cholesterol-lowering drug—colesevelam—is discussed separately below because of its recognized role in managing diabetes.

Type 2 Diabetes

As with type 1 diabetes, preventing long-term complications requires a comprehensive treatment plan. Lifestyle measures (diet and exercise) and drug therapy are the foundation of glycemic control. Because patients are often obese, the usual dietary goal is to promote weight loss. Exercise provides the additional benefit of promoting glucose uptake by muscle, even when insulin levels are low. In addition to glycemic control, the plan should address other factors that can increase morbidity and mortality. Accordingly, all patients should be screened and treated for hypertension, nephropathy, retinopathy, and neuropathy. In addition, dyslipidemias (high LDL cholesterol, low HDL cholesterol, and high triglycerides) should be corrected.

Recommendations for glycemic control have changed. Until recently, treatment was started with lifestyle measures *alone*; drugs were added only if these measures failed. Today, treatment is started with lifestyle measures *plus* drug therapy. We no longer wait to use drugs. As a result, glycemic control is established sooner, and hence the risk of long-term complications is made lower.

Type 2 diabetes can be treated with a variety of oral and injectable drugs. Among the oral drugs, metformin and the sulfonylureas (eg, glipizide [Glucotrol]) are used most widely. Among the injectable drugs, insulin is used most widely. Although wide use of insulin may surprise you, it shouldn't. Remember, as type 2 diabetes progresses, less and less insulin is produced. As a result, up to 40% of patients with advanced disease eventually require insulin therapy.

Given the many drugs available for type 2 diabetes, which ones are preferred? Evidence of safety and efficacy is best for *metformin*, *sulfonylureas*, and *insulin*, as discussed in a 2009 guideline—*Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy*—issued jointly by the ADA and the European Association for the Study of Diabetes. To treat type 2 diabetes, the guideline recommends a three-step approach:

- Step 1.* At diagnosis, initiate lifestyle changes *plus* metformin.
- Step 2.* Continue lifestyle changes plus metformin, and *add* a second drug, either basal insulin or a sulfonylurea.
- Step 3.* Continue lifestyle changes plus metformin, and switch from basal insulin or a sulfonylurea to intensive insulin therapy.

Treatment should start at step 1, and then climb to steps 2 and 3 if needed. The guideline suggests alternative drugs (eg, pio-

glitazone [Actos], exenatide [Byetta]) if the preferred drugs are ineffective or poorly tolerated.

Tight Glycemic Control

The process of maintaining glucose levels within a normal range, around-the-clock, is referred to as tight glycemic control. In terms of A1c, the recommended target is less than 7%. Maintaining tight glycemic control is difficult but can be worth the trouble, especially for patients with type 1 diabetes. However, for many patients with type 2 diabetes, the risks of tight control may be greater than the benefits.

Type 1 Diabetes

Benefits. The benefits of tight glycemic control in type 1 diabetes were demonstrated conclusively in the Diabetes Control and Complications Trial (DCCT), in which patients received either *conventional insulin therapy* (1 or 2 injections a day) or *intensive insulin therapy* (4 injections a day). After 6.5 years, the patients who received intensive therapy experienced a 50% decrease in clinically significant kidney disease, a 35% to 57% decrease in neuropathy, and a 76% decrease in serious ophthalmic complications. Moreover, onset of ophthalmic problems was delayed and progression of existing problems was slowed. In addition to reducing these *microvascular* complications, tight control decreased *macrovascular* complications: 17-year follow-up data from the DCCT showed a significant reduction in myocardial infarction, coronary revascularization, and angina. Hence, with rigorous control of blood glucose, the high degree of morbidity and mortality traditionally associated with type 1 diabetes can be markedly reduced.

Drawbacks. The greatest concern is *hypoglycemia*. Because glucose levels are kept relatively low, the possibility of hypoglycemia increases. Why? Because even a modest overdose with insulin can cause blood glucose to fall too low. Also, a meal that is skipped or exercise that is too strenuous can do the same. Results of the DCCT showed that, compared with patients using conventional therapy, those using intensive insulin experienced 3 times as many hypoglycemic events requiring the assistance of another person, and 3 times as many episodes of hypoglycemia-induced coma or seizures. In addition, patients on intensive insulin experienced greater *weight gain* (about 10 pounds, on average). Other disadvantages are greater inconvenience, increased complexity, and a need for greater patient motivation. Finally, the cost is higher: Whereas traditional therapy costs about \$1700/year, intensive therapy costs about \$4000/year (for multiple daily injections) or \$5800 (for continuous infusion with a pump). The cost of test strips for the patient's glucometer adds substantially more to the bill.

Type 2 Diabetes

In patients with type 2 diabetes, benefits of tight glycemic control are limited mainly to *microvascular* complications; tight control does little to reduce *macrovascular* complications. Furthermore, benefits accrue more to younger adults with *recent-onset* disease, than to older adults with *well-established* disease. As in type 1 diabetes, tight glycemic control poses a significant risk of *hypoglycemia* and *weight gain*. In addition, tight control may increase the risk of *death*.

The effects of tight glycemic control in type 2 diabetes were demonstrated in four landmark trials:

- United Kingdom Prospective Diabetes Study (UKPDS)
- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
- Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE)
- Veterans Affairs Diabetes Trial (VDAT)

These large randomized trials differed in patient populations: Whereas the UKPDS trial enrolled younger adults with recent-onset diabetes and no prior cardiovascular events, the ACCORD, ADVANCE, and VDAT trials enrolled older adults with long-standing diabetes as well as established CVD or cardiovascular risk factors.

Results of the UKPDS trial, released in 1998, showed a significant reduction in *microvascular* complications—but little or no reduction in *macrovascular* complications or death. In one branch of the study, nonobese patients were given either intensive therapy or conventional therapy. Mean values for A1c were 7% in the intensive group and 7.9% in the conventional group. Compared with patients in the conventional group, patients in the intensive group had a 12% reduction in total diabetes-related endpoints (cardiovascular, retinal, and renal damage). However, a reduction in microvascular complications (especially retinal damage) accounted for most of the benefit.

Results of ACCORD, ADVANCE, and VDAT were released in 2008. As in the UKPDS trial, tight glycemic control failed to reduce stroke, amputations, all-cause mortality, or mortality from cardiovascular causes. In fact, in the ACCORD trial, intensive therapy was associated with an *increased* risk of death. Tight control also increased the risk of severe hypoglycemia and weight gain. The ADVANCE trial did show a reduction in microvascular outcomes, but the ACCORD trial did not.

Taken together, these four studies suggest that tight glycemic control is most appropriate for younger adults who have recent-onset type 2 diabetes and no cardiovascular complications. Because even short periods of hyperglycemia increase the risk of microvascular and macrovascular complications, intensive therapy should be started as soon as diabetes is diagnosed.

Who should *not* receive intensive therapy? Intensive glycemic control may be inappropriate for patient with

- Long-standing type 2 diabetes
- Advanced microvascular or macrovascular complications
- Extensive comorbid conditions
- A history of severe hypoglycemia
- Limited life expectancy

For these patients, an A1c goal above 7% may be more appropriate than a goal below 7%.

Monitoring Treatment

We need monitoring to (1) determine whether glucose levels are being maintained in a safe range, both short term and long term, and to (2) guide changes in the regimen when the range is not satisfactory or safe. Self-measurement of blood glucose levels is the standard method for day-to-day monitoring. A1c

TABLE 57-4 ■ Hemoglobin A1c Levels and Their Corresponding eAG Levels*

A1c Level (% of Total Hb)	Corresponding eAG Level	
	mg/dL	mmol/L
6	126	7
6.5	140	7.8
7 [†]	154	8.6
7.5	169	9.4
8	183	10.1
8.5	197	10.9
9	212	11.8
9.5	226	12.6
10	240	13.4

eAG = estimated Average Glucose in blood.

*The formula to convert from A1c (%) to average glucose concentration equivalents (expressed in mg/dL) is: $eAG = (A1c \times 28.7) - 46.7$.

[†]7% A1c (corresponding to an eAG of 154 mg/dL) is considered to be the maximum acceptable level for long-term glycemic control. For many patients, achieving this degree of control is difficult or impossible.

Data from American Diabetes Association.

is measured to assess long-term glycemic control. Target levels for these tests are summarized in Table 57-4.

Self-Monitoring of Blood Glucose

SMBG is recommended for all patients who use insulin. That is, SMBG is recommended for all patients with type 1 diabetes, and for all patients with type 2 diabetes receiving insulin. Many devices for measuring blood glucose (generally called glucometers) are available. With most of them, the patient places a small drop of capillary blood (eg, from a “finger stick”) on a chemically treated strip, which is then analyzed by the machine. The test is rapid and can be performed in almost any setting. Information on blood glucose concentration provides a guide for “fine tuning” dosages of insulin and other antidiabetic drugs. SMBG should be done 3 or more times a day—typically upon awakening, and before or after exercise or a meal. Target values for blood glucose are 70 to 130 mg/dL before meals and 100 to 140 mg/dL at bedtime.

Newly diagnosed patients tend to be diligent about testing their blood. This is good because it provides essential information for adjusting treatment on a day-to-day basis. Unfortunately, just as many patients start out getting proper exercise and eating right, and then go back to their old habits; they often follow the same pattern regarding SMBG.

A final note on SMBG. Glucometers are both amazing and sophisticated—and often not used to their full potential. By pushing a few buttons, you can get the current blood glucose measurement, and can label the reading as to when it was taken (eg, after exercise, before a meal). Many meters can calculate the average glucose level at a given time of day; track trends in glucose levels over a variety of time ranges; or give just about any other information you might want or need. However, there's a problem: In order to use a glucometer properly, and take full advantage of the information it can provide, you need to be able to read, understand, and follow the directions—directions that can be both complicated and lengthy (the manual may be 50 pages long). Clearly, the task can be daunting, especially for older people. Why? Just ask someone older—say your mom or dad—if they can program and use all the features of their cordless phone, never mind the HDTV, DVD player, and other high-tech games in the house. More likely than not, they can't. The glucometer is no different.

Monitoring of Hemoglobin A1c

Measurement of hemoglobin A1c—also called *glycosylated hemoglobin* or *glycated hemoglobin*—provides an index of average glucose levels over the prior 2 to 3 months. Glucose interacts spontaneously with hemoglobin in red blood cells to form glycosylated derivatives, the most prevalent being A1c. With prolonged hyperglycemia, levels of A1c gradually increase. Since red blood cells have a long life span (120 days), levels of A1c reflect average glucose levels over an extended time. Hence, by measuring A1c every 3 to 6 months, we can get a picture of long-term glycemic control. Please note, however, that measuring A1c tells us nothing about acute, hour-to-hour swings in blood glucose. Accordingly, although measuring A1c is an important part of diabetes management, it is clearly no substitute for SMBG.

How is testing done? Current tests use a tiny capillary blood sample from a “finger stick,” and yield results in minutes, while the patient is still in the office.

How are test results expressed? Results are usually reported as a percent of total hemoglobin in blood (eg, 7%). In addition, they may be reported as a value for *estimated Average Glucose* (eAG), expressed as mg glucose/dL of blood (ie, the same units patients see every day when doing SMBG). Selected A1c values and their eAG equivalents are listed in Table 57-4.

What's the A1c target level? For most patients with diabetes, the goal is to keep A1c below 7% of total hemoglobin. According to a 2008 statement issued jointly by the ADA and the European Association for the Study of Diabetes, A1c should be measured every 3 months until the value drops to 7%, and at least every 6 months thereafter. As noted above, a value of 6.5% or greater is considered diagnostic of diabetes.

Although an A1c goal of below 7% is good for most patients, a less stringent goal (eg, below 8%) may be appropriate for some patients, such as those with a history of severe hypoglycemia, limited life expectancy, or advanced microvascular or macrovascular complications.

INSULIN

Insulin is used to treat all patients with type 1 diabetes, and up to 40% of those with type 2 diabetes. Our discussion of insulin is divided into three sections: physiology, preparations and administration, and therapeutic use.

PHYSIOLOGY

Structure

The structure of insulin is depicted in Figure 57-1. As indicated, insulin consists of two amino acid chains: the “A” (acidic) chain and the “B” (basic) chain. The A and B chains are linked to each other by two disulfide bridges.

Biosynthesis

Insulin is synthesized in the pancreas by beta cells within the islets of Langerhans. The immediate precursor of insulin is called proinsulin (see Fig. 57-1).

Proinsulin consists of insulin itself plus a peptide loop that runs from the A chain to the B chain. This loop is named *connecting peptide* or *C-peptide*. In the final step of insulin syn-

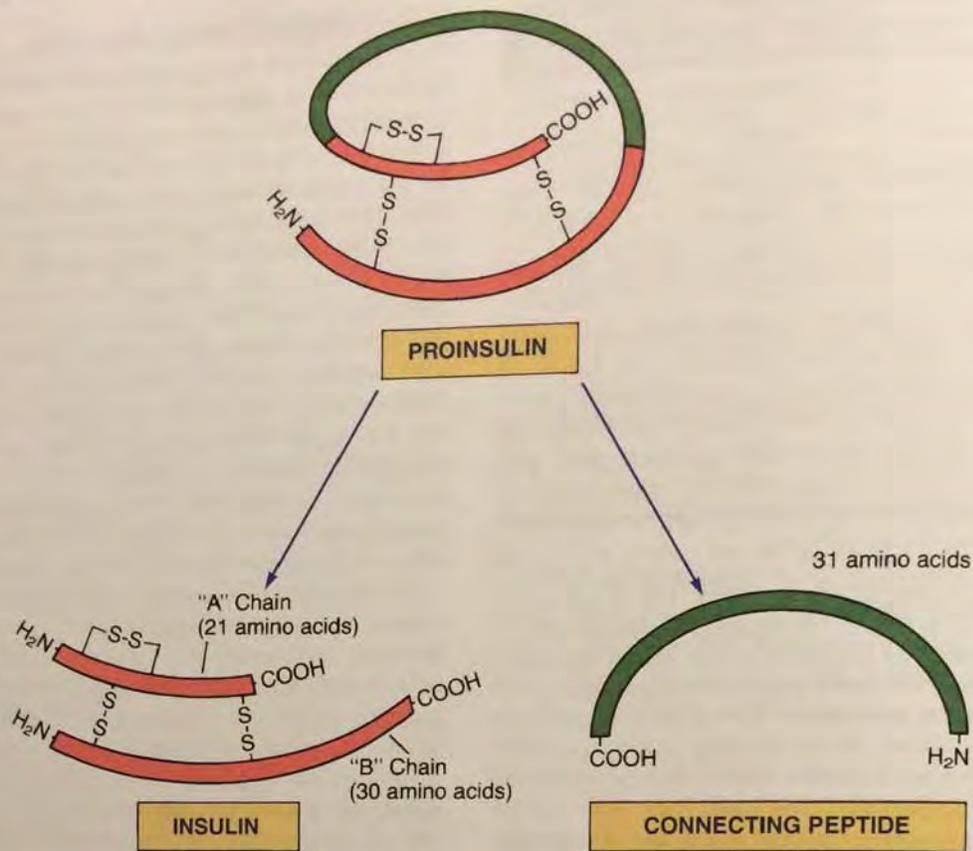


Figure 57-1 ■ Conversion of proinsulin to insulin.
 Proinsulin is the immediate precursor of the insulin secreted by our pancreas. Enzymes clip off connecting peptide (C-peptide) to release active insulin, composed of two peptide chains (A and B) connected by two disulfide (S-S) bonds. Since C-peptide arises only from endogenous insulin, its presence in blood indicates that at least some pancreatic insulin is being made.

thesis, C-peptide is enzymatically clipped from the proinsulin molecule.

Measurement of plasma C-peptide levels offers a way to assess residual capacity for insulin synthesis. Since commercial insulin preparations lack C-peptide, and since endogenous C-peptide is only present as a by-product of insulin biosynthesis, the presence of C-peptide in the blood indicates the pancreas is still producing some insulin of its own.

Secretion

The principal stimulus for insulin release is a rise in blood glucose. And the most common cause of glucose elevation is eating a meal, especially one rich in carbohydrates. Under normal conditions, there is tight coupling between rising levels of blood glucose and increased secretion of insulin. Insulin release may also be triggered by amino acids, fatty acids, and ketone bodies.

The sympathetic nervous system provides additional control of release. Activation of beta₂-adrenergic receptors in the pancreas *promotes* secretion of insulin. Conversely, activation of alpha-adrenergic receptors in the pancreas *inhibits* insulin release. Of the two modes of regulation, activation of beta receptors is more important.

Metabolic Actions

The metabolic actions of insulin are primarily *anabolic* (ie, conservative, constructive). Insulin promotes conservation of energy and buildup of energy stores, such as glycogen. The hormone also promotes cell growth and division.

TABLE 57-5 ■ Metabolic Actions of Insulin

Substance Affected	Insulin Action	Site of Action
Carbohydrates	↑ Glucose uptake	Muscle, adipose tissue
	↑ Glucose oxidation	Muscle
	↑ Glucose storage	Muscle, liver
	↑ Glycogen synthesis	
	↓ Glycogenolysis	
	Gluconeogenesis*	Liver
Amino Acids and Proteins	↑ Amino acid uptake	Muscle
	↓ Amino acid release	Muscle
	↑ Protein synthesis	Muscle
Lipids	↑ Triglyceride synthesis	Adipose tissue
	↓ Release of FFA [†] and glycerol	Adipose tissue
	↓ Oxidation of FFA to ketoacids [‡]	Liver

*Because of decreased delivery of substrate (fatty acids and amino acids) to the liver.

[†]FFA = free fatty acids.

[‡]Because of decreased delivery of FFA to the liver.

Insulin acts in two ways to promote anabolic effects. First, it stimulates cellular transport (uptake) of glucose, amino acids, nucleotides, and potassium. Second, insulin promotes synthesis of complex organic molecules. Under the influence

of insulin and other factors, glucose is converted into glycogen (the liver's way to store glucose for later use), amino acids are assembled into proteins, and fatty acids are incorporated into triglycerides. The principal metabolic actions of insulin are summarized in Table 57-5.

Metabolic Consequences of Insulin Deficiency

Insulin deficiency puts the body into a *catabolic* mode (ie, a metabolic state that favors the breakdown of complex molecules into their simpler constituents). Hence, in the absence of insulin, glycogen is converted into glucose, proteins are degraded into amino acids, and fats are converted to glycerol (glycerin) and free fatty acids. These catabolic effects contribute to the signs and symptoms of diabetes. Note that the catabolic effects resulting from insulin deficiency are opposite to the anabolic effects when insulin levels are normal.

Insulin deficiency promotes *hyperglycemia* by three mechanisms: (1) increased glycogenolysis, (2) increased gluconeogenesis, and (3) reduced glucose utilization. *Glycogenolysis*, by definition, generates free glucose by breaking down glycogen. The raw materials that allow increased *gluconeogenesis* are the amino acids and fatty acids produced by metabolic breakdown of proteins and fats. *Reduced glucose utilization* occurs because insulin deficiency decreases cellular uptake of glucose, and decreases conversion of glucose to glycogen.

PREPARATIONS AND ADMINISTRATION

There are many insulin preparations or formulations. All of them have identical mechanisms. Major differences concern time course, appearance (clear or cloudy), concentration, and route of administration. Because of these differences, insulin preparations cannot be used interchangeably. In fact, if a patient is given the wrong preparation, the consequences can be dire. Unfortunately, medication errors with insulins remain all too common, which explains why insulin appears on all lists of "high-alert" agents.

Sources of Insulin

All forms of insulin currently manufactured in the United States are produced using recombinant DNA technology. Some products, referred to as *human insulin*, are identical to insulin produced by the human pancreas. Other products, referred to as *human insulin analogs*, are modified forms of human insulin. The analogs have the same pharmacologic actions as human insulin, but have different time courses.

Types of Insulin

There are seven types of insulin: "natural" insulin (also known as regular insulin or native insulin) and six modified insulins. Three of the modified insulins—insulin lispro, insulin aspart, and insulin glulisine—act more rapidly than natural insulin but have a shorter duration of action. The other modified insulins act more slowly than natural insulin but have a longer duration. Two processes are used to prolong insulin effects: (1) complexing natural insulin with a protein, and (2) altering the insulin molecule itself. When the insulin molecule has been altered, we refer to the product as a *human insulin analog*. Specific alterations made to create the insulin analogs are summarized in Table 57-6.

When classified according to time course, insulin preparations fall into three major groups: short duration, intermediate duration, and long duration (Table 57-7). The short-duration insulins can be subdivided into two groups: rapid acting (insulin lispro, insulin aspart, and insulin glulisine) and slower acting (regular or "natural" insulin). Time courses for different insulin types are depicted graphically in Figure 57-2. Selected properties of insulin types are summarized in Table 57-8.

Short Duration: Rapid Acting

Short-duration insulins are administered in association with meals to control the postprandial rise in blood glucose. To provide glycemic control between meals and at night,

TABLE 57-6 ■ Amino Acids Substitutions in Human Insulin Analogs*

Insulin Type	Amino Acids in A-Chain Position			Amino Acids in B-Chain Position					
	A8	A10	A21	B3	B28	B29	B30	B31	B32
Human Insulin									
Native [†]	Thr	Ile	Asn	Asn	Pro	Lys	Thr	—	—
Human Insulin Analogs									
Glargine	Thr	Ile	Gly	Gly	Pro	Lys	Thr	Arg	Arg
Aspart	Thr	Ile	Asn	Asn	Asp	Lys	Thr	—	—
Lispro	Thr	Ile	Asn	Asn	Lys	Pro	Thr	—	—
Glulisine	Thr	Ile	Asn	Lys	Pro	Glu	Thr	—	—
Detemir	Thr	Ile	Asn	Asn	Pro	Lys [‡]	†	—	—

Arg = arginine, Asn = asparagine, Asp = aspartic acid, Glu = glutamine, Gly = glycine, Ile = isoleucine, Lys = lysine, Pro = proline, Thr = threonine.

*The human insulin analogs have the same physiologic effects as native human insulin—they just have different pharmacokinetics, such as onset and duration of action.

[†]Human insulin (ie, the form of insulin made by the human pancreas) is also known as *native insulin*.

[‡]A fatty-acid chain has been added to the lysine in position B29.

[§]The amino acid normally in position B30 has been deleted.

TABLE 57-7 ■ Types of Insulin: Time Course of Action After Subcutaneous Injection

Generic Name	Trade Name	Time Course		
		Onset (min)	Peak (hr)	Duration (hr)
Short Duration: Rapid Acting				
Insulin lispro	Humalog	15–30	0.5–2.5	3–6
Insulin aspart	NovoLog	10–20	1–3	3–5
Insulin glulisine	Apidra	10–15	1–1.5	3–5
Short Duration: Slower Acting				
Regular insulin	Humulin R, Novolin R	30–60	1–5	6–10
Intermediate Duration				
NPH insulin	Humulin N, Novolin N	60–120	6–14	16–24
Insulin detemir	Levemir	60–120	12–24	Varies*
Long Duration				
Insulin glargine	Lantus	70	None [†]	24

*Duration is dose dependent: At 0.2 units/kg, duration is 12 hours; at 0.4 units/kg, duration is 20 to 24 hours.

[†]Levels are steady with no discernible peak.

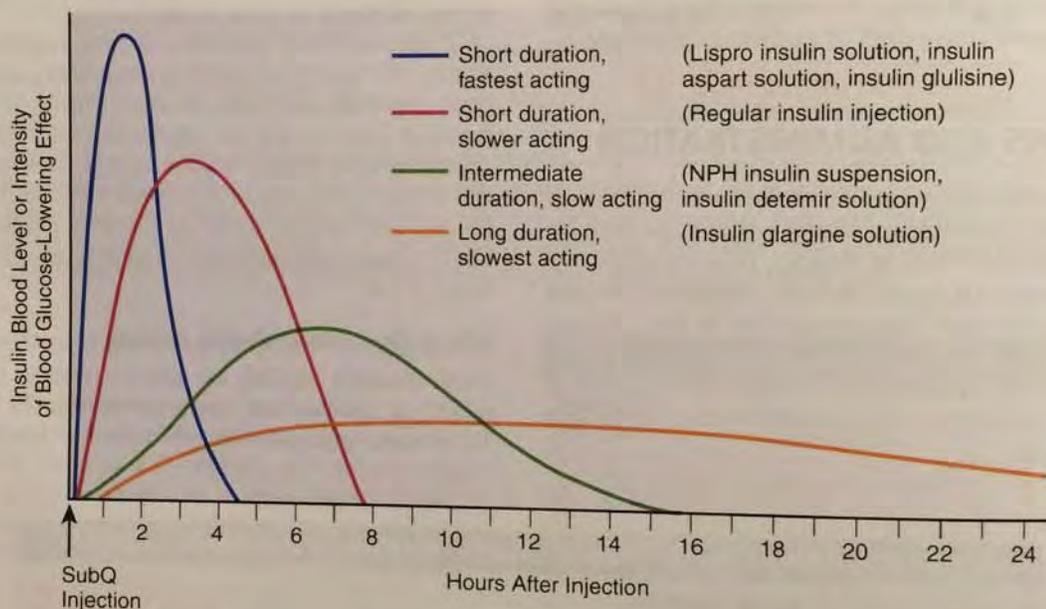


Figure 57-2 ■ Time-effect relationship for different types of insulin following subcutaneous injection.

short-acting insulins must be used in conjunction with an intermediate- or long-acting agent. *All three of the rapid-acting insulins are formulated as clear solutions*, and all three require a prescription. For routine therapy, all three are given subQ. If needed, all three may also be given IV.

Insulin Lispro. Insulin lispro [Humalog] is a rapid-acting analog of regular insulin. Effects begin within 15 to 30 minutes of subQ injection and persist for 3 to 6 hours. Insulin lispro acts faster than regular insulin but has a shorter duration of action. Because of its rapid onset, insulin lispro can be administered immediately before eating, or even after eating. In contrast, regular insulin is generally administered 30 to 60 minutes before meals. The usual route is subQ. Intravenous infusion may be done in an emergency.

The structure of insulin lispro is nearly identical to that of natural insulin. The only difference is that the positions of two amino acids have been switched. Because of this switch, molecules of insulin lispro aggregate less than do molecules of regular insulin, which explains why insulin lispro acts more rapidly.

Insulin Aspart. Insulin aspart [NovoLog] is an analog of human insulin with a rapid onset (10 to 20 minutes) and short duration (3 to 5 hours). The drug is structurally identical to human insulin except that one amino acid—proline in position 28 of the B chain—has been changed to aspartic acid. Insulin aspart is very similar to insulin lispro.

Insulin aspart (100 units/mL) is available in 10-mL vials and 3-mL PenFill cartridges. Dosing is almost always done by subQ injection or subQ infusion, although IV infusion may be

TABLE 57-8 ■ Properties of Insulin Types

Generic Name [Trade Name]	Class*	Rx or OTC†	Strength‡	Appearance	Route	Administration Options§
Short Duration: Rapid Acting						
Insulin lispro [Humalog]	HA	Rx	U-100	Clear	subQ, IV	<i>subQ inj</i> : within 15 min before or just after meals <i>subQ inj</i> : continuous, with bolus just before meals
Insulin aspart [NovoLog]	HA	Rx	U-100	Clear	subQ, IV	<i>subQ inj</i> : 5–10 min before meals <i>subQ inf</i> : continuous, with bolus 5–10 min before meals <i>IV</i> : approved route, but rarely used
Insulin glulisine [Apidra]	HA	Rx	U-100	Clear	subQ, IV	<i>subQ inj</i> : within 15 min before meals or within 20 min after <i>subQ inf</i> : continuous, with bolus 15–20 min before meals <i>IV</i> : approved route, but rarely used
Short Duration: Slower Acting						
Regular insulin [Humulin R, Novolin R]	H	OTC¶	U-100, U-500	Clear	subQ, IV, IM	<i>subQ inj</i> : 30 min before meals <i>subQ inf</i> : continuous, with bolus 20–30 min before meals <i>IV</i> : for emergencies (unlabeled use, never use U-500 IV) <i>IM</i> : approved route, but rarely used
Intermediate Duration						
NPH insulin [Humulin N, Novolin N]	H	OTC	U-100	Cloudy	subQ	<i>subQ inj</i> : twice daily at the same times each day; gently agitate before use
Insulin detemir [Levemir]	HA	Rx	U-100	Clear	subQ	<i>subQ inj</i> : twice daily or once daily (at evening meal or bedtime)
Long Duration						
Insulin glargine [Lantus]	HA	Rx	U-100	Clear	subQ	<i>subQ inj</i> : once daily at the same time each day

*H = human insulin, HA = human insulin analog.

†Rx = prescription needed, OTC = over the counter (no prescription needed).

‡U-100 = 100 units/mL, U-500 = 500 units/mL.

§inj = injection, inf = infusion.

¶U-100 formulations are OTC, the U-500 formulation is Rx.

used in emergencies. Because insulin aspart acts rapidly, injections should be made 5 to 10 minutes before meals.

Insulin Glulisine. Like insulin lispro and insulin aspart, insulin glulisine [Apidra] is a synthetic analog of natural human insulin with a rapid onset (10 to 15 minutes) and short duration (3 to 5 hours). Owing to its rapid onset, the drug should be administered close to the time of eating (within 15 minutes before and 20 minutes after starting to eat). Because of its short duration, insulin glulisine should be used in conjunction with an intermediate- or long-acting insulin to provide basal glycemic control. Administration is almost always by subQ injection or continuous subQ infusion. Intravenous dosing may be done in emergencies. Insulin glulisine differs from natural insulin by two amino acids.

Short Duration: Slower Acting

Regular Insulin Injection. Regular insulin [Humulin R, Novolin R] is unmodified human insulin. The product has four approved routes: subQ injection, subQ infusion, IM injection (used rarely), and oral inhalation (approved but not

currently used). In addition, regular insulin is used off-label for intravenous therapy. For IV therapy, only the U-100 formulation should be used.

For routine treatment of diabetes, regular insulin can be (1) injected before meals to control postprandial hyperglycemia, and (2) infused subQ to provide basal glycemic control. Following *subQ injection*, molecules of regular insulin form small aggregates (dimers and hexamers) at the injection site. As a result, absorption is slightly delayed. Effects begin in 30 to 60 minutes, peak in 1 to 5 hours, and last up to 10 hours. Onset is slower than with the rapid-acting insulins, and faster than with the longer acting insulins.

Regular insulin is supplied as a clear solution. Two concentrations are available: U-100 (100 units/mL) and U-500 (500 units/mL). Regular insulin is the only type available in a U-500 strength. U-100 preparations are used by most patients. The U-500 concentration is reserved for patients with insulin resistance. Because it is so concentrated, U-500 insulin should never be given IV. Except for the U-500 formulation, all formulations of regular insulin are available without prescription.

Intermediate Duration

Neutral Protamine Hagedorn (NPH) Insulin Suspension. NPH insulin [Humulin N, Novolin N], also known as *isophane insulin*, is prepared by conjugating regular insulin with protamine (a large protein). The presence of protamine decreases the solubility of NPH insulin and thereby retards absorption. As a result, onset of action is delayed and duration of action is extended. Because onset is delayed, NPH insulin cannot be administered at mealtime to control postprandial hyperglycemia. Rather, the drug is injected twice daily to provide glycemic control between meals and during the night. Of the longer acting insulins in current use, NPH insulin is the only one suitable for mixing with short-acting insulins. Because protamine is a foreign protein, allergic reactions are possible. NPH insulins are supplied as cloudy suspensions that must be gently agitated before administration. Administration is by subQ injection only. Like regular insulin, NPH insulins are available without prescription.

Insulin Detemir. Insulin detemir [Levemir] is a human insulin analog with a slow onset and dose-dependent duration of action. At low doses (0.2 units/kg), effects persist about 12 hours. At higher doses (0.4 units/kg), effects persist 20 to 24 hours. Because of its slow onset and prolonged duration, insulin detemir is used to provide basal glycemic control. It is not given before meals to control postprandial hyperglycemia. Compared with NPH insulin, insulin detemir has a slower onset and longer duration.

Insulin detemir differs from natural insulin in two ways. First, one amino acid has been removed. Second, a 14-carbon fatty-acid chain has been attached to the B chain. Because of these structural changes, molecules of insulin detemir adhere strongly to each other, and hence absorption is delayed. Because of the fatty-acid chain, insulin detemir binds strongly with plasma albumin, and hence distribution to target sites is delayed even further.

Insulin detemir is supplied as a clear, colorless solution (100 units/mL) in 10-mL vials, 3-mL cartridges, a 3-mL *FlexPen*, and a 3-mL *Innolet* dosing device. Dosing is done once or twice daily by subQ injection. Insulin detemir should not be mixed with other insulins, and must not be given IV. The drug is available by prescription only.

Long Duration

Insulin Glargine. Insulin glargine [Lantus] is a modified human insulin with a prolonged duration of action (at least 24 hours). The drug is indicated for once-daily subQ dosing to treat adults and children with type 1 diabetes and adults with type 2 diabetes. Dosing may be done any time of day (morning, afternoon, or evening), but should be done at the same time every day.

Insulin glargine differs from natural human insulin by four amino acids (see Table 57-6). Because of these modifications, insulin glargine has low solubility at physiologic pH. Hence, when injected subQ, it forms microprecipitates that slowly dissolve, and thereby release insulin glargine in small amounts over an extended time. In contrast to other long-acting insulins (ie, NPH insulin, insulin detemir), whose blood levels rise to a distinct peak and then fall to a trough, insulin glargine achieves blood levels that are relatively steady over 24 hours. As a result, there is less risk of hypoglycemia (from excessive levels) or hyperglycemia (from insufficient levels).

Insulin glargine is supplied as a *clear solution* in 10-mL vials containing 100 units/mL, and in 3-mL cartridges for use

in an *OptiClik Pen*. As with other long-acting insulins, administration is by subQ injection. The drug should not be mixed with other insulins, and should never be given IV.

Appearance

In the past, most insulins were formulated as cloudy suspensions, and this was an easy tip-off that the drug must not be injected intravenously. Today, the opposite is true: with the exception of NPH insulins, all insulins made in the United States are formulated as *clear, colorless solutions*. NPH insulin is still a cloudy suspension. Patients should inspect their insulin before using it, and should discard the vial if the insulin looks abnormal.

Because most insulin preparations—and not just regular insulin—are now formulated as clear solutions, generalities that applied in the past are no longer true. Accordingly, patients and providers should note the following changes:

In the past: All insulins available as clear solutions were short acting. This was true when regular insulin was the only preparation available as a clear solution.

Today: Of the insulins available as clear solutions, four preparations—regular, lispro, aspart, and glulisine insulin—are short acting, and two preparations—detemir and glargine insulin—have more prolonged actions.

In the past: All insulins available as clear solutions could be administered IV. Again, this was true when regular insulin was the only preparation available as a clear solution.

Today: Of the insulins available as clear solutions, four preparations—regular, aspart, lispro, and glulisine insulin—can be administered IV. The rest—detemir and glargine insulin—cannot.

In the past: All insulins that were clear solutions could be mixed in the same syringe with other insulins. Again, this was true when regular insulin was the only preparation available as a clear solution.

Today: Of the insulins available as clear solutions, only the short-acting preparations—regular, lispro, aspart, and glulisine insulin—can be mixed with other insulins (usually NPH insulin).

Concentration

In the United States, insulin is available in two concentrations: 100 units/mL (U-100) and 500 units/mL (U-500). Preparations containing 40 units/mL are available in other countries but not here. U-100 insulins are employed for routine replacement therapy. All insulin types are available in U-100 formulations. Only one product—the *Humulin R* brand of regular insulin—is formulated in the U-500 strength. This product, which is available from the manufacturer by special request, is reserved for emergencies and for patients with severe insulin resistance, defined as needing more than 200 units/day.

Mixing Insulins

When the treatment plan calls for using a short-acting insulin in combination with a longer acting insulin, it is usually desirable to mix the preparations (in a single syringe) rather than

TABLE 57-9 ■ Premixed Insulin Combinations

Description	Trade Name	Time Course		
		Onset (min)	Peak (hr)	Duration (hr)
70% NPH insulin/30% regular insulin	Humulin 70/30	30-60	1.5-16	Up to 24
	Novolin 70/30	30-60	2-12	Up to 24
70% insulin aspart protamine/30% insulin aspart	NovoLog Mix 70/30	10-20	1-4	Up to 24
75% insulin lispro protamine/25% insulin lispro	Humalog Mix 75/25	15-30*	1-6.5	Up to 24
50% insulin lispro protamine/50% insulin lispro	Humalog Mix 50/50	15-30	0.8-4.8	22 or more

*Use only after the dosages and ratios of the components have been established as correct for the patient.

inject them separately, so as to eliminate the need for an additional shot. However, although mixing offers convenience, it can alter the time course of the response. Therefore, to ensure a consistent response, mixing should be done only with insulins of proven compatibility. Of the three longer acting insulins in current use, *only NPH insulin is appropriate for mixing with short-acting insulins* (ie, regular, lispro, aspart, and glulisine insulins). When a mixture is prepared, the short-acting insulin should be drawn into the syringe first. Why? To avoid contaminating the stock vial of the short-acting insulin with NPH insulin. As a rule, the mixtures are stable for 28 days. Commercially available premixed combinations are described in Table 57-9.

Administration

Subcutaneous Injection

Insulin is usually given by subQ injection. Why? Owing to its peptide structure, insulin would be inactivated by the digestive system if it were given by mouth. All types of insulins may be injected subQ.

Preparing for Injection. Initial preparation depends on whether the insulin product is in solution or suspension. With the exception of NPH insulins, all insulins available today are supplied as clear, colorless solutions. These solutions are ready to use—*unless they have become colored or cloudy, or contain a precipitate*, in which case they should be discarded. Because NPH insulins are suspensions, their particles must be evenly dispersed prior to loading the syringe. Dispersion is accomplished by rolling the vial between the palms of the hands. Mixing must be gentle, because vigorous agitation will cause frothing and render accurate dosing impossible. If granules or clumps remain after gentle agitation, the vial should be discarded.

Before loading the syringe, the bottle cap should be swabbed with alcohol. Air bubbles should be eliminated from the syringe and needle after loading. The skin should be cleaned with alcohol (or soap and water) prior to injection.

Injection Sites. The most common sites of subQ injection are the upper arm, thigh, and abdomen. Absorption is fastest and most consistent following abdominal injection, and slowest following injection in the thigh. Because rates of absorption vary among sites, patients should make all injections into the same general area (eg, thigh or abdomen). To

reduce the risk of lipodystrophy (see below), injections within the chosen area should be made in different spots, preferably about 1 inch apart. Ideally, each spot should be used only once a month.

Injection Devices. Syringe and Needle. Syringes and needles for insulin injection are manufactured in several sizes, so they can be matched to individual needs. Three syringe sizes are available: 1 cc, 1/2 cc, and 1/3 cc, which can deliver up to 100, 50, and 30 units of insulin, respectively. Patients should choose the syringe that best matches their dosage. For example, a patient who injects 25 units of insulin per dose should choose a 1/3-cc syringe, which can deliver up to 30 units of insulin. Patients should use the smallest syringe that will hold the required volume.

Needles for injecting insulin are available in three lengths: 12.7 mm (1/2 inch), 8 mm (5/16 inch), and 5 mm (3/16 inch). Since the objective is to penetrate the skin and enter the subcutaneous fat, the longest needle might be best for an overweight adult, whereas the shortest might be best for a small child.

Injection technique can affect the rate of insulin absorption, and hence can alter glycemic control. Accordingly, consistent delivery into subQ fat is important. If the needle is not inserted deep enough, insulin will be injected intradermally. Conversely, if the needle is inserted too deep, insulin will be injected into muscle. Intramuscular injection will accelerate insulin absorption, and hence will shorten the period of glycemic control. Also, IM injection hurts more.

Pen Injectors. These devices are similar to a syringe and needle but are more convenient. Pen injectors look like a fountain pen but have a disposable needle (where the writing tip would be) and a disposable insulin-filled cartridge inside. Administration is accomplished by sticking the needle under the skin and injecting the insulin manually. Dosage can be adjusted in 2-unit increments.

Jet Injectors. These devices shoot insulin directly through the skin into subcutaneous tissue. No needle is used. Hence, for patients who dislike needles, a jet injector may be attractive. However, these devices do have a downside. They're expensive (\$500 to \$900) and can be difficult to use. Moreover, because insulin is delivered under high pressure, jet injectors can cause stinging, burning, and pain. In addition, bruising can occur in people with reduced subcutaneous fat (children, the elderly, thin people).

Subcutaneous Infusion

Portable Insulin Pumps. These computerized devices deliver a basal infusion of insulin (regular, lispro, aspart, or glulisine) plus bolus doses before each meal. The basal infusion is usually about 1 unit/hr and can be programmed to match the patient's metabolic requirements. Mealtime boluses are calculated to match caloric intake. The pumps are about the size of a small cell phone, weigh only 4 ounces, and are worn on the belt or in a pocket. An infusion set delivers insulin from the pump to a subcutaneous catheter, usually located on the abdomen. The infusion set should be replaced every 1 to 3 days, at which time the needle should be moved to a new site (at least 1 inch away from the old one). Because the pump delivers short-acting insulin, insulin levels will drop quickly if the pump is removed. Accordingly, the pump should remain in place most of the day. However, it can be removed for an hour or two on special occasions. External insulin pumps cost between \$3000 and \$5000. Infusion sets, insulin, and glucose monitoring materials add another \$300 per month to the bill. Aside from expense, the main drawback of the pumps is delivery of too little insulin owing to formation of insulin microdeposits.

Implantable Insulin Pumps. These devices are surgically implanted in the abdomen and deliver insulin either intraperitoneally or intravenously. Like external pumps, internal pumps deliver a basal insulin infusion plus bolus doses with meals. Insulin delivery is adjusted by external telemetry. Compared with multiple daily injections, implantable pumps produce superior glycemic control, cause less hypoglycemia and weight gain, and improve quality of life. As with external pumps, delivery of insulin can be impeded by formation of insulin microprecipitates. Implantable pumps are experimental and not yet available for general use.

Intravenous Infusion

Intravenous infusion is reserved for emergencies that require a rapid reduction in blood glucose. Not long ago, regular insulin (U-100 strength) was the only formulation considered safe for IV use. Today, three other short-acting insulins—insulin aspart [Novolog], insulin lispro [Humalog], and insulin glulisine [Apidra]—may also be used. When given IV, all of these products, including regular insulin, should be diluted to a concentration of 0.05 to 1 unit/mL.

Inhalation

Inhalation of insulin is an attractive alternative to needle-based dosing. In clinical trials, patient satisfaction with inhaled insulin has been much higher than with insulin injections. Several delivery systems for insulin inhalation have been in development, and, in 2006, one of them—Exubera—received Food and Drug Administration (FDA) approval. However, sales of this product were so poor that it was voluntarily withdrawn in 2007. Factors underlying poor sales included complaints about side effects (cough and bitter taste), hypoglycemia, high cost relative to injectable insulins, and an administration device that many patients found cumbersome. In addition, there were growing concerns about allergic reactions, pulmonary irritation, and even lung cancer. Do these problems apply to *all* inhaled insulins? No. At least one product, still in development, provides good glycemic control with a low incidence of hypoglycemia—and has little or no effect on pulmonary function. These data suggest we are likely to have inhaled insulin available once again.

Storage

Insulin in *unopened vials* should be stored *under refrigeration* until needed. Vials should not be frozen. When stored *unopened under refrigeration*, insulin can be used up to the expiration date on the vial.

The vial in current use can be kept at room temperature for up to 1 month without significant loss of activity. Direct sunlight and extreme heat must be avoided. Partially filled vials should be discarded after several weeks if left unused. Injecting insulin stored at room temperature causes less pain than injecting cold insulin and reduces the risk of lipodystrophy.

Mixtures of insulin prepared in vials are stable for 1 month at room temperature and for 3 months under refrigeration.

Mixtures of insulin in pre-filled syringes (plastic or glass) should be stored in a refrigerator, where they will be stable for at least 1 week and perhaps 2. The syringe should be stored vertically with the needle pointing up to avoid clogging the needle. Prior to administration, the syringe should be agitated gently to resuspend the insulin.

THERAPEUTIC USE

Indications

The principal indication for insulin is *diabetes mellitus*. Insulin is required by all patients with type 1 diabetes and by up to 40% of patients with type 2 diabetes. Intravenous insulin is used to treat *diabetic ketoacidosis*. Because of its ability to promote cellular uptake of potassium and thereby lower plasma potassium levels, insulin infusion is employed to treat *hyperkalemia*. Lastly, insulin can aid the *diagnosis of growth hormone (GH) deficiency*.^{*} The use of insulin in diabetes is discussed below.

Insulin Therapy of Diabetes

Insulin is given to all patients who have type 1 diabetes and to many who have type 2. In addition, insulin is the preferred drug to manage gestational diabetes. In treating these disorders, the objective is to prevent complications by keeping blood glucose within an acceptable range (see Table 57-3). When therapy is successful, both hyperglycemia and hypoglycemia are avoided, and the long-term complications of diabetes are minimized.

Dosage

To achieve tight glucose control, insulin dosage must be closely matched with insulin needs. If caloric intake is increased, insulin dosage must be increased too. When a meal is missed or is low in calories, or when exercise gets excessive, the dosage of insulin must be decreased. Dosing requires additional adjustments to meet specialized needs. For example, insulin needs are *increased* by infection, stress, obesity, the adolescent growth spurt, and pregnancy after the first trimester. Conversely, insulin needs are *decreased* by exercise and during the first trimester of pregnancy. To ensure that insulin dosage is coordinated with insulin requirements, the patient and the healthcare team must work together to establish an integrated program of nutrition, exercise, insulin replacement therapy, and rigorous blood glucose monitoring.

^{*}The *insulin hypoglycemia test* can aid diagnosis of suspected GH deficiency in preadolescent children who are not growing as fast as their peers. The test is based on the fact that even modest insulin-induced hypoglycemia can trigger GH release, causing blood levels of GH to rise. In children with GH deficiency, the rise in blood GH will be lower than in children with normal pituitary function.

TABLE 57-10 ■ Insulin Therapy of Diabetes Mellitus: Conventional Versus Intensive Conventional Therapy

Regimen	Insulin Type and Dosing Schedule			
	Breakfast	Lunch	Supper	Bedtime
Conventional therapy*	Regular + NPH	None	Regular + NPH	None
Intensive conventional therapy†	Regular	Regular	Glargine	

*Dosage is *fixed* (two-thirds of daily total in AM, one-third of daily total in PM). As a result, flexibility of timing and composition of meals is not possible.

†Dosage of regular insulin is *adjusted for each meal*; hence, timing and composition of meals can be varied.

Total daily dosages may range from 0.1 unit/kg body weight to more than 2.5 units/kg. For patients with type 1 diabetes, initial dosages typically range from 0.5 to 0.6 units/kg/day. For patients with type 2 diabetes, initial dosages typically range from 0.2 to 0.6 units/kg/day.

Dosing Schedules

The schedule of insulin administration helps determine the extent to which tight glucose control is achieved. Three dosing schedules are compared below. These modes are referred to as (1) conventional therapy, (2) intensive conventional therapy, and (3) continuous subcutaneous insulin infusion.

Conventional Therapy. Several dosing schedules fall under the heading of conventional therapy. A representative schedule is summarized in Table 57-10. In this schedule, a combination of regular insulin (a short-acting, fast-onset preparation) plus NPH insulin (an intermediate-acting preparation) is administered 15 to 30 minutes before breakfast and again before the evening meal. No insulin is administered with the noon meal. Typically, two-thirds of the total daily dose is given in the morning and the remainder is given late in the day. Dosage remains rigidly fixed from one day to the next.

Conventional therapy does not provide tight glucose control. The weak point of this schedule is that there is no provision for adjusting insulin dosage in response to ongoing changes in insulin needs. Hence, if a meal is abnormally large, insulin levels will be insufficient, causing hyperglycemia. Conversely, if a meal is delayed, reduced in size, or missed entirely, hypoglycemia will follow.

Intensive Conventional Therapy (ICT). This form of therapy is designed to provide tight glucose control. A representative regimen is presented in Table 57-10. In this regimen, the patient injects insulin glargine (a long-acting preparation) in the evening and also injects regular insulin (a short-acting, fast-onset preparation) 15 to 30 minutes before each meal.* Insulin glargine provides a *basal* level of insulin throughout the night and the following day. The mealtime doses of *regular* insulin accommodate the acute needs that occur at times of caloric loading. Note that insulin is injected *4 times each day*, rather than just twice as in conventional therapy.

The most significant feature of ICT is *adaptability*. Unlike conventional therapy, in which doses never change, the pre-

prandial doses in ICT are adjusted to match the caloric content of each meal: if no meal is eaten, no insulin is administered; if a meal is delayed, so is the dose of regular insulin; if a meal is larger than usual, the insulin dose is increased proportionately. Because insulin dosage is determined by the timing and size of each meal, ICT offers patients a degree of glycemic control and dietary flexibility that is not possible with conventional therapy.

SMBG is an essential component of ICT. For patients with type 1 diabetes, blood glucose should be measured 3 to 5 times a day. SMBG is discussed above under *Monitoring Treatment*.

Continuous Subcutaneous Insulin Infusion. Continuous subcutaneous insulin infusion (CSII) is accomplished using a portable infusion pump connected to an indwelling subcutaneous catheter. Four types of insulin may be used: regular, lispro, aspart, and glulisine. To provide a basal level of insulin, the pump is set to infuse insulin continuously at a slow but steady rate. To accommodate insulin needs created by eating, the pump is triggered manually to provide a bolus dose matched in size to the caloric content of each meal. Hence, like ICT, CSII can adapt to altered insulin needs. As with ICT, SMBG is essential. CSII is equivalent to ICT for achieving tight glucose control. Infusion pumps are discussed above in the section on *Subcutaneous Infusion under Administration*.

Achieving Tight Glucose Control

As we have seen, the primary requirement for achieving tight glucose control is a method of insulin delivery that permits dosage adjustments that accommodate ongoing variations in insulin needs. ICT and CSII meet this criterion. In addition to an adaptable method of insulin delivery, achieving tight glucose control requires the following:

- Careful attention to all elements of the treatment program (diet, exercise, insulin replacement therapy)
- A defined glycemic target (see Tables 57-3 and 57-4)
- Self-monitoring of blood glucose 3 to 5 times a day (for patients with type 1 diabetes)
- A high degree of patient motivation
- Extensive patient education

Tight glucose control cannot be achieved without the informed participation of the patient. Accordingly, patients must receive thorough instruction on the following:

- The nature of diabetes
- The importance of tight glucose control

*Insulin lispro, insulin aspart, or insulin glulisine can be used instead of regular insulin. The advantage of these alternatives is that they can be injected just a few minutes before eating, and one of them—insulin aspart—can even be injected after eating.

- The major components of the treatment routine (insulin replacement, SMBG, diet, exercise)
- Procedures for purchasing insulin, syringes, and needles
- The importance of avoiding arbitrary changes between insulins from different manufacturers
- Methods of insulin storage
- Procedures for mixing insulins
- Calculation of dosage adjustments
- Techniques of insulin administration
- Methods for monitoring blood glucose

In the final analysis, responsibility for managing diabetes rests with the patient. The healthcare team can design a treatment program and provide education and guidance. However, tight glucose control can only be achieved if the patient is actively involved in his or her own therapy.

Complications of Insulin Treatment

Hypoglycemia

Hypoglycemia (blood glucose below 50 mg/dL) occurs when insulin levels exceed insulin needs. A major cause of insulin excess is overdose. Imbalance between insulin levels and insulin needs can also result from reduced intake of food, vomiting and diarrhea (which reduce absorption of nutrients), excessive consumption of alcohol (which promotes hypoglycemia), unusually intense exercise (which promotes cellular glucose uptake and metabolism), and childbirth (which reduces insulin requirements).

Diabetic patients and their families should be familiar with the signs and symptoms of hypoglycemia. Some symptoms result from activation of the sympathetic nervous system; others arise from the central nervous system (CNS). When glucose levels fall *rapidly*, activation of the sympathetic nervous system occurs, resulting in tachycardia, palpitations, sweating, and nervousness. However, if glucose declines *gradually*, symptoms may be limited to those of CNS origin. Mild CNS symptoms include headache, confusion, drowsiness, and fatigue. If hypoglycemia is severe, convulsions, coma, and death may follow.

Rapid treatment of hypoglycemia is mandatory: If hypoglycemia is allowed to persist, irreversible brain damage or even death may result. In conscious patients, glucose levels can be restored with a fast-acting oral sugar (eg, glucose tablets, orange juice, sugar cubes, honey, corn syrup, nondiet soda). However, if the swallowing reflex or the gag reflex is suppressed, nothing should be administered by mouth. In cases of severe hypoglycemia, IV glucose is the preferred treatment. Parenteral *glucagon* is an alternative treatment. (The pharmacology of glucagon is discussed at the end of the chapter.)

In anticipation of hypoglycemic episodes, diabetic patients should always have an oral carbohydrate available (eg, sugared candy, sugar cubes, glucose tablets). Some prescribers recommend that patients keep glucagon on hand too. Patients should carry some sort of identification (eg, Medic Alert bracelet) to inform emergency personnel of their condition.

In some patients, hypoglycemia occurs without producing the symptoms noted above. As a result, the patient remains unaware of hypoglycemia until blood sugar has become dangerously low. Hypoglycemia unawareness is a particular prob-

lem among patients practicing tight glucose control. The risk of dangerous hypoglycemia can be minimized by frequently monitoring blood glucose.

Both severe hypoglycemia and diabetic ketoacidosis (see below) can produce coma. Of the two causes, hypoglycemia is more common. Since treatment of these two conditions is very different (hypoglycemia involves withholding insulin, whereas ketoacidosis requires giving insulin), it is essential that coma from these causes be differentiated. The most definitive diagnosis is made by measuring plasma glucose levels: in hypoglycemic coma, glucose levels are very low; in ketoacidosis, glucose levels are very high.

Other Complications

Hypokalemia. Insulin promotes uptake of potassium by cells. How? By activating a membrane-bound enzyme— Na^+, K^+ -ATPase—that pumps potassium into cells and pumps sodium out. Hence, in addition to lowering blood levels of glucose, insulin can lower blood levels of potassium too. When insulin dosage is proper, effects on potassium are unremarkable. However, if insulin dosage is excessive, clinically significant hypokalemia can result. Effects on the heart are of greatest concern: Hypokalemia can reduce contractility and can cause potentially fatal dysrhythmias.

Lipohypertrophy. Lipohypertrophy (accumulation of subcutaneous fat) can occur when insulin is injected too frequently at the same site. Fat accumulates because insulin stimulates fat synthesis. When use of the site is discontinued, excess fat is eventually lost. Lipohypertrophy can be minimized through systematic rotation of injection sites.

Allergic Reactions. Rarely, patients experience systemic allergic responses. These reactions develop rapidly, and are characterized by the widespread appearance of red and intensely itchy welts. Breathing difficulty may develop. If severe allergy develops in a patient who nonetheless must continue insulin use, a desensitization procedure can be performed. This process entails giving small initial doses of human insulin, followed by a series of progressively larger doses.

Drug Interactions

Hypoglycemic Agents. Drugs that lower blood glucose levels can intensify hypoglycemia induced by insulin. Among these drugs are *sulfonylureas*, *glinides*, *beta-adrenergic blocking agents*, and *alcohol* (used acutely or long term in excessive doses). When these drugs are combined with insulin, special care must be taken to ensure as best as possible that blood glucose does not fall too low.

Hyperglycemic Agents. Drugs that raise blood glucose (eg, *thiazide diuretics*, *glucocorticoids*, *sympathomimetics*) can counteract the desired effects of insulin. When these agents are combined with insulin, insulin dosage may need to be increased.

Beta-Adrenergic Blocking Agents. Beta blockers can delay awareness of and response to hypoglycemia by masking signs that are associated with stimulation of the sympathetic nervous system (eg, tachycardia, palpitations) that hypoglycemia normally causes. Furthermore, since beta blockade impairs glycogenolysis, and since glycogenolysis is one means by which the body can respond to and counteract a fall in blood glucose, beta blockers can make insulin-induced hypoglycemia even worse.

DRUGS FOR TYPE 2 DIABETES

The drugs for type 2 diabetes fall into two major groups: oral drugs and injectable drugs. Their actions and major adverse effects are summarized in Table 57-11.

TABLE 57-11 ■ Drugs for Type 2 Diabetes

Class and Specific Agents	Actions	Major Adverse Effects
ORAL DRUGS		
Biguanide		
Metformin [Fortamet, Glucophage, Glumetza, Riomet]	Decreases glucose production by the liver, increases tissue response to insulin	GI symptoms: decreased appetite, nausea, diarrhea Lactic acidosis (rarely)
Second-Generation Sulfonylureas		
Glimepiride [Amaryl] Glipizide [Glucotrol] Glyburide* [DiaBeta, Glynase PresTab]	Promote insulin secretion by the pancreas; may also increase tissue response to insulin	Hypoglycemia
Thiazolidinediones (Glitazones)		
Pioglitazone [Actos] Rosiglitazone† [Avandia]	Decrease insulin resistance, and thereby increase glucose uptake by muscle and adipose tissue, and decrease glucose production by the liver	Hypoglycemia, but only in the presence of excessive insulin Heart failure Bladder cancer Fractures (in women) Ovulation, and hence possible unintended pregnancy
Glinides		
Nateglinide [Starlix] Repaglinide [Prandin, GlucoNorm♦]	Promote insulin secretion by the pancreas	Hypoglycemia
Alpha-Glucosidase Inhibitors		
Acarbose [Precose, Glucobay♦] Miglitol [Glyset]	Inhibit carbohydrate digestion and absorption, thereby decreasing the postprandial rise in blood glucose	GI symptoms: flatulence, cramps, abdominal distention, borborygmus
Gliptins (DPP-4 Inhibitors)		
Linagliptin [Tradjenta] Saxagliptin [Onglyza] Sitagliptin [Januvia]	Enhance the activity of incretins (by inhibiting their breakdown by DPP-4), and thereby increase insulin release, reduce glucagon release, and decrease hepatic glucose production	Pancreatitis Hypersensitivity reactions
Dopamine Agonist		
Bromocriptine [Cycloset]	Activates dopamine receptors in the CNS. How it improves glycemic control is unknown	Orthostatic hypotension Exacerbation of psychosis
INJECTED DRUGS		
Incretin Mimetics		
Exenatide [Byetta] Liraglutide [Victoza]	These drugs lower blood glucose by slowing gastric emptying, stimulating glucose-dependent insulin release, suppressing postprandial glucagon release, and reducing appetite	Hypoglycemia GI symptoms: nausea, vomiting, diarrhea Pancreatitis Renal insufficiency Thyroid cancer? (liraglutide only)
Amylin Mimetics		
Pramlintide [Symlin]	Delays gastric emptying and suppresses glucagon secretion, and thereby decreases the postprandial rise in glucose	Hypoglycemia Nausea Injection-site reactions

*Commonly known as *glibenclamide* outside the United States.

†Owing to a risk of sudden cardiac death, rosiglitazone is available only through a restricted distribution program.

ORAL DRUGS

There are six main families of oral antidiabetic drugs: biguanides, sulfonylureas, glinides (meglitinides), thiazolidinediones (glitazones), alpha-glucosidase inhibitors, and gliptins. These agents are used only for type 2 diabetes. In the past, the oral agents were used only after a program of diet modifica-

tion and exercise had failed to yield glycemic control. Today, one oral agent—metformin—is usually started immediately after type 2 diabetes has been diagnosed.

For two reasons, the oral agents are not used for patients with type 1 diabetes. First, since all of these patients must use insulin, there's no need for additional antidiabetic medication. And second, even if additional medication were needed, most

of the oral agents couldn't help much. Why? Because, with the exception of the alpha-glucosidase inhibitors, the oral agents work, at least in part, by increasing insulin release and/or reducing insulin resistance. In either case, insulin is needed for full benefits of these drugs, and type 1 patients don't have any.

The oral agents work in two basic ways. Some of them—namely the sulfonylureas, glitazones, and glinides—actively drive blood glucose down. Others—notably metformin (a biguanide) and the alpha-glucosidase inhibitors—don't drive blood glucose down; rather, they simply modulate the rise in glucose that happens after a meal. This distinction is not just academic: If taken when blood glucose is normal or low, agents that drive glucose down can cause *hypoglycemia*. Hypoglycemia is not a risk with the drugs that simply impair the postprandial rise in blood glucose.

A note on nomenclature: Traditionally, the oral drugs for diabetes have been referred to as *oral hypoglycemic drugs* or *oral hypoglycemics*. However, this description is inaccurate and hence is not used in this book. Why is it inaccurate? Because, as discussed immediately above, only some of these drugs drive glucose levels down, and hence only some deserve to be called *hypoglycemics*. A better name for these drugs is *oral antidiabetic agents*. Why? Because this name applies to all drugs in the group, not just the ones that actively reduce levels of glucose.

Biguanides: Metformin

Metformin [Glucophage, Glucophage XR, Fortamet, Glumetza, Riomet], classified chemically as a biguanide, is the drug of choice for initial therapy in most patients with type 2 diabetes. Typically, metformin is started immediately after the type 2 diabetes is diagnosed. The most common side effects are GI disturbances. Lactic acidosis, a potentially fatal complication, is rare.

Mechanism of Action. Metformin lowers blood glucose and improves glucose tolerance in three ways. First, it inhibits glucose production in the liver. Second, it reduces (slightly) glucose absorption in the gut. And third, it sensitizes insulin receptors in target tissues (fat and skeletal muscle), and thereby increases glucose uptake in response to whatever insulin may be available. In contrast to the sulfonylureas (see below), metformin does not stimulate insulin release from the pancreas. As a result, metformin does not actively drive blood glucose levels down, and hence poses little if any added risk of hypoglycemia when used alone.

Pharmacokinetics. Following oral dosing, metformin is slowly absorbed from the small intestine. Of particular interest, metformin is not metabolized. Rather it is excreted unchanged by the kidneys. Hence, in the event of renal impairment, metformin can accumulate to toxic levels.

Therapeutic Uses. Glycemic Control. Metformin is used to lower blood sugar in patients with type 2 diabetes. In the past, treatment was reserved for patients who had not responded adequately to a program of diet modification and exercise. Today, however, treatment is usually begun as soon as type 2 diabetes is diagnosed.

Metformin may be used alone or in combination with a sulfonylurea, a glitazone, or exenatide. When used alone, metformin lowers basal and postprandial blood glucose levels. When metformin is combined with a sulfonylurea, a glitazone, or exenatide, the combination lowers blood sugar

more effectively than either drug alone—which is to be expected because they act by different mechanisms.

Metformin is well suited for patients who tend to skip meals. Here's why. When meals are skipped, blood sugar can drop below a level that is healthy. Because metformin does not lower blood glucose any further, it won't make the situation any worse. In contrast, drugs that actively lower blood glucose, such as the glitazones and sulfonylureas, can drop a normal or slightly low blood glucose into clinically significant hypoglycemia.

Prevention of Type 2 Diabetes. Data from the Diabetes Prevention Program (DPP), a large study sponsored by the National Institutes of Health, indicate that metformin can delay development of type 2 diabetes in high-risk individuals. The DPP enrolled 3234 people ages 25 to 85. All participants had impaired glucose tolerance (as determined by an oral glucose tolerance test) and all were severely overweight. Participants were randomly assigned to one of three protocols: (1) intensive lifestyle changes with the aim of reducing body weight by 7% through moderate exercise (eg, vigorous walking 30 minutes a day 5 days a week) combined with a low-fat diet, (2) treatment with metformin (850 mg twice daily), or (3) treatment with placebo. The results? Metformin reduced the risk of developing type 2 diabetes by 31%. However, benefits were limited primarily to younger patients and to those who were most overweight; the drug was relatively ineffective in older patients and those less overweight. It must be stressed, however, that metformin is not a substitute for diet and exercise. In fact, the DPP showed that lifestyle changes are even more effective than metformin: The combination of moderate exercise plus weight loss (5% to 7% of initial weight) reduced the average risk of type 2 diabetes by 58%. Benefits were greatest (71%) for people over the age of 60.

Gestational Diabetes. For decades, insulin was considered the preferred, if not the only, antidiabetic drug for managing diabetes during pregnancy, whether the mother had type 1 or type 2 diabetes. Recent clinical studies have compared metformin with insulin in pregnant women with type 2 diabetes. Multiple outcomes were assessed, including glycemic control in the mother, and blood glucose and Apgar scores in the neonate. The result? Outcomes with metformin were essentially the same as those with insulin, the traditional agent for managing gestational diabetes—suggesting that metformin may become an acceptable alternative for many women. (Note: The data obtained with metformin do *not* apply to other classes of oral agents, such as the sulfonylureas and glitazones.)

Polycystic Ovary Syndrome (PCOS). PCOS is a combined endocrine/metabolic disorder characterized by androgen excess and insulin resistance. It affects about 5% to 10% of women of reproductive age. Symptoms include irregular periods, anovulation, infertility, acne, and hirsutism. Although not approved for PCOS, metformin can be very helpful. Metformin treatment increases insulin sensitivity and decreases insulin levels, which, through an indirect mechanism, lowers androgen levels. The net result is improved glucose tolerance, improved ovulation, and increased pregnancy rates. PCOS and its management are discussed further in Chapter 63.

Side Effects. The most common side effects are decreased appetite, nausea, and diarrhea. These generally subside over time. However, in 3% to 5% of patients, GI side effects lead to discontinuation of treatment.

Metformin decreases absorption of vitamin B₁₂ and folic acid, and can thereby cause deficiencies of both. Deficiency of B₁₂, in turn, can contribute to peripheral neuropathy, a common long-term consequence of diabetes. However, there is no proof (yet) that metformin actually makes diabetic nephropathy worse. Likewise, there is no current recommendation about prescribing vitamin B₁₂ for patients who are taking the drug. As discussed in Chapter 81, deficiency of folic acid during pregnancy can impair development of the central nervous system, resulting in neural tube defects, which manifest as anencephaly or spina bifida. Nonetheless, metformin appears to be a safe drug for use during pregnancy.

In contrast with sulfonylureas (see below), metformin does not cause weight gain. In fact, patients *lose* an average of 7 to 8 pounds. As a result, metformin is considered a “weight-negative” antidiabetic drug, in contrast with other antidiabetic drugs that tend to increase weight (“weight-positive”). Appetite suppression and weight loss in response to metformin can occur both in the presence and absence of nausea, indicating that reduced food intake because of metformin-induced nausea is not the only reason for weight loss.

Toxicity: Lactic Acidosis. Metformin and other biguanides inhibit mitochondrial oxidation of lactic acid, and can thereby cause lactic acidosis. This condition is a medical emergency and has a mortality rate of about 50%. Fortunately, lactic acidosis is rare (about 3 cases/100,000 patient-years) when metformin is used at recommended doses in patients with good renal function. However, in patients with renal insufficiency, metformin can rapidly accumulate to toxic levels. Accordingly, the drug must never be used by these people. In addition, metformin must be avoided in patients who are prone to increased lactic acid production. Among these are patients with liver disease, severe infection, or a history of lactic acidosis; patients who consume alcohol to excess; and patients with shock and other conditions that can result in hypoxemia.

All patients taking metformin should be informed about early signs of lactic acidosis—hyperventilation, myalgia, malaise, and unusual somnolence—and instructed to report these to the prescriber. Metformin should be withdrawn until lactic acidosis has been ruled out. If lactic acidosis is diagnosed, hemodialysis can correct the condition and remove accumulated metformin.

Because heart failure (HF) can predispose to lactic acidosis, metformin is contraindicated for people with failing hearts. However, in one study, patients with HF who took the drug were *less* likely to die than those who took a sulfonylurea. These data suggest that use of metformin in HF is much safer than previously believed.

Drug Interactions. Alcohol. Like metformin, alcohol can inhibit breakdown of lactic acid, and can thereby intensify lactic acidosis caused by metformin. To minimize risk, patients should avoid consuming alcohol in excess, whether acutely or long term. Discontinuing alcohol entirely would be even safer.

Cimetidine. Cimetidine [Tagamet], a histamine₂ (H₂) blocker used to induce gastric acidity, can increase the risk of lactic acidosis. Accordingly, if an H₂ blocker is indicated, another member of the family should be used, since cimetidine is the only H₂ blocker that poses this risk.

Iodinated Radiocontrast Media. Intravenous radiocontrast media that contain iodine pose a risk of acute renal failure, which could exacerbate metformin-induced lactic acidosis. To reduce risk, patients should discontinue metformin a day or two before elective radiography. Metformin can

then be resumed 48 hours after the procedure, provided lab tests show that renal function is normal.

Preparations, Dosage, and Administration. Metformin is available *alone* in immediate-release (IR) tablets (500, 850, and 1000 mg) as *Glucophage*; in extended-release (ER) tablets (500, 750, and 1000 mg) as *Glucophage XR*, *Fortamet*, and *Glumetza*; and in an oral solution (500 mg/5 mL) as *Riomet*. In addition, the drug is available in several fixed-dose combinations with other drugs for type 2 diabetes mellitus (see below).

With the IR tablets and oral solution, the recommended initial dosage is 500 mg twice daily (taken with the morning and evening meals) or 850 mg once daily, taken with a meal. The usual maintenance dosage is 850 mg twice daily. The maximum dosage is 850 mg 3 times a day (for adults) or 2000 mg/day (for children 10 to 16 years old).

With the ER tablets, dosing is done once daily with the *evening* meal. Why the evening meal? Because this timing may enhance absorption owing to slower GI transit time at night. For previously untreated patients, the initial dosage is 500 mg a day (or 1000 mg once a day using *Fortamet*). For patients already taking metformin, the total daily dosage remains the same; it's simply taken all at once. The maximum daily dosage is 2000 mg (or 2500 mg using *Fortamet*).

Sulfonylureas

The sulfonylureas, introduced in the 1950s, were the first oral antidiabetics available. They work by promoting insulin release, and hence can only be used in type 2 diabetes. The sulfonylureas were a major advance in diabetes therapy: For the first time, some patients could be treated with an oral medication, rather than with daily injections of insulin. The major side effect with these drugs is hypoglycemia.

The sulfonylureas fall into two groups: *first-generation (older) agents* and *second-generation (newer) agents*. Both generations reduce glucose levels to the same extent. How do the generations differ? The second-generation agents are *much more potent* than the first-generation agents, and hence dosages are much lower (as much as 1000 times lower in some cases). More importantly, with the second-generation agents *significant drug-drug interactions are less common*, and the outcomes tend to be milder. Because of these differences, the second-generation agents have largely replaced the first-generation agents in clinical practice.

Six sulfonylureas are available: three first-generation agents and three second-generation agents (Table 57-12). All have similar actions and side effects, and they all share the same application: treatment of type 2 diabetes.

Mechanism of Action. Sulfonylureas act primarily by stimulating the release of insulin from pancreatic islets. If the pancreas is incapable of insulin synthesis, sulfonylureas will be ineffective—which is why they don't work in patients with type 1 diabetes. With prolonged use, sulfonylureas may increase target cell sensitivity to insulin.

How do sulfonylureas promote insulin release? They bind with and thereby block ATP-sensitive potassium channels in the cell membrane. As a result, the membrane depolarizes, thereby permitting influx of calcium, which in turn causes insulin release. The extent of release is glucose dependent, and diminishes when plasma glucose declines.

Therapeutic Use. Sulfonylureas are indicated only for type 2 diabetes. These drugs are of no help to patients with type 1 diabetes. Like all other drugs for type 2 diabetes, the sulfonylureas should be used in conjunction with a program of caloric restriction and exercise. The sulfonylureas may be used alone or together with other antidiabetic drugs.

TABLE 57-12 ■ Sulfonylureas: Time Course and Dosage

Generic Name [Trade Name]	Duration (hr)	Dosage*	Approximate Equivalent Dose (mg/24 hr) [†]
First-Generation Agents[‡]			
Tolbutamide [Orinase]	6-12	<i>Initial:</i> 1-2 gm/day in 1-3 doses <i>Maximum:</i> 2-3 gm/day in 1-3 doses	1000-1500
Tolazamide (generic only)	12-24	<i>Initial:</i> 100-250 mg/day with breakfast <i>Maximum:</i> 0.75-1 gm/day in 2 doses	250-375
Chlorpropamide (generic only)	24-60	<i>Initial:</i> 250 mg/day with breakfast <i>Maximum:</i> 750 mg once a day	250-375
Second-Generation Agents			
Glipizide <i>Immediate release</i> [Glucotrol]	10-24	<i>Initial:</i> 5 mg/day with breakfast <i>Maximum:</i> 40 mg/day in 2 doses	10
<i>Sustained release</i> [Glucotrol XL]	24	<i>Initial:</i> 5 mg/day with breakfast <i>Maximum:</i> 20 mg/day with breakfast	10
Glyburide <i>Nonmicronized</i> [DiaBeta]	16-24	<i>Initial:</i> 2.5-5 mg day with breakfast <i>Maximum:</i> 20 mg/day in 1 or 2 doses	5
<i>Micronized</i> [Glynase PresTab]	12-24	<i>Initial:</i> 1.5-3 mg/day with breakfast <i>Maximum:</i> 12 mg/day in 1 or 2 doses	3
Glimepiride [Amaryl]	24	<i>Initial:</i> 1-2 mg/day with breakfast <i>Maximum:</i> 8 mg/day with breakfast	2

*Elderly patients should use a smaller dose than those noted here.

[†]These values reflect differences in potency, and can be used to estimate what dose to use when switching from one sulfonylurea to another.

[‡]The first-generation agents are used only rarely.

Adverse Effects. Hypoglycemia. Sulfonylureas cause a dose-dependent reduction in blood glucose, and can thereby cause hypoglycemia. Importantly, regardless of what the glucose level is—high, normal, or low—sulfonylureas will make it go lower. If the level is high, reducing it will be therapeutic. However, if the level is normal, reducing it will cause mild hypoglycemia. And if the level is already low, reducing it can cause severe hypoglycemia.

Although sulfonylurea-induced hypoglycemia is usually mild, severe and even fatal cases have occurred. Hypoglycemia is sometimes persistent, requiring infusion of dextrose for several days. Hypoglycemic reactions are more likely in patients with kidney or liver dysfunction. Why? Because sulfonylureas are eliminated by hepatic metabolism and renal excretion, and hence may accumulate to dangerous levels when liver or kidney function is impaired. If signs of hypoglycemia develop (fatigue, excessive hunger, profuse sweating, palpitations), the prescriber should be notified.

Cardiovascular Toxicity. There has been controversy regarding the possibility of adverse cardiovascular reactions to oral antidiabetic drugs. In 1970, the large multicenter University Group Diabetes Program (UGDP) published results indicating that tolbutamide (the first sulfonylurea available), was linked to an increased risk of mortality from sudden cardiac death. In the UGDP study, cardiac mortality was 2.5 times greater among subjects treated with a combination of diet plus tolbutamide than among control subjects who received diet therapy alone. The UGDP study has been criticized on several

grounds, including design, patient selection, dosing, and compliance. Subsequent clinical trials, including the UKPDS, failed to confirm the conclusions of the UGDP report. The American Diabetes Association, which initially endorsed the UGDP study, has since withdrawn its support. Nonetheless, the risk of sudden cardiac death remains a concern—albeit small—and hence appropriate caution should be exercised.

Use in Pregnancy and Lactation. Sulfonylureas should be avoided during pregnancy. Although adequate studies in humans are lacking, sulfonylureas are teratogenic in animals. Furthermore, since sulfonylurea therapy during pregnancy often fails to provide good glycemic control, and since even mild hyperglycemia may be hazardous to the fetus, insulin is generally preferred for managing the diabetic pregnancy.

It is especially important to avoid sulfonylureas near term. Newborns exposed to these agents at the time of delivery have experienced severe hypoglycemia lasting as long as 4 to 10 days. Hence, if a sulfonylurea has been taken during pregnancy, it should be discontinued at least 48 hours prior to the anticipated time of delivery.

Sulfonylureas should not be taken by women who are nursing. These drugs are excreted into breast milk, posing a risk of hypoglycemia to the infant. If a woman wishes to breast-feed, she should substitute insulin for the sulfonylurea.

Drug Interactions. Alcohol. When alcohol is combined with a sulfonylurea (especially a first-generation agent), a disulfiram-like reaction may occur. This syndrome includes flushing, palpitations, and nausea. Disulfiram reactions are discussed fully in Chapter 38. Also, alcohol can potentiate the

hypoglycemic effects of sulfonylureas. Accordingly, patients using the drug must be warned against alcohol consumption.

Drugs That Can Intensify Hypoglycemia. A variety of drugs, acting by diverse mechanisms, can intensify hypoglycemic responses to most sulfonylureas. Included are *nonsteroidal anti-inflammatory drugs*, *sulfonamide antibiotics*, *alcohol* (used acutely in large amounts), and *cimetidine*. Caution must be exercised when a sulfonylurea is used in combination with these drugs.

Beta-Adrenergic Blocking Agents. Beta blockers can diminish the benefits of sulfonylureas by suppressing insulin release. (Recall that activation of beta receptors is one way to promote insulin release.) In addition, because beta blockers can mask sympathetic responses (primarily tachycardia) to declining blood glucose, use of beta blockers can delay awareness of sulfonylurea-induced hypoglycemia.

Preparations, Dosage, and Administration. This information is presented in Table 57-12.

Thiazolidinediones (Glitazones)

The thiazolidinediones, also known as *glitazones* or simply *TZDs*, reduce glucose levels primarily by decreasing insulin resistance. These drugs are not related chemically or functionally to sulfonylureas or biguanides. Their only indication is type 2 diabetes, mainly as an add-on to metformin.

The glitazones have a troubled past and an uncertain future. Troglitazone [Rezulin] was the first to receive FDA approval, followed by rosiglitazone [Avandia] and pioglitazone [Actos]. Soon after its approval, troglitazone was withdrawn, owing to a high incidence of severe liver damage, which proved fatal in some patients. After that, rosiglitazone came under scrutiny: The drug is associated with myocardial infarction and sudden cardiac death, and hence is available only under a restricted access program. That leaves pioglitazone as the last TZD on the market. Accordingly, it will be the focus of our discussion about these drugs.

Pioglitazone

Actions and Use. Pioglitazone [Actos] reduces insulin resistance, and may also decrease glucose production. The underlying mechanism is activation of a specific receptor type in the cell nucleus, known as the *peroxisome proliferator-activated receptor gamma* (PPAR gamma). By activating PPAR gamma, pioglitazone turns on insulin-responsive genes that help regulate carbohydrate and lipid metabolism. As a result, cellular responses to insulin are increased, thereby promoting (mainly) increased glucose uptake by skeletal muscle and adipose cells, and (partly) decreased glucose production by the liver. Since pioglitazone enhances responses to insulin, insulin must be present for the drug to work.

Pioglitazone is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The drug can be used as monotherapy, but is usually combined with metformin, a sulfonylurea, and/or supplemental insulin. Because insulin is required for pioglitazone to work, the drug is not effective in patients with type 1 diabetes, and must not be used by these people.

Pharmacokinetics. Pioglitazone is well absorbed from the GI tract. Blood levels peak about 2 hours after dosing. Food slows absorption (blood levels peak 3 to 4 hours after dosing), but does not reduce the extent of absorption. Pioglitazone undergoes conversion to active and inactive metabolites, mainly by CYP2C8 (the 2C8 isozyme of cytochrome P450). Metabolites and parent drug are excreted in the feces (mainly) and urine. The half-lives of pioglitazone

and its metabolites are 3 to 7 hours and 16 to 24 hours, respectively.

Adverse Effects. Pioglitazone is generally well tolerated. The most common reactions are upper respiratory tract infection (13%), headache (9%), sinusitis (6%), and myalgia (5%).

The greatest concern is *heart failure* secondary to renal retention of fluid. For most patients, fluid retention is not clinically significant. However, for patients with heart failure, especially severe or uncompensated heart failure, increased fluid retention can make heart failure worse. Accordingly, pioglitazone should be used with caution in patients with *mild* heart failure, and should be avoided by those with *severe* failure. Patients should be informed about signs of heart failure (dyspnea, edema, fatigue, rapid weight gain), and instructed to consult the prescriber immediately if these develop. If heart failure is diagnosed, pioglitazone should be discontinued or used in reduced dosage. Unlike rosiglitazone, pioglitazone has not been associated with myocardial infarction.

Pioglitazone poses a risk of *hypoglycemia*, especially when combined with insulin or with drugs that inhibit pioglitazone metabolism. Use these combinations with caution.

Pioglitazone can cause ovulation in anovulatory premenopausal women, thereby posing a risk of unintended pregnancy. This effect has not been studied in clinical trials, and hence the incidence is unknown. Women should be informed about the potential for ovulation, and educated about contraceptive options.

Postmarketing data indicate an increased risk of *bladder cancer*, associated mainly with long-term, high-dose therapy. Package labeling warns against using pioglitazone in patients with active bladder cancer or with a history of bladder cancer. Patients should be informed about signs of bladder cancer (eg, blood in urine, worsening urinary urgency, painful urination), and instructed to contact their prescriber if these develop.

Pioglitazone appears to increase the risk of *fractures* in women, but not in men. Most fractures have occurred in the foot, hand, or upper arm, not the spine. Risk appears greater with long-term, high-dose therapy. Fracture risk can be reduced through measures to maintain bone health. Among these are exercise, assuring adequate intake of calcium and vitamin D, and, if indicated, use of drugs for osteoporosis (see Chapter 75).

Pioglitazone is related to troglitazone (a highly hepatotoxic TZD), and hence there is concern that pioglitazone might be *hepatotoxic* too. However, although pioglitazone has been associated with rare cases of hepatic failure, a causal relationship has not been established. Nonetheless, serum alanine aminotransferase (ALT), a marker of liver function, should be measured at baseline and periodically thereafter (eg, every 3 to 6 months). If ALT levels rise to more than 3 times the upper limit of normal, or if jaundice develops, pioglitazone should be withdrawn. Patients should be informed about symptoms of liver injury (nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, jaundice) and instructed to notify the prescriber if these develop.

Pioglitazone has mixed effects on *plasma lipids*. One effect—elevation of LDL cholesterol—increases cardiovascular risk. Two other effects—elevation of HDL cholesterol and reduction of triglycerides—reduce cardiovascular risk. The net effect appears to be either (1) a reduction in cardiovascular risk or, at worst, (2) no increase in cardiovascular risk.

Drug Interactions. Like pioglitazone, insulin promotes fluid retention, and hence the combination poses an increased risk of heart failure. Accordingly, using pioglitazone and insulin together should be done with caution.

Drugs that induce or inhibit CYP2C8 can alter pioglitazone levels, and can thereby alter the glycemic response. Strong inhibitors of CYP2C8—such as atorvastatin (our most widely used cholesterol-lowering drug) and ketoconazole (an antifungal drug)—can increase pioglitazone levels and prolong its half-life, necessitating a reduction in pioglitazone dosage. Conversely, strong inducers of CYP2C8—such as rifampin (a drug for tuberculosis) and cimetidine (a gastric acid suppressant)—can reduce pioglitazone levels and shorten its half-life, necessitating an increase in pioglitazone dosage.

Preparations, Dosage, and Administration. Pioglitazone [Actos] is available in 15-, 30-, and 45-mg tablets. The initial dosage for monotherapy is 15 or 30 mg once a day, taken with or without food. The maximum dosage is 45 mg once a day (for patients not using insulin), but only 30 mg once a day (for patients who are using insulin).

Rosiglitazone

Rosiglitazone [Avandia], our featured glitazone in the previous edition of this book, is used only rarely today. Why? Because we now know that it increases the risk of myocardial infarction and sudden cardiac death. Because of this risk, rosiglitazone is now indicated only for patients with type 2 diabetes who are either (1) already taking the drug or (2) not already taking it but cannot achieve glycemic control with any other antidiabetic agents. Rosiglitazone has been withdrawn in Europe and, in the United States, is available only through a restricted distribution program, known as the AVANDIA-Rosiglitazone Medicines Access Program. Among other things, the program requires that (1) the risk of cardiovascular events be explained thoroughly to the patient, (2) the patient sign an informed consent form, and (3) prescriptions be filled only by mail order through a certified pharmacy.

Meglitinides (Glinides)

Meglitinides—also known as *glinides*—are antidiabetic agents that have the same mechanism as the sulfonylureas: stimulation of pancreatic insulin release. Only two glinides are available: repaglinide and nateglinide.

Repaglinide

Actions and Uses. Like the sulfonylureas, repaglinide [Prandin, GlucoNorm[◆]] blocks ATP-sensitive potassium channels on pancreatic beta cells, and thereby facilitates calcium influx, which leads to increased insulin release. In clinical trials, repaglinide was about as effective as glyburide and glipizide (second-generation sulfonylureas). Over time, repaglinide can lower A1c by about 1.7%. The drug is approved for type 2 diabetes only. Because repaglinide has the same mechanism as the sulfonylureas, patients who do not respond to sulfonylureas will not respond to this agent either. Repaglinide is approved for monotherapy or combined therapy with metformin or a glitazone.

Pharmacokinetics. Repaglinide undergoes rapid absorption followed by rapid elimination. Blood levels peak within 1 hour of oral dosing and return to baseline about 4 hours later. Elimination results from hepatic metabolism followed by biliary excretion. The drug's half-life is only 1 hour. Blood levels of insulin rise and fall in parallel with levels of repaglinide—and since levels of repaglinide rise and fall quickly, so do blood levels of insulin.

Adverse Effects. Repaglinide is generally well tolerated. The only significant adverse effect is *hypoglycemia*. In patients with liver dysfunction, metabolism of repaglinide may

be slowed, and hence the risk of hypoglycemia may be increased. Because of possible hypoglycemia, it is imperative that patients eat no later than 30 minutes after taking the drug.

Drug Interactions. Gemfibrozil [Lopid], a drug used to lower triglyceride levels, can inhibit the metabolism of repaglinide, thereby causing its level to rise. Hypoglycemia can result. If possible, the combination should be avoided. Fenofibrate can be used instead of gemfibrozil.

Preparations, Dosage, and Administration. Repaglinide [Prandin, GlucoNorm[◆]] is available in 0.5-, 1-, and 2-mg tablets. Administration must always be associated with a meal. For patients who have not used another oral antidiabetic drug, the initial dosage is 0.5 mg taken 0 to 30 minutes before each meal. Patients who have used another oral antidiabetic drug may take 1 or 2 mg before each meal. The maximum daily dose is 16 mg (4 mg with each meal for up to four meals).

Nateglinide

Basic Pharmacology and Therapeutic Use. The pharmacology of nateglinide [Starlix] is nearly identical to that of repaglinide. Both drugs have the same indication: treatment of type 2 diabetes, either as monotherapy or the same mechanism combined with metformin or a glitazone. They also have the same mechanism of action (promotion of insulin release), and major adverse effect (hypoglycemia), and perhaps the same major drug interaction (elevation of their blood level by gemfibrozil). The two drugs differ primarily with respect to time course. Specifically, nateglinide has a slightly faster onset (30 minutes vs. 1 hour) and a significantly shorter duration (2 hours vs. 4 hours). Because of its more rapid onset, nateglinide may be better suited for controlling the postprandial rise in glucose. However, because of its shorter duration, nateglinide is less effective than repaglinide (or metformin or a sulfonylurea) for controlling fasting glucose. Because the glinides and sulfonylureas have the same mechanism of action, nateglinide, like repaglinide, will not work in patients who have not responded to a sulfonylurea. Nateglinide undergoes extensive metabolism by cytochrome P450 enzymes, followed by rapid and complete excretion, primarily in the urine.

Preparations, Dosage, and Administration. Nateglinide [Starlix] is available in 60- and 120-mg tablets. The initial dosage is 120 mg 3 times a day taken 0 to 30 minutes before a meal. For patients with A1c concentrations close to the target value, the initial dosage is lower: 60 mg 3 times a day taken 0 to 30 minutes before a meal. Please note that dosing must always be associated with a meal. Otherwise, nateglinide-induced insulin release could cause hypoglycemia. Nateglinide costs a little more than repaglinide, and much more than sulfonylureas.

Alpha-Glucosidase Inhibitors

The alpha-glucosidase inhibitors—acarbose and miglitol—act in the intestine to delay absorption of carbohydrates. These drugs are indicated for type 2 diabetes.

Acarbose

Mechanism of Action. Acarbose [Precose, Glucobay[◆]] delays absorption of dietary carbohydrates, and thereby reduces the rise in blood glucose after a meal. In order to be absorbed, oligosaccharides and complex carbohydrates must be broken down to monosaccharides by alpha-glucosidase, an enzyme located on the brush border of cells that line the intestine. Acarbose inhibits this enzyme, and thereby slows digestion of carbohydrates, which reduces the postprandial rise in blood glucose.

Of note, the alpha-glucosidase inhibitors are the only oral antidiabetic agents whose effects do not depend at all on the presence of insulin. All of the other oral agents act, at least in part, by increasing insulin secretion and/or decreasing insulin resistance.

Therapeutic Use. Acarbose is indicated for patients with type 2 diabetes in conjunction with a program of diet modification and exercise. The drug may be used alone or in combination

tion with insulin, metformin, or a sulfonylurea. In clinical trials, 24 weeks of therapy with acarbose alone reduced mean peak postprandial glucose levels by 57 mg/dL, compared with 71 mg/dL for tolbutamide (a sulfonylurea) alone and 85 mg/dL for acarbose plus tolbutamide. In addition to lowering glucose levels after meals, acarbose lowers A1c levels, indicating an overall improvement in glycemic control.

Pharmacokinetics. Acarbose is administered by mouth, and only 2% is absorbed as active drug. As a result, systemic effects are minimal. Because acarbose acts locally in the intestine, lack of absorption is considered beneficial. In the gut, acarbose is converted to inactive products by bacteria and digestive enzymes.

Adverse Effects and Interactions. Acarbose frequently causes flatulence, cramps, abdominal distention, borborygmi (rumbling bowel sounds), and diarrhea. These responses result from bacterial fermentation of unabsorbed carbohydrates in the colon. In addition to its GI effects, acarbose can decrease absorption of iron, thereby posing a risk of anemia.

Hypoglycemia does not occur with acarbose alone, but may develop when acarbose is combined with insulin or a sulfonylurea. When hypoglycemia develops, sucrose cannot be used for oral therapy. Why? Because acarbose will impede its hydrolysis and thereby delay absorption. Accordingly, in patients taking acarbose, oral therapy of hypoglycemia must be accomplished with glucose itself.

Long-term, high-dose therapy may cause liver dysfunction. Asymptomatic elevation of plasma transaminases (which come from damaged liver cells) occurs in about 15% of patients. However, overt jaundice is rare. Liver function tests should be monitored every 3 months for the first year, and periodically thereafter. Liver dysfunction reverses when acarbose is discontinued.

The combination of metformin and acarbose should probably be avoided. Both drugs cause significant GI side effects, and hence the combination could be very unpleasant. Furthermore, acarbose decreases metformin absorption.

Preparations, Dosage, and Administration. Acarbose [Precose, Glucobay] is available in tablets (25, 50, and 100 mg) to be taken with the first bite of main meals. The recommended initial dosage is 25 mg 3 times a day. Depending on tolerability and postprandial blood glucose levels, the dosage may be increased at 4- to 8-week intervals. The maximum dosage is 50 mg 3 times a day (for patients under 60 kg) and 100 mg 3 times a day (for patients over 60 kg).

Miglitol

Miglitol [Glyset] is the second alpha-glucosidase inhibitor approved in the United States. Like acarbose, miglitol delays conversion of oligosaccharides and complex carbohydrates to glucose and other monosaccharides, and thereby reduces the postprandial rise in blood glucose. In clinical trials, the drug was especially effective among Latinos and African Americans. Hypoglycemia does not occur with miglitol monotherapy, but may occur if the drug is combined with insulin or a sulfonylurea. Like acarbose, miglitol causes flatulence, abdominal discomfort, and other GI effects. In contrast to acarbose, miglitol has not been associated with liver dysfunction. As with acarbose therapy, oral sucrose cannot be used to treat hypoglycemia. Rather, oral glucose must be given. Miglitol is available in 25-, 50-, and 100-mg tablets. The initial dosage is 25 mg 3 times daily before meals. The maintenance dosage is 50 or 100 mg 3 times a day.

Gliptins (DPP-4 Inhibitors)

Drugs in this family promote glycemic control by enhancing the actions of incretin hormones. Reduction in A1c are modest. Hypoglycemia is uncommon when these drugs are used

alone. Pancreatitis and severe hypersensitivity reactions occur rarely.

Currently, the American Diabetes Association considers the gliptins to be third-line drugs for diabetes. Accordingly, they should be used only after preferred drugs (eg, metformin plus a sulfonylurea) have failed to provide adequate glycemic control. When a gliptin is added to the regimen, the resulting decrease in A1c is about 0.7%. However, for some patients, even this small improvement can be clinically significant.

Sitagliptin

Mechanism of Action. Sitagliptin [Januvia] enhances the actions of *incretin hormones*, endogenous compounds that (1) stimulate glucose-dependent release of insulin and (2) suppress postprandial release of glucagon (a hormone that decreases glucose production in the liver). Both actions help keep blood glucose from climbing too high. How does sitagliptin boost incretin actions? It inhibits dipeptidyl peptidase 4 (DPP-4), an enzyme that inactivates the incretin hormones. As discussed below, another drug—exenatide—also boosts incretin actions, but by a different mechanism: rather than preventing incretin breakdown, it mimics incretin actions.

Therapeutic Use. Sitagliptin is indicated for type 2 diabetes, either as monotherapy or combined with another anti-diabetic drug (eg, metformin, glimepiride, or a glitazone). Since benefits are largely dependent on insulin, the drug will not work in patients with type 1 diabetes. Like all the other agents for managing diabetes, sitagliptin should be used as an adjunct to diet and exercise. As noted above, sitagliptin is considered a third-line drug for diabetes.

Pharmacokinetics. Sitagliptin undergoes rapid and nearly complete absorption, both in the presence and absence of food. Blood levels peak about 1 to 4 hours after dosing. Most of the drug is excreted unchanged in the urine. The elimination half-life is about 12 hours.

Adverse Effects and Interactions. Sitagliptin is generally well tolerated. In clinical trials, the most common side effects were upper respiratory tract infection (6.3%), headache (5.1%), and inflammation of the nasal passages and throat (5.2%)—rates similar to those seen with placebo. The incidence of hypoglycemia was about 1.2%, compared with 0.9% with placebo—again a nonsignificant difference.

Rarely, patients have developed pancreatitis, including fatal hemorrhagic or necrotizing pancreatitis. Patients should be informed about signs and symptoms of pancreatitis (eg, severe and persistent abdominal pain, with or without vomiting) and instructed to stop sitagliptin immediately. If pancreatitis is confirmed, sitagliptin should not be resumed. We don't know if patients with a history of pancreatitis are at increased risk.

There have been postmarketing reports of serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson syndrome. However, a causal relationship has not been established. Nonetheless, if a hypersensitivity reaction is suspected, sitagliptin should be discontinued.

Sitagliptin has no known clinically relevant drug interactions, and no contraindications, including pregnancy.

Preparations, Dosage, and Administration. Sitagliptin [Januvia] is supplied in film-coated tablets (25, 50, and 100 mg). The usual dosage is 100 mg once daily, taken with or without food. Because sitagliptin is eliminated primarily by renal excretion, dosages should be reduced in patients with renal impairment, as indicated by reduced creatinine clearance. Dosage

should be reduced to 50 mg once daily (in moderate renal disease) and 25 mg once daily (in severe renal disease).

Two fixed-dose combinations—sitagliptin/metformin [Janumet] and sitagliptin/simvastatin [Juvissync]—are discussed below.

Saxagliptin

Actions and Therapeutic Use. Like sitagliptin, saxagliptin [Onglyza] is an incretin enhancer indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Unfortunately, reductions in A1c are modest. Saxagliptin may be used as monotherapy or combined with other antidiabetic agents. In general, the drug should be used only after treatment with preferred agents has failed.

Pharmacokinetics. Saxagliptin is well absorbed, both in the presence and absence of food. Plasma levels peak about 2 hours after dosing. Saxagliptin undergoes conversion to an active metabolite by CYP3A4/5 (the 3A4/5 isozyme of cytochrome P450). Parent drug and metabolite are excreted in the urine (75%) and feces (22%). To avoid toxicity, dosage must be reduced in patients taking strong CYP3A4/5 inhibitors (eg, clarithromycin, ketoconazole, nefazodone, nelfinavir, ritonavir) and in those with significant renal impairment.

Adverse Effects. In clinical trials, the most common adverse effects were upper respiratory infection, urinary tract infection, and headache. Saxagliptin can intensify hypoglycemia caused by a sulfonylurea, but causes little or no hypoglycemia when used alone. Like sitagliptin, saxagliptin has been associated with rare cases of pancreatitis and severe hypersensitivity reactions. If symptoms of either develop, saxagliptin should be withdrawn.

Preparations, Dosage, and Administration. Saxagliptin [Onglyza] is supplied in 2.5- and 5-mg tablets for dosing once daily without regard to meals. The usual daily dosage is 5 mg. In patients with mild-to-moderate renal impairment, and in those taking a strong inhibitor of CYP3A4/5, dosage should be reduced to 2.5 mg/day.

Linagliptin

Actions and Therapeutic Use. Linagliptin [Tradjenta], approved in 2011, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. As with other gliptins, benefits, which are modest, derive from preserving incretins through inhibition of DPP-4. Like other gliptins, linagliptin should be reserved for patients who have not responded adequately to more traditional antidiabetic drugs.

Pharmacokinetics. About 30% of each dose is absorbed, both in the presence and absence of food. Plasma levels peak 1.5 hours after dosing. Linagliptin undergoes minimal metabolism. Most of the drug (90%) is excreted unchanged—80% in the feces and 5% in the urine. The effective half-life is 12 hours.

Adverse Effects. Linagliptin is generally well tolerated. The drug has caused hypoglycemia when combined with metformin plus a sulfonylurea, but not when used alone or when combined with just metformin or pioglitazone. Like sitagliptin and saxagliptin, linagliptin has been associated with rare cases of pancreatitis and hypersensitivity reactions. If either of these develop, linagliptin should be withdrawn.

Drug Interactions. Linagliptin is a substrate for P-glycoprotein, a transporter that promotes excretion of linagliptin and other drugs. In theory, drugs that induce P-glycoprotein could reduce levels of linagliptin. Accordingly, the manufacturer recommends that linagliptin not be used with rifampin and other P-glycoprotein inducers.

Preparations, Dosage, and Administration. Linagliptin [Tradjenta] is supplied as 5-mg tablets. The dosage is 5 mg once a day, taken without regard to meals. Unlike dosing with saxagliptin or sitagliptin, dosage needn't be reduced in patients with renal impairment.

Colesevelam

Colesevelam [Welchol] is best known as a bile-acid sequestrant used to lower plasma cholesterol (see Chapter 50). However, the drug can also help lower blood glucose. Accordingly, in 2008, the FDA approved colesevelam to treat type 2 diabetes. Since many patients with diabetes also have high cholesterol, a drug with the potential to treat both disorders is welcome. The pharmacology of colesevelam is discussed at length in Chapter 50.

Bromocriptine

Bromocriptine, marketed as *Cycloset*, is now approved as an adjunct to diet and exercise to treat type 2 diabetes. The same drug, marketed as *Parlodel*, has been available for years to treat Parkinson's disease (see Chapter 21) and hyperprolactinemia (see Chapter 63). In patients with diabetes, bromocriptine

may be used as monotherapy or combined with metformin, a sulfonylurea, or other oral antidiabetic drugs. Combined use with insulin has not been studied. Unfortunately, benefits in diabetes are modest: The typical reduction in A1c is only 0.5%.

How does bromocriptine improve glycemic control? The mechanism is unclear. We do know that bromocriptine is a dopamine agonist that can activate dopamine receptors in the brain. By activating these receptors in the hypothalamus, the drug may reverse an abnormal hypothalamic drive that raises plasma levels of glucose, triglycerides, and free fatty acids in insulin-resistant patients.

We also know that, by activating these receptors, bromocriptine can reverse circadian rhythms in people with type 2 diabetes. This action, in turn, may reverse some of the metabolic changes associated with insulin resistance.

Principal adverse effects are nausea, drowsiness, and orthostatic hypotension, which can cause dizziness and fainting. Bromocriptine can also exacerbate psychoses. Of note, the drug appears devoid of cardiovascular toxicity.

For treatment of diabetes, bromocriptine [Cycloset] is available in 0.8-mg tablets, which should be taken with food to decrease GI side effects. Dosing is done once daily, within 2 hours of waking in the morning. The daily dosage is 0.8 mg initially, and then increased by 0.8 mg each week until the maximal dose is reached (4.8 mg) or until side effects become intolerable.

Dapagliflozin

Dapagliflozin is an investigational first-in-class inhibitor of *sodium-glucose transport protein* (SGLT), the kidney enzyme responsible for tubular reuptake of filtered glucose. By inhibiting SGLT, dapagliflozin suppresses glucose reuptake from tubular urine, and thereby increases urinary glucose excretion. As result, blood levels of glucose decline. One caveat: the drug does not work well in patients with moderate-to-severe renal impairment. Dapagliflozin has been associated with an increased risk of urinary tract infections, probably because glucose-rich urine is a good medium for bacteria growth. There is some concern about increased risk of breast or bladder cancer, but so far the risk appears to be low.

Combination Products

Many patients with type 2 diabetes take two different oral drugs, often metformin combined with a second-generation sulfonylurea. Once the efficacy and safety of the regimen has been established by taking separate pills, we can simplify dosing by switching to a combination product that has the same amounts of the same drugs. Keep in mind, however, that combination products have drawbacks. First, they are more expensive than taking the components separately. And second, they limit dosing flexibility. The ten available combination products are discussed below. Note that seven of these contain *metformin*, reflecting the importance of metformin in type 2 diabetes management.

Metformin/Glyburide [Glucovance]

Metformin (a biguanide) and glyburide (a sulfonylurea) are available in a combination sold as *Glucovance*. Glyburide acts primarily by increasing insulin secretion; metformin acts primarily by decreasing hepatic glucose production, and partly by increasing glucose uptake and utilization by muscle.

Glucovance is indicated for initial therapy for patients with type 2 diabetes and for previously treated patients when glucose control has been inadequate with metformin or a sulfonylurea alone. The only advantage of the combination (over taking separate doses of metformin and a sulfonylurea) is convenience. Although Glucovance is approved for initial therapy, it would seem prudent to try either component alone initially, reserving the combination for patients who don't respond adequately to either.

Adverse effects of Glucovance are basically the sum of the adverse effects of glyburide and metformin. Glyburide poses a risk of hypoglycemia. Metformin can cause GI disturbances (nausea, diarrhea) and appetite reduction. Of greater concern, metformin poses a risk of lactic acidosis. Because of this risk, the combination is contraindicated for patients with renal insufficiency, metabolic acidosis, heart failure, or any of the other contraindications noted above for metformin.

Glucovance tablets are available in three metformin/glyburide strengths: 250/1.25 mg, 500/2.5 mg, and 500/5 mg. For previously untreated patients, the initial dosage is 250/1.25 mg once or twice daily. For previously treated patients, the recommended dosage is either 500/2.5 mg or 500/5 mg twice daily. The maximum dosage is 2000/20 mg/day. All doses are taken with meals.

Metformin/Glipizide [Metaglip]

Metformin and glipizide are available in a combination sold as *Metaglip*. The product is nearly identical to metformin/glyburide [Glucovance], having the same indications, actions, and adverse effects.

Metaglip tablets are available in three metformin/glipizide strengths: 250/2.5 mg, 500/2.5 mg, and 500/5 mg. For previously untreated patients, the initial dosage is 250/2.5 mg once a day. For previously treated patients, the recommended dosage is either 500/2.5 mg or 500/5 mg twice daily. The maximum dosage is 2000/20 mg/day, administered in divided doses. All doses are taken with meals.

Metformin/Pioglitazone [Actoplus Met, Actoplus Met XR]

Metformin and pioglitazone are available in combination as *Actoplus Met* and *Actoplus Met XR*. Pioglitazone acts by decreasing insulin resistance; metformin acts primarily by decreasing hepatic glucose production, and partly by increasing glucose uptake and utilization by muscle. Metformin/pioglitazone is indicated for treating type 2 diabetes in previously treated patients who (1) have not responded adequately to pioglitazone or metformin alone or (2) have responded adequately to pioglitazone plus metformin, but want to simplify dosing. The combination is not approved for initial therapy of type 2 diabetes.

Adverse effects of metformin/pioglitazone are simply the sum of the adverse effects of pioglitazone and metformin. With pioglitazone, the principal concern is *heart failure* secondary to *renal retention of fluid*. Accordingly, the combination should be used with caution in patients with *mild* heart failure, and should be avoided in those with *severe* failure. Insulin increases the risk of heart failure, and hence metformin/pioglitazone and insulin should not be combined. With metformin, the principal concern is *lactic acidosis*. Accordingly, the combination should be avoided by patients prone to developing acidosis, including those with renal insufficiency, metabolic acidosis, and heart failure. In addition to lactic acidosis, metformin can cause *GI disturbances* (nausea, diarrhea) and *appetite reduction*.

Metformin/pioglitazone is marketed under two trade names: *Actoplus Met* (pioglitazone/immediate-release [IR] metformin) and *Actoplus Met XR* (pioglitazone/extended-release [ER] metformin). *Actoplus* is available in two pioglitazone/IR metformin strengths: 15 mg/500 mg and 15 mg/850 mg. Similarly, *Actoplus Met XR* is available in two pioglitazone/ER metformin strengths: 15/1000 mg and 30/1000 mg. For *Actoplus Met*, the initial dosage is 15/500 mg or 15/850 mg taken once or twice daily with food, and the maximum daily total is 45/2550 mg. For *Actoplus Met XR*, the initial dosage is 15/1000 mg or 30/1000 mg taken once daily with the evening meal, and the maximum daily total is 45/2000 mg.

Metformin/Repaglinide [Prandimet]

Metformin and repaglinide are available in combination as *Prandimet* for treating patients with type 2 diabetes. Benefits derive from the insulin-releasing effects of repaglinide and from metformin's three-pronged attack on glycemic control: inhibition of hepatic glucose production, sensitization of insulin receptors on target cells, and a slight reduction in GI glucose absorption. *Prandimet* is available in two metformin/repaglinide strengths: 500/1 mg and 500/2 mg. Patients may start with either combination. Dosing is done 2 or 3 times a day with food. According to the package insert, the maximum *single* dose is 1000 mg metformin/4 mg repaglinide. The *daily total* should not exceed 2500 mg metformin/10 mg repaglinide.

Metformin/Saxagliptin [Kombiglyze XR]

Metformin and saxagliptin are available in a fixed-dose, immediate-release formulation marketed as *Kombiglyze XR* for treatment of type 2 diabetes. The combination provides better glycemic control than either agent taken alone. Metformin/saxagliptin can be administered along with a sulfonylurea, but the risks of hypoglycemia go up, and so the glycemic response needs to be monitored closely. Metformin/saxagliptin shares the same adverse effects of metformin and saxagliptin alone, including the risk of metformin-induced lactic acidosis. Three metformin/saxagliptin strengths are available: 500/5 mg, 1000/2.5 mg, and 1000/5 mg. Dosing is done once daily with the evening meal (to reduce GI upset). For patients switching from metformin alone, the initial dose is based on the current metformin dose. The maximum daily dose is 2000 mg metformin/5 mg saxagliptin.

Metformin/Sitagliptin [Janumet]

Metformin and sitagliptin are available in combination under the trade name *Janumet* for treatment of type 2 diabetes. Sitagliptin inhibits the breakdown of incretin hormones (by inhibiting DPP-4), and thereby increases pancreatic secretion of insulin and decreases pancreatic secretion of glucagon. Metformin decreases hepatic glucose production, increases insulin sensitivity, and decreases GI absorption of glucose. Since adverse effects of sitagliptin are

minimal (see above), adverse effects of the combination are primarily those of metformin: GI disturbances and, rarely, lactic acidosis. *Janumet* is available in two metformin/sitagliptin strengths: 500/50 mg and 1000/50 mg. Dosing is done twice daily with meals (to reduce GI upset). The starting dose is based on the patient's current regimen. The maximum daily dose is 2000 mg metformin and 100 mg sitagliptin.

Pioglitazone/Glimepiride [Duetact]

Pioglitazone (a glitazone) and glimepiride (a sulfonylurea) are available in combination under the trade name *Duetact* for treatment of type 2 diabetes. Pioglitazone increases insulin sensitivity in target tissues (liver, fat, skeletal muscle) and glimepiride enhances insulin secretion from the pancreas. *Duetact* carries two types of risks. First, both components can cause dose-related *hypoglycemia* and, since they do so by different mechanisms, the combined risk is greater than with either drug alone. Second, both drugs can cause adverse cardiovascular effects: glimepiride poses a risk, albeit small, of sudden cardiac death, and pioglitazone poses a risk of fluid retention, which can cause or exacerbate heart failure. *Duetact* tablets are available in two pioglitazone/glimepiride strengths: 30/2 mg and 30/4 mg. Dosing is done once daily with the first main meal of the day. Initial dosage is based on the current regimen. The maximum recommended daily dose is 30 mg pioglitazone/4 mg glimepiride, which is lower than the maximum when each drug is taken separately (45 mg pioglitazone and 8 mg glimepiride).

Rosiglitazone/Glimepiride [Avandaryl]

Rosiglitazone (a glitazone) and glimepiride (a sulfonylurea) are available in combination under the trade name *Avandaryl* for treatment of type 2 diabetes. The actions and adverse effects of *Avandaryl* are similar to those of pioglitazone/glimepiride [*Duetact*], but with one important exception: the risk of sudden cardiac death with rosiglitazone is much higher than with pioglitazone. *Avandaryl* tablets are formulated in six strengths: 4 mg rosiglitazone plus either 1, 2, or 4 mg glimepiride; and 8 mg rosiglitazone plus either 1, 2, or 4 mg glimepiride. Owing to the risk of sudden cardiac death, *Avandaryl* is available only through a restricted distribution program.

Rosiglitazone/Metformin [Avandamet]

Rosiglitazone and metformin are available in combination as *Avandamet*. The actions and adverse effects of *Avandamet* are similar to those of pioglitazone/metformin [*Actoplus Met*, *Actoplus Met XR*], but with one important exception, the risk of sudden cardiac death with rosiglitazone is much higher than with pioglitazone. *Avandamet* tablets are available in three metformin/rosiglitazone strengths: 500/1 mg, 500/2 mg, and 500/4 mg. The maximum dosage is 2000/8 mg/day. Owing to the risk of sudden cardiac death, *Avandamet* is available only through a restricted distribution program.

Sitagliptin/Simvastatin [Juvissync]

This combination of sitagliptin and simvastatin, sold as *Juvissync*, differs from all the other combinations noted so far. In what way? All the other combinations contain *two antidiabetic* drugs, whereas *Juvissync* contains *one antidiabetic* drug (sitagliptin) and *one drug for lowering cholesterol* (simvastatin). Sitagliptin lowers blood glucose by inhibiting DPP-4. As discussed in Chapter 50, simvastatin lowers cholesterol by inhibiting an enzyme known as HMG-CoA reductase. Why do we have such a combination? Because many patients with type 2 diabetes also have hypercholesterolemia, both of which are major risk factors for cardiovascular disease. Hence, by giving *Juvissync*, we can reduce both risk factors with a single pill. Major adverse effects of sitagliptin are pancreatitis and hypersensitivity reactions. Major adverse effects of simvastatin are rhabdomyolysis (muscle breakdown) and liver injury.

Juvissync tablets contain 100 mg of sitagliptin plus either 10, 20, or 40 mg of simvastatin. Dosing is done once daily in the evening. If the patient is not already taking simvastatin, the recommended starting dose is 100 mg sitagliptin/40 mg simvastatin. If the patient is already taking simvastatin, the initial dose of *Juvissync* should match the dose of simvastatin already in use.

INJECTED DRUGS (OTHER THAN INSULIN)

In addition to insulin, we now have three other injectable drugs for diabetes. One of the drugs—pramlintide—is indicated for type 1 and type 2 diabetes. The other two drugs—exenatide and liraglutide—are indicated for type 2 diabetes only.

Exenatide

Exenatide [Byetta], approved in 2005, was the first *incretin mimetic*. The drug is used to improve glucose control in patients with type 2 diabetes who are taking metformin or a sulfonylurea. Nausea is common, and hypoglycemia can occur. Long-term effects—both beneficial and adverse—are unknown.

Description and Actions. Exenatide is a synthetic analog of glucagon-like peptide-1 (GLP-1), a peptide hormone in the *incretin* family. Under physiologic conditions, GLP-1 and other incretins are released from cells of the GI tract after a meal. Exenatide activates receptors for GLP-1, and thereby causes the same effects as endogenous incretins. That is, it slows gastric emptying, stimulates glucose-dependent release of insulin, inhibits postprandial release of glucagon, and suppresses appetite. As discussed above, another drug—sitagliptin—has identical effects. However, it works by a different mechanism: rather than activating incretin receptors directly, sitagliptin increases concentrations of endogenous incretins (by inhibiting their breakdown by DPP-4).

Therapeutic Use. Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, or both. In clinical trials, injecting exenatide (5 or 10 mcg) subQ before meals produced a modest decrease in fasting blood glucose and a large decrease in postprandial blood glucose. Patients did not gain any weight, and many lost weight.

Pharmacokinetics. Plasma levels peak 2.1 hours after subQ injection, and decline with a half-life of 2.4 hours. Exenatide is excreted unchanged in the urine. In patients with mild to moderate renal impairment, clearance is reduced only slightly, and hence no dosage reduction is needed. By contrast, in patients with end-stage renal disease, clearance is reduced significantly, and hence the drug should not be used.

Adverse Effects. Dose-related *hypoglycemia* is common when exenatide is combined with a sulfonylurea (but not when combined with metformin). To minimize hypoglycemia, sulfonylurea dosage may need a reduction. *Gastrointestinal effects*—nausea (44%), vomiting (13%), and diarrhea (13%)—are common. In some patients, *anti-exenatide antibodies* develop. These antibodies do not cause adverse effects, but they can reduce exenatide's effects.

Exenatide poses a risk of *pancreatitis*. Severe cases have led to pancreatic necrosis, pancreatic hemorrhage, and even death. Patients should be informed about signs and symptoms of pancreatitis—typically severe and persistent abdominal pain, with or without vomiting—and instructed to stop exenatide immediately. If pancreatitis is confirmed, exenatide should not be resumed. Patients with a history of pancreatitis should probably not use this drug.

Exenatide can cause *renal impairment*, sometimes requiring hemodialysis or a kidney transplant. Fortunately, the incidence is low—about 1 case for every 13,000 patients. Risk of renal impairment may be increased by nausea, vomiting, or diarrhea, or any other event that can cause dehydration. Exenatide should be avoided in patients with severe renal impairment, and should be used with caution in kidney transplant recipients.

In pregnant animals, doses of exenatide only 3 times the human dose caused *fetal harm*, manifesting as reduced growth and skeletal abnormalities. At this time, the drug is classified in FDA Pregnancy Risk Category C, and hence should be used only if the benefits are believed to outweigh the fetal

risk. Furthermore, given the established safety and efficacy of insulin in pregnancy, there seems to be little reason to even try exenatide.

There have been postmarketing reports of serious *hypersensitivity reactions*, including anaphylaxis and angioedema. If severe reaction occurs, patients should stop taking exenatide and seek immediate medical attention.

Drug Interactions. Exenatide delays gastric emptying, and hence can slow the absorption of oral drugs, thereby decreasing peak plasma levels and prolonging the time to peak serum levels. Reduced absorption is of particular concern with oral contraceptives and antibiotics, which require high peak concentrations to be maximally effective. To minimize this interaction, give oral drugs at least 1 hour before exenatide.

Preparations, Dosage, and Administration. Exenatide [Byetta] is supplied in pre-filled, 60-dose injector pens that deliver 5 or 10 mcg per dose. Injections are made subQ into the thigh, abdomen, or upper arm. The initial dosage is 5 mcg twice daily, administered 0 to 60 minutes before the morning and evening meals—never after the meal. After 1 month, the dosage may be increased to 10 mcg twice daily. If the patient is taking a sulfonylurea, its dosage may need a reduction (to avoid hypoglycemia). If the patient is taking metformin, no dosage reduction is needed. Because of greatly reduced clearance, exenatide should not be used by patients with severe renal impairment.

Liraglutide

Actions and Uses. Liraglutide [Victoza], approved in 2010, is an *incretin mimetic* similar to exenatide. The drug is indicated as an adjunct to diet and exercise to enhance glycemic control in adults with type 2 diabetes. Like exenatide, liraglutide is an analog of human GLP-1 that causes direct activation of GLP-1 receptors, and thereby slows gastric emptying, stimulates glucose-dependent insulin release, and inhibits postprandial release of glucagon. Liraglutide is more convenient than exenatide (dosing is done just once a day without regard to meals, rather than twice a day before meals), but may pose a risk of thyroid cancer.

Liraglutide can be used alone or combined with other antidiabetic drugs. However, it is not recommended as first-line therapy in patients not adequately controlled by diet and exercise. Most often, the drug is combined with metformin, a sulfonylurea, or both. Because sulfonylureas actively drive down blood glucose levels, adding liraglutide to a sulfonylurea regimen increases the risk of hypoglycemia. Reducing the sulfonylurea dosage at the start of liraglutide treatment seems to lower the risk.

Liraglutide has been shown effective as an add-on to rosiglitazone, a drug that is all but gone from use. Although liraglutide has not been studied as an add-on to pioglitazone (the only other glitazone still on the market), it seems likely that liraglutide would be effective with pioglitazone too.

Pharmacokinetics. Pharmacokinetics of liraglutide are unremarkable. Plasma levels peak 8 to 13 hours after subQ dosing. The drug undergoes metabolic breakdown followed by excretion in the urine and feces. The plasma half life is 13 hours—long enough to permit once-daily dosing.

Adverse Effects. Dose-related *GI effects* are common, developing in 41% of patients. Specific effects include nausea (28%), diarrhea (17%), and constipation (10%). *Hypoglycemia* can also occur, especially when liraglutide is combined with a sulfonylurea (but not with metformin).

In clinical trials, 8.6% of patients developed *anti-liraglutide antibodies*. This is surprising, given that liraglutide is identical to human GLP-1, and hence should not be antigenic. In theory, these antibodies could neutralize liraglutide. However, to date, there is no evidence this has happened.

Like exenatide, liraglutide has been associated with rare cases of *pancreatitis*. If pancreatitis is suspected, liraglutide should be discontinued immediately. If pancreatitis is confirmed, the drug should never be used again. However, if pancreatitis is ruled out, use of liraglutide can resume.

Like exenatide, liraglutide has been associated with rare cases of *renal impairment*, including new acute renal failure and worsening of chronic renal failure. Most cases occurred in patients who had experienced nausea, vomiting, or diarrhea, or any other event that can cause dehydration. Renal impairment may reverse with supportive treatment and discontinuation of liraglutide and any other potentially causative agents.

There is concern that liraglutide may cause thyroid C-cell tumors, including *medullary thyroid carcinoma* (MTC). In tests on rodents, clinically relevant doses have caused C-cell tumors. However, there is no proof that liraglutide has caused these tumors in humans. Nonetheless, the package label bears

a black box warning about possible thyroid cancer, including a contraindication against using the drug in patients with a family history of MTC or in those with multiple endocrine neoplasia syndrome type 2.

Drug Interactions. As noted, combined use with a *sulfonylurea* can increase the risk of hypoglycemia. Dosage of the sulfonylurea may need a reduction.

Because liraglutide delays gastric emptying, it might delay the absorption of some oral drugs, thereby reducing their peak serum levels and prolonging the time to peak serum levels.

Preparations, Dosage, and Administration. Liraglutide [Victoza] is supplied in pre-filled multidose injector pens that deliver 0.6, 1.2, or 1.8 mg/dose. Administration is by subQ injection into the abdomen, thigh, or upper arm. Dosing is done once a day, at any time and independent of meals. The initial dosage is low—0.6 mg once a day—to minimize GI side effects. After 1 week, dosage is increased to 1.2 mg once a day. If that dosage proves inadequate, it can be increased to 1.8 mg once a day.

Pramlintide

Pramlintide [Symlin] is the first member of a new class of antidiabetic agents, the *amylin mimetics*. The drug is used to complement the effects of insulin in patients with type 1 or type 2 diabetes. Severe hypoglycemia is a concern, and nausea is common.

Description and Actions. Pramlintide is a synthetic analog of *amylin*, a peptide hormone made in the pancreas and released with insulin. Both amylin and pramlintide, which mimics the effects of amylin, reduce postprandial levels of glucose, mainly by delaying gastric emptying and suppressing glucagon secretion. In addition, both agents act in the brain to increase the sense of satiety, and can thereby lower caloric intake.

Therapeutic Use. Pramlintide is indicated as a supplement to mealtime insulin in patients with type 1 or type 2 diabetes who have failed to achieve glucose control despite optimal insulin therapy. Patients with type 2 diabetes may combine insulin and pramlintide with metformin and/or a sulfonylurea. In clinical trials, adding subQ pramlintide to mealtime insulin decreased postprandial glucose levels, smoothed out glucose fluctuations, and reduced the needed mealtime dose of insulin. Mean reductions in A1c were about 0.39% for those with type 1 diabetes and 0.55% for those with type 2 diabetes.

Pharmacokinetics. Blood levels peak about 20 minutes after subQ injection and decline with a half-life of 49 minutes. Unlike most drugs, pramlintide is metabolized in the kidneys rather than the liver. One active metabolite has been identified.

Adverse Effects. *Hypoglycemia* is the biggest concern. Pramlintide does not cause hypoglycemia when used alone, but poses a risk of severe hypoglycemia when combined with insulin, especially in patients with type 1 diabetes. As a rule, hypoglycemia develops within 3 hours of dosing. To reduce risk, insulin dosage must be decreased, at least initially. Also, pramlintide should not be given to patients who have hypoglycemia unawareness, an A1c level above 7%, or a history of poor adherence to their insulin regimen, poor adherence to SMBG, or recurrent hypoglycemia needing assistance.

Nausea occurs early in therapy and is more common in patients with type 1 diabetes (37% to 48%) than type 2 diabetes (28% to 30%). The incidence and severity of nausea can be reduced by gradual titration of dosage.

Injection-site reactions—redness, swelling, or itching—may occur, but generally resolve within a few days to weeks.

Drug Interactions. By delaying gastric emptying, pramlintide can delay the absorption of oral drugs. Accordingly, oral drugs should be taken 1 hour before injecting pramlintide or 2 hours after. Pramlintide should not be combined with other drugs that slow intestinal motility (eg, antimuscarinic agents, opioid analgesics) or with drugs that slow the absorption of nutrients (eg, acarbose, miglitol).

Preparations, Dosage, and Administration. Pramlintide [Symlin] is supplied in solution (0.6 mg/mL) in 5-mL vials, which should be stored under refrigeration, but not frozen. Open vials, which can be kept cool or at room temperature, should be discarded after 28 days.

Dosing is done prior to major meals that contain at least 250 kcal or 30 gm of carbohydrates. Injections are made subQ into the abdomen or thigh, using a U-100 insulin syringe (preferably the 0.3-mL size). The manufacturer recommends against mixing pramlintide with insulin in the same syringe. However, research has shown that mixing does not affect the absorption of either drug.

In patients with *type 1 diabetes*, the initial dosage is 15 mcg before meals. If there is no serious nausea for 3 days, dosage can be increased in 15-mcg steps to a maximum of 60 mcg. If 30 mcg causes too much nausea, discontinuation should be considered.

In patients with *type 2 diabetes*, the initial dosage is 60 mcg before meals. If there is no serious nausea for 3 to 7 days, dosage may be increased to 120 mcg.

In patients with *type 1* or *type 2 diabetes*, the premeal dose of rapid- or short-acting insulin should be decreased by 50% (to reduce the risk of hypoglycemia). When the maintenance dosage of pramlintide is established, the insulin dosage can be titrated up.

ACUTE COMPLICATIONS OF POOR GLYCEMIC CONTROL

Uncontrolled diabetes will lead to hyperglycemia, which in turn can lead to *diabetic ketoacidosis* (DKA) or *hyperglycemic hyperosmolar nonketotic syndrome* (HHNS). The cardinal feature of both conditions is hyperglycemic crisis and associated loss of fluid and electrolytes. Both conditions can be life threatening, and hence immediate treatment should be implemented. As indicated in Table 57-13, these disorders have two principal differences. First, hyperglycemia is more severe in HHNS. Second, whereas ketoacidosis is characteristic of DKA, it is absent in HHNS. Treatment of both disorders is similar.

TABLE 57-13 ■ Contrasts Between Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Nonketotic Syndrome

Characteristic	Diabetic Ketoacidosis	Hyperglycemic Hyperosmolar Nonketotic Syndrome
Patient population	Mainly in type 1 diabetes	More likely in type 2 diabetes
Onset	Rapid	Gradual
Blood glucose (mg/dL)	≥300	≥600
Plasma osmolality (mOsm/L)*	<320	>320
pH of arterial blood	≤7.3	≥7.3
Blood ketones	Large increase	Little or no change
Urine ketones	Large increase	Normal or small increase
Urine and breath odor	Urine smells like rotten apples; breath smells sweet or like acetone (nail polish)	Normal

*The normal range is 285 to 295 mOsm/L.

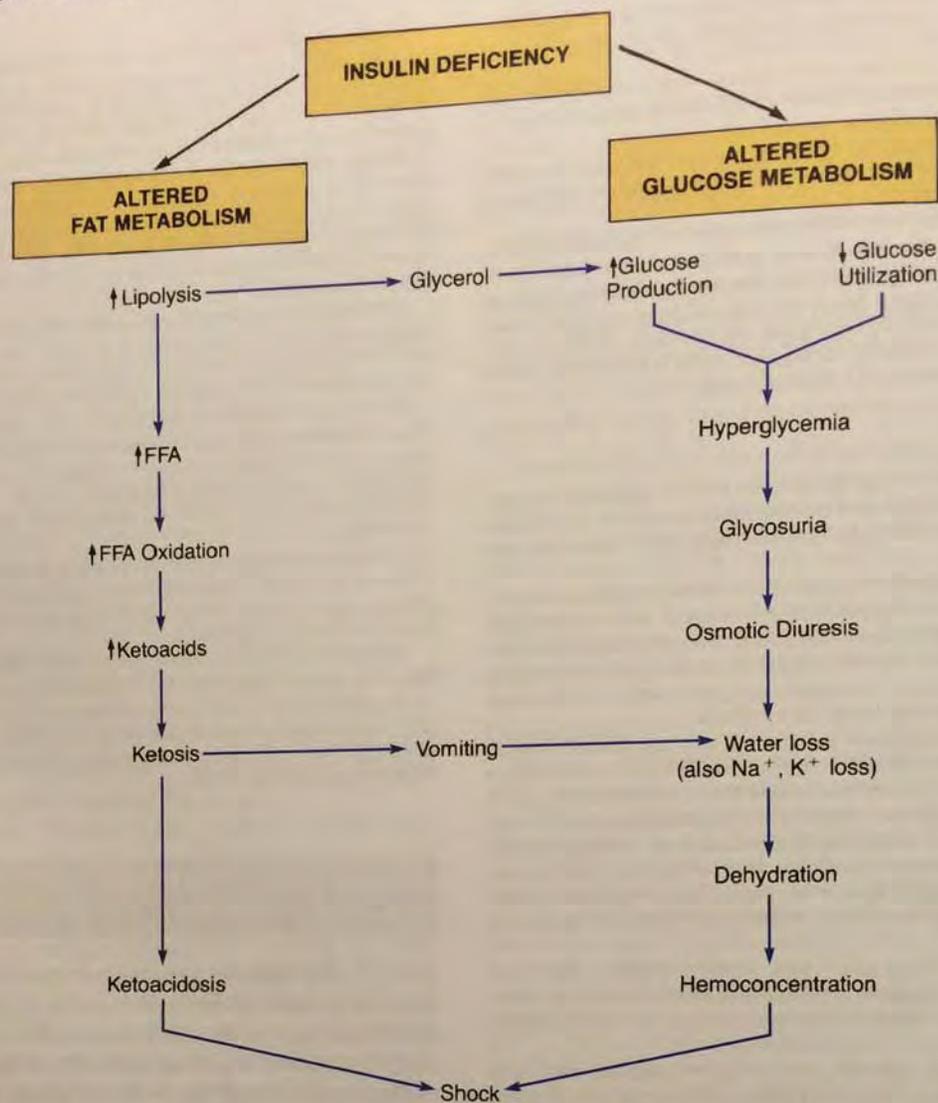


Figure 57-3 ■ Pathogenesis of diabetic ketoacidosis.

The syndrome of diabetic ketoacidosis (DKA) is caused by severe derangements of glucose metabolism and fat metabolism that occur in response to lack of insulin (see text for details). (FFA = free fatty acids.)

Diabetic Ketoacidosis

Diabetic ketoacidosis is a severe manifestation of insulin deficiency. This syndrome is characterized by hyperglycemia, production of ketoacids, hemoconcentration, acidosis, and coma. These symptoms typically evolve quickly, over a period of several hours to a couple of days. Before insulin became available, practically all patients with type 1 diabetes died from ketoacidosis. Today, DKA remains a common complication in pediatric patients, and the leading cause of diabetes-related death in this group. DKA occurs much more often in patients with type 1 diabetes than in those with type 2 diabetes.

Pathogenesis

DKA is brought on by derangements of glucose and fat metabolism. Altered glucose metabolism causes hyperglycemia, water loss, and hemoconcentration. Altered fat metabolism causes production of ketoacids. Figure 57-3 outlines the se-

quence of metabolic events by which ketoacidosis develops. Note that, in its final stages, the syndrome consists of hemoconcentration and shock in addition to ketoacidosis itself. The alterations in fat and glucose metabolism that lead to ketoacidosis are described in detail below.

Altered Fat Metabolism. Alterations in fat metabolism lead to production of ketoacids. As indicated in Figure 57-3, insulin deficiency promotes lipolysis (breakdown of fats) in adipose tissue. The products of lipolysis are glycerol and free fatty acids (FFA). Both of these metabolites are transported to the liver. In the liver, oxidation of FFA results in the production of two ketoacids (beta-hydroxybutyric acid and acetoacetic acid), also known as ketone bodies. Accumulation of ketoacids puts the body in a state of ketosis. As buildup of ketoacids increases, frank acidosis develops. At this point, the patient's condition changes from ketosis to ketoacidosis. (Ketoacidosis can be distinguished from ketosis by the presence of hyperventilation.) Acidosis contributes to the development of shock.

Ketosis imparts characteristic smells to the urine and breath, which can be useful clues to the patient's condition. Ketones in the urine smell like rotten or decaying apples. Ketones in expired air give off a sweet smell, sometimes called *Juicy Fruit breath*, because it smells much like that flavorful

chewing gum. Alternatively, the breath may smell like nail-polish remover, which contains the ketone acetone. To some degree, the breath of a ketotic person smells like the breath of someone who has been drinking alcohol. Because of this smell—coupled with the neurologic sequelae of ketosis (reduced alertness, impaired gait and balance)—some patients with DKA have been arrested for drunk driving, even though they hadn't been drinking at all.

Altered Glucose Metabolism. Deranged glucose metabolism leads to hyperglycemia, water loss, and hemoconcentration. As shown in Figure 57-3, insulin deficiency has two direct effects on the metabolism of glucose: (1) an increase in glucose production and (2) a decrease in glucose utilization. (The glycerol released by lipolysis is a substrate for glucose synthesis, and therefore helps increase glucose production.) Because more glucose is being made and less is being used, plasma levels of glucose rise, causing hyperglycemia. Glycosuria develops when plasma glucose content becomes so high that the amount of glucose filtered by the glomeruli exceeds the capacity of the renal tubules for glucose reuptake. As the concentration of glucose in the urine increases, osmotic diuresis develops, resulting in the loss of large volumes of water. Vomiting is a direct source of fluid loss and, more importantly, is an impediment to rehydration with oral fluids. (It should be noted that, along with loss of water, sodium and potassium are lost too. These ions are excreted in conjunction with ketone bodies, compounds that carry a negative charge.) As dehydration becomes more severe, hemoconcentration develops. Hemoconcentration causes cerebral dehydration, which, together with acidosis, leads to shock.

Treatment

Diabetic ketoacidosis is a life-threatening emergency. Treatment is directed at correcting hyperglycemia and acidosis, replacing lost water and sodium, and normalizing potassium balance. We begin with IV fluids and electrolytes, followed as soon as possible by IV insulin. Although it might seem reasonable to drive glucose levels down quickly with lots of insulin, doing so is unsafe and should be avoided. Instead, glucose levels should be reduced slowly, by about 50 mg/dL/hr.

Insulin Replacement. Insulin levels are restored with an initial IV bolus of regular insulin (0.1 to 0.15 units/kg body weight) followed by continuous infusion at a rate of 0.1 units/kg/hr. When plasma glucose has fallen to 250 mg/dL, the infusion rate should be reduced to 0.05 to 0.2 units/kg/hr, and a dextrose solution (5% in half-normal saline) should be infused at a rate of 150 to 200 mL/hr. Thereafter, the insulin dosage should be adjusted as needed to maintain plasma glucose levels at 200 mg/dL until acidosis has resolved. Switching to subQ insulin is common and acceptable once the patient recovers from the acute episode.

Intravenous insulin is preferred to subQ insulin for initial management. Here's why. First, in patients with DKA, absorption of subQ insulin is apt to be both slow and erratic, making accurate dosing difficult. Second, when insulin is administered subQ, insulin levels cannot be lowered quickly in response to inadvertent excessive dosing, and hence avoiding hypoglycemia may be difficult. Intravenous dosing avoids these problems: Blood levels of insulin are established immediately; there is no uncertainty about the amount "absorbed"; and, if the blood level of insulin is too high, it can be quickly lowered by stopping the infusion, thereby permitting good control of blood glucose content.

Bicarbonate for Acidosis. Treating acidosis with bicarbonate is controversial. Studies have failed to demonstrate any benefit of giving bicarbonate to patients with severe acidosis (blood pH 6.9 to 7.1). Nonetheless, some authorities recommend empiric therapy with bicarbonate if blood pH is below 6.9. The dose is 44.6 mEq of sodium bicarbonate (dissolved in 500 mL of 0.45% saline) infused over 1 hour. Because bicarbonate promotes hypokalemia, potassium should be infused along with the bicarbonate, unless hypokalemia (serum potassium above 5.5 mEq/L) is present.

Water and Sodium Replacement. Dehydration and sodium loss are both corrected with IV saline. Depending on the specific needs of the patient, either 0.9% or 0.45% saline is employed. Adults usually require between 8 and 10 L of fluid during the first 12 hours of treatment. In elderly patients and patients with heart disease, central venous pressure should be monitored.

Potassium Replacement. Hypokalemia of DKA is a serious problem and must be corrected. As a rule, potassium is replenished by IV administration. Because hypokalemia predisposes the patient to dysrhythmias, electrocardiographic monitoring is essential.

Treatment of potassium loss is tricky. Why? Because plasma potassium levels may be normal even though intracellular potassium is very low. When insulin is administered, causing cellular uptake of potassium to increase, severe hypokalemia can develop as plasma potassium rushes into potassium-depleted cells. Because of this relationship between insulin administration and plasma potassium levels, the following guidelines apply: (1) if plasma potassium is normal, no potassium should be administered until plasma potassium declines in response to insulin; (2) if plasma potassium is low, potassium should be given immediately (and then re-administered if potassium levels fall following insulin administration).

Normalization of Glucose Levels. Treatment of ketoacidosis with insulin may convert hyperglycemia into hypoglycemia. Because cellular uptake of glucose is impaired by insulin deficiency, ketoacidosis is likely to be associated with a reduction in intracellular glucose—despite elevations in plasma glucose content. Under these conditions, giving insulin will cause plasma glucose to rush into the glucose-depleted cells, thereby causing plasma levels of glucose to drop precipitously. If insulin therapy induces hypoglycemia, plasma glucose can be restored by giving glucagon or glucose itself.

Hyperglycemic Hyperosmolar Nonketotic Syndrome

Hyperglycemic hyperosmolar nonketotic syndrome (HHNS), also known as hyperglycemic hyperosmolar syndrome, (HHS), is similar to DKA in some respects and different in others. As noted, the central characteristic in both disorders is severe hyperglycemia brought on by insulin deficiency. In HHNS, as in DKA, a large amount of glucose is excreted in the urine, carrying a large volume of water with it. The result is dehydration and loss of blood volume, which greatly increases the blood concentrations of electrolytes and nonelectrolytes (particularly glucose)—hence the term *hyperosmolar*. Loss of blood volume also increases the hematocrit. As a result, the blood "thickens" and blood flow becomes sluggish. How does HHNS differ from DKA? As its name indicates, HHNS is nonketotic: There is little or no change in ketoacid levels in blood, and hence little or no change in blood pH. In contrast, blood levels of ketoacids rise dramatically in DKA, causing blood pH to fall. Since ketone levels remain close to normal in HHNS, the sweet or acetone-like smell imparted to the urine and breath of the DKA patient is absent. Finally, whereas DKA occurs mainly in patients with type 1 diabetes and develops quickly (usually in association with infection, acute illness, or some other stress), HHNS occurs more often in patients with type 2 diabetes and evolves slowly: metabolic changes typically begin a month or two before signs and symptoms become apparent. If HHNS goes untreated, severe dehydration will eventually lead to coma, seizures, and death. As with DKA, management of HHNS is directed at correcting hyperglycemia and dehydration by use of intravenous insulin, fluids, and electrolytes.

GLUCAGON FOR INSULIN OVERDOSE

Insulin overdose can cause severe hypoglycemia. The preferred treatment is IV glucose. However, if this option is not available, blood glucose can be restored with glucagon.

Glucagon, a polypeptide hormone produced by alpha cells of the pancreas, has effects on carbohydrate metabolism that are opposite to those of insulin. Specifically, glucagon promotes the breakdown of glycogen to glucose, reduces conversion of glucose to glycogen, and stimulates biosynthesis of glucose. Hence, whereas insulin acts to lower plasma glucose, glucagon causes plasma glucose to rise. In addition to these metabolic effects, glucagon acts on GI smooth muscle to promote relaxation.

Glucagon is used to treat hypoglycemia resulting from insulin overdose. However, in patients with severe hypoglycemia, IV glucose is preferred. Why? Because IV glucose raises blood glucose immediately, whereas responses to glucagon are somewhat delayed. Accordingly, glucagon should be used only if IV glucose is not an option. When IV glucagon is administered to unconscious patients, the subsequent rise in blood glucose usually restores consciousness in 20 minutes or so. Once consciousness is sufficient for swallowing, oral carbohydrates should be given. These will help prevent recurrence of hypoglycemia and will help replenish hepatic glycogen stores.

Glucagon cannot correct hypoglycemia resulting from starvation. Why? Because glucagon acts in large part by promoting glycogen breakdown, and people who are starved have little or no glycogen left.

Glucagon is administered parenterally (IM, subQ, and IV). The drug is supplied in powder form and must be reconstituted to a concentration of 1 mg/mL (or less) using the diluent supplied by the manufacturer. A dose of 0.5 to 1 mg is usually effective.

KEY POINTS

- Diabetes is characterized by sustained hyperglycemia.
- Initial metabolic changes involve glucose and other carbohydrates. If the disease progresses, metabolism of fats and proteins changes as well.
- Diabetes has two major forms: type 1 diabetes, formerly called insulin-dependent diabetes mellitus or juvenile-onset diabetes, and type 2 diabetes, formerly called non-insulin-dependent diabetes mellitus or adult-onset diabetes.
- Symptoms of type 1 diabetes result from a complete absence of insulin. The underlying cause is autoimmune destruction of pancreatic beta cells.
- Early in the disease process, symptoms of type 2 diabetes result mainly from cellular resistance to insulin's actions, not from insulin deficiency. However, later in the disease process, insulin deficiency develops.
- Type 1 diabetes and type 2 diabetes share the same long-term complications: hypertension, heart disease, stroke, blindness, renal failure, neuropathy, lower limb amputations, erectile dysfunction, and gastroparesis.
- Diabetes is diagnosed if (1) A1c is 6.5% or higher, (2) fasting plasma glucose is 126 mg/dL or higher, or (3) casual blood glucose is 200 mg/dL or higher, and the patient has the classic signs and symptoms of diabetes: polyuria, polydipsia, and sudden weight loss that cannot be attributed to other common causes.
- With both type 1 and type 2 diabetes, the goal of treatment is to reduce long-term complications, including death.
- Type 1 diabetes is treated with insulin replacement. Oral antidiabetic agents are ineffective.
- Type 2 diabetes is treated with oral antidiabetic drugs or, if needed, with insulin or another injectable drug—but always in conjunction with diet modification and exercise.
- In the past, drugs for type 2 diabetes were started only after a program of diet modification and exercise had failed to yield glycemic control. Today, drugs (usually metformin) are started immediately after diagnosis, but always in conjunction with diet modification and exercise.
- In type 1 diabetes, tight glycemic control can markedly reduce long-term complications, as demonstrated in the Diabetes Control and Complications Trial (DCCT).
- In type 2 diabetes, tight glycemic control can decrease microvascular complications, but not macrovascular complications or mortality, as shown in the ACCORD, ADVANCE, and VADT trials.
- Tight glycemic control increases the risk of severe hypoglycemia and weight gain, and possibly the risk of death.
- For patients with type 1 diabetes, and for patients with type 2 diabetes who use insulin, self-monitoring of blood glucose (SMBG) is the standard method for day-to-day monitoring of therapy. The premeal target is 70 to 130 mg/dL, and the peak postmeal target is 180 mg/dL or lower.
- For patients with type 1 or type 2 diabetes, hemoglobin A1c should be measured every 3 to 6 months to assess long-term glycemic control.
- Insulin is an anabolic hormone. That is, it promotes conservation of energy and buildup of energy stores.
- Insulin has two basic effects: it (1) stimulates cellular uptake of glucose, amino acids, and potassium; and (2) promotes synthesis of complex organic molecules (glycogen, proteins, triglycerides).
- Insulin deficiency puts the body into a catabolic mode. As a result, glycogen is converted to glucose, proteins are degraded to amino acids, and fats are converted to glycerol (glycerin) and free fatty acids.
- Insulin deficiency promotes hyperglycemia by increasing glycogenolysis and gluconeogenesis and by decreasing glucose utilization.
- Seven types of insulin are used in the United States: regular insulin (human insulin), NPH insulin, and five human insulin analogs: insulin lispro, insulin aspart, insulin glulisine, insulin detemir, and insulin glargine.
- All insulins used in the United States are produced by recombinant DNA technology. Insulin extracted from beef or pork pancreas is no longer available.
- Insulin lispro, insulin aspart, and insulin glulisine have a very rapid onset and short duration.
- Regular (native) insulin, when used subQ, has a moderately rapid onset and short duration.
- NPH insulin and insulin detemir have intermediate durations.
- Insulin glargine has a prolonged duration, with no definite "peak" in either blood levels or hypoglycemic effects.
- All insulins can be administered subQ, and four preparations—regular, aspart, lispro, and glulisine insulin—can be administered IV as well.
- One insulin preparation—NPH insulin—is a *suspension*. It looks cloudy and should be gently agitated before being drawn into a syringe. All other insulins are *solutions*. They look clear and do not require agitation.
- Insulin is used to treat all patients with type 1 diabetes and up to 40% of patients with type 2 diabetes.
- To achieve tight glucose control, patients with type 1 or type 2 diabetes must practice intensive insulin therapy, consisting of either (1) an evening injection of insulin glargine supplemented with mealtime injections of regular, lispro, aspart, or glulisine insulin; or (2) continuous subQ infusion of regular, lispro, aspart, or glulisine insulin supplemented with mealtime bolus doses. With both approaches, the mealtime dose is adjusted to match caloric intake. Tight glucose control cannot be achieved with conventional insulin therapy (ie, one or two injections a day).
- SMBG is an essential component of intensive insulin therapy. Blood glucose should be measured 3 to 5 times a day.
- The most important and common adverse effect of insulin therapy is hypoglycemia (blood glucose below 50 mg/dL), which occurs whenever insulin levels exceed insulin needs. Symptoms include tachycardia, palpitations, sweating, headache, confusion, drowsiness, and fatigue. If hypoglycemia is severe, convulsions, coma, and death may follow.
- Beta blockers can delay awareness of hypoglycemia by masking hypoglycemia-induced signs that are caused by activation of the sympathetic nervous system (eg, tachycardia, palpitations). In addition, beta blockers inhibit the

breakdown of glycogen to glucose, and can thereby impede glucose replenishment.

- Insulin-induced hypoglycemia can be treated with a fast-acting oral sugar (eg, glucose tablets, orange juice, sugar cubes), IV glucose, or parenteral glucagon. (Oral sucrose—aka table sugar—acts slowly, and will barely work at all in patients taking acarbose, a drug that prevents intestinal conversion of sucrose into glucose and fructose.)
- The oral antidiabetic drugs—metformin, sulfonylureas, glinides, thiazolidinediones, alpha-glucosidase inhibitors, and gliptins—are indicated only for type 2 diabetes. They are not used for type 1 diabetes.
- Metformin (a biguanide) decreases glucose production by the liver and increases glucose uptake by muscle and adipose tissue. In patients who need to lose weight, metformin can also help by reducing appetite.
- The major adverse effects of metformin are GI disturbances: decreased appetite, nausea, and diarrhea. Metformin does *not* cause hypoglycemia.
- Very rarely, metformin causes lactic acidosis, which can be fatal. The risk of lactic acidosis is greatly increased by renal impairment, which decreases metformin excretion and thereby causes levels to rise rapidly.
- Sulfonylureas stimulate release of insulin from the pancreas. They may also increase cellular sensitivity to insulin.
- The major adverse effect of sulfonylureas is hypoglycemia. They may also increase the risk of sudden cardiac death.
- Pioglitazone, a thiazolidinedione (glitazone) for type 2 diabetes, increases insulin sensitivity of target cells, and thereby increases glucose uptake by muscle and adipose tissue, and decreases glucose production by the liver.

- Pioglitazone promotes water retention, and can thereby increase the risk of heart failure. In addition, pioglitazone can cause liver damage, bladder cancer, and fractures, and can cause ovulation in anovulatory premenopausal women, thereby posing a risk of unintended pregnancy.
- Like the sulfonylureas, pioglitazone poses a risk of hypoglycemia, especially when combined with insulin or with drugs that inhibit pioglitazone metabolism.
- Acarbose, an alpha-glucosidase inhibitor for type 2 diabetes, inhibits digestion and absorption of carbohydrates, and thereby reduces the postprandial rise in blood glucose. To be effective, acarbose must be taken with every meal.
- The major adverse effects of acarbose are GI disturbances: flatulence, cramps, and abdominal distention.
- Exenatide, an incretin mimetic for type 2 diabetes, is injected subQ before meals to supplement the actions of metformin and/or a sulfonylurea. The drug delays gastric emptying, suppresses glucagon release, and stimulates glucose-dependent release of insulin.
- Exenatide poses a risk of hypoglycemia in patients taking a sulfonylurea, but not in those taking metformin. Nausea is common.
- Pramlintide, an amylin mimetic, is injected subQ before meals to enhance the effects of mealtime insulin in patients with type 1 or type 2 diabetes. The drug delays gastric emptying and suppresses glucagon release, and thereby helps reduce postprandial hyperglycemia.
- The combination of pramlintide plus insulin poses a risk of severe hypoglycemia. Nausea is common.

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Summary of Major Nursing Implications*

INSULIN

Preadministration Assessment

Therapeutic Goal

Insulin is required by all patients with type 1 diabetes and by some with type 2 diabetes. The goal of insulin therapy is to maintain plasma levels of glucose and A1c within an acceptable range (see Table 57-3).

Baseline Data

Assess for clinical manifestations of diabetes (eg, polyuria, polydipsia, polyphagia, weight loss) and for indications of hyperglycemia. Baseline laboratory tests may include casual plasma glucose, FPG, an OGTT, hemoglobin A1c, urinary glucose and ketones, and serum electrolytes.

Assess for baseline knowledge of diabetes and readiness to learn.

Identifying High-Risk Patients

Special care is needed in patients taking drugs that can raise or lower blood glucose levels, including sympathomimetics,

beta blockers, glucocorticoids, sulfonylureas, metformin, glinides (eg, repaglinide), thiazolidinediones (eg, pioglitazone), and pramlintide.

Implementation: Administration

Routes

All insulins may be administered subQ, and four preparations—regular, aspart, lispro, and glulisine insulin—may be administered IV too.

Preparing for Subcutaneous Injection

Teach the patient to prepare for subQ injections as follows:

- Before loading the syringe, disperse insulin suspensions (ie, NPH insulin preparations) by rolling the vial gently between the palms. Vigorous agitation causes frothing and must be avoided. If granules or clumps remain after mixing, discard the vial.
- Except for NPH insulin, all preparations are formulated as clear, colorless solutions, and hence can be administered

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

- without resuspension. If a preparation becomes cloudy or discolored, or if a precipitate develops, discard the vial.
- Before loading the syringe, swab the bottle cap with alcohol.
- Eliminate air bubbles from the syringe and needle after loading.
- Cleanse the skin (with alcohol or soap and water) prior to injection.

Sites of Injection

Provide the patient with the following instructions regarding sites of subQ injection:

- Usual sites of injection are the abdomen, upper arm, and thigh. To minimize variability in responses, make all injections in just one of these areas. Injections in the abdomen provide the most consistent insulin levels and effects.
- Rotate the injection site within the general area employed (eg, the abdomen).
- Allow about 1 inch between sites. If possible, use each site just once a month.

Insulin Storage

Teach the patient the following about insulin storage:

- Store unopened vials of insulin in the refrigerator, but do not freeze. When stored under these conditions, insulin can be used up to the expiration date on the vial.
- The vial in current use can be stored at room temperature for up to 1 month, but must be kept out of direct sunlight and extreme heat. Discard partially filled vials after several weeks if left unused.
- Mixtures of insulin prepared in vials may be stored for 1 month at room temperature, and for 3 months under refrigeration.
- Mixtures of insulin in pre-filled syringes (plastic or glass) should be stored in a refrigerator, where they will be stable for at least 1 week, and perhaps 2. Store the syringe vertically (needle pointing up) to avoid clogging the needle. Gently agitate the syringe prior to administration to resuspend the insulin.

Dosage Adjustment

The dosing goal is to maintain blood glucose levels within an acceptable range. Dosage must be adjusted to balance changes in caloric intake and other factors that can decrease insulin needs (strenuous exercise, pregnancy during the first trimester) or increase insulin needs (illness, trauma, stress, adolescent growth spurt, pregnancy after the first trimester).

Regular insulin can adsorb in varying amounts onto IV infusion sets. Dosage adjustments made to compensate for losses are based on the therapeutic response

Patient and Family Education

Patient and family education is an absolute requirement for safe and successful glycemic control. **Ensure that patients and their families receive thorough instruction on the following:**

- The nature of diabetes
- The importance of tight glucose control
- The major components of the treatment routine—insulin, SMBG, diet, exercise, A1c tests—emphasizing the importance of proper diet and adequate exercise even though insulin is in use
- Procedures for purchasing insulin, syringes, and needles
- Methods of insulin storage
- Procedures for mixing insulins
- Calculation of dosage adjustments
- Techniques of insulin injection
- Rotation of injection sites
- Measurement of blood glucose
- Signs and management of hypoglycemia
- Signs and management of hyperglycemia
- Special problems of diabetic pregnancy
- The procedure for obtaining Medic Alert registration
- The importance of avoiding arbitrary switches between insulins made by different manufacturers

Ongoing Evaluation and Interventions

Measures to Evaluate and Enhance Therapeutic Effects

SMBG should be employed to evaluate day-to-day treatment. Teach patients how to use the glucometer, and encourage them to measure blood glucose before meals and at bedtime. Hemoglobin A1c should be measured 2 to 4 times a year to assess long-term glycemic control. Measuring urinary glucose is not helpful.

Minimizing Adverse Effects

Hypoglycemia. Hypoglycemia occurs whenever insulin levels exceed insulin needs. **Inform the patient about potential causes of hypoglycemia (eg, insulin overdose, reduced food intake, vomiting, diarrhea, excessive alcohol intake, unaccustomed exercise, termination of pregnancy), and teach the patient and family members to recognize the early signs and symptoms of hypoglycemia (tachycardia, palpitations, sweating, nervousness, headache, confusion, drowsiness, fatigue).**

Rapid treatment is mandatory. If the patient is conscious, oral carbohydrates are indicated (eg, glucose tablets, orange juice, sugar cubes, honey, corn syrup, nondiet soda). However, if the swallowing or gag reflex is suppressed, nothing should be administered PO. For unconscious patients, IV glucose is the treatment of choice. Parenteral glucagon is an alternative.

Hypoglycemic coma must be differentiated from coma of diabetic ketoacidosis (DKA). The differential diagnosis is made by measuring plasma or urinary glucose: Hypoglycemic coma is associated with very low levels of glucose, whereas high levels signify DKA.

Lipohypertrophy. Accumulation of subcutaneous fat can occur at sites of frequent insulin injection. **Inform the patient that lipohypertrophy can be minimized by systematic rotation of the injection site within the area selected (eg, abdomen).**

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Allergic Reactions. Systemic reactions (widespread urticaria, impairment of breathing) are rare. If systemic allergy develops, it can be reduced through desensitization (ie, giving small initial doses of human insulin followed by a series of progressively larger doses).

Minimizing Adverse Interactions

Hypoglycemic Agents. Several drugs, including *sulfonylureas*, *glinides*, *alcohol* (used acutely), and *beta blockers*, can intensify hypoglycemia induced by insulin. When any of these drugs is combined with insulin, special care must be taken to ensure that blood glucose content does not fall too low.

Hyperglycemic Agents. Several drugs, including thiazide diuretics, glucocorticoids, and sympathomimetics, can raise blood glucose concentration and can thereby counteract the beneficial effects of insulin. When these agents are combined with insulin, increased insulin dosage may be needed.

Beta Blockers. Beta blockade can mask sympathetic responses (eg, tachycardia, palpitations, tremors) to a steep drop in glucose levels, and can thereby delay awareness of insulin-induced hypoglycemia. Also, because beta blockade impairs hepatic conversion of glycogen to glucose (glycogenolysis), beta blockers can make insulin-induced hypoglycemia even worse, and can delay recovery from a hypoglycemic event.

METFORMIN

Preadministration Assessment

Therapeutic Goal

Metformin is used in conjunction with calorie restriction and exercise to help maintain glycemic control in patients with type 2 diabetes. The drug is also used to prevent type 2 diabetes and to treat women with polycystic ovary syndrome. Metformin is not used for, nor is it effective in, type 1 diabetes.

Identifying High-Risk Patients

Metformin is *contraindicated* or should be used with great caution in patients with or at imminent risk of developing renal insufficiency, liver disease, severe infection, heart failure, a history of lactic acidosis, or shock or other conditions that can cause hypoxemia. It should not be administered to patients who consume excessive amounts of alcohol acutely or long term, until and unless alcohol consumption can be cut back markedly. Likewise, patients for whom the drug is prescribed should be cautioned and encouraged to drink alcohol in moderation.

Implementation: Administration

Route

Oral.

Administration

Advise patients to take immediate-release tablets twice daily, with the morning and evening meals.

Advise patients to take extended-release metformin once daily with the evening meal.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Lactic Acidosis. Rarely, metformin causes lactic acidosis, a medical emergency with a 50% mortality rate. Avoid metformin in patients with renal insufficiency and other conditions that increase acidosis risk (eg, liver disease, severe infection, shock), and use with caution in patients with heart failure. **Inform patients about early signs of lactic acidosis—hyperventilation, myalgia, malaise, and unusual somnolence—and instruct them to seek immediate medical attention if these develop.** Withhold metformin until lactic acidosis has been ruled out. If lactic acidosis is diagnosed, hemodialysis may correct the condition and remove accumulated metformin.

Gastrointestinal Effects. Metformin can cause nausea, diarrhea, and appetite reduction, which usually subside over time. If these reactions are intolerable and the drug must be stopped, suitable alternative drugs should be started.

Vitamin Deficiency. Metformin can reduce absorption of vitamin B₁₂ and folic acid. Supplements may be needed.

Minimizing Adverse Interactions

Alcohol. Inform patients that alcohol increases the risk of lactic acidosis, and therefore must be avoided or, at least, consumed in moderation.

SULFONYLUREAS

First-Generation Agents (Rarely Used)

Chlorpropamide
Tolazamide
Tolbutamide

Second-Generation Agents

Glimepiride
Glipizide
Glyburide (glibenclamide)

Preadministration Assessment

Therapeutic Goal

Sulfonylureas are used in conjunction with calorie restriction and exercise to maintain glycemic control in patients with type 2 diabetes. These drugs do not work in patients with type 1 diabetes.

Identifying High-Risk Patients

Sulfonylureas are *contraindicated* during pregnancy and breast-feeding. Sulfonylureas should not be used in conjunction with alcohol.

Use with *caution* in patients with kidney or liver dysfunction.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Implementation: Administration

Route

Oral.

Administration

Advise patients to administer with food if GI upset occurs. Note that dosages for the second-generation agents, which are preferred, are much lower than dosages for first-generation agents (see Table 57-12).

Sulfonylureas are intended only as supplemental therapy of type 2 diabetes. Encourage patients to maintain their established program of exercise and caloric restriction.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hypoglycemia. Inform patients about signs of hypoglycemia (palpitations, tachycardia, sweating, fatigue, excessive hunger), and instruct them to notify the prescriber if these occur. Treat severe hypoglycemia with IV glucose.

Minimizing Adverse Interactions

Alcohol. Alcohol increases the risk of lactic acidosis. Instruct patients to avoid alcohol.

Use in Pregnancy and Lactation

Pregnancy. Discontinue sulfonylureas during pregnancy. If an antidiabetic agent is needed, insulin is the drug of choice.

Lactation. Sulfonylureas are excreted into breast milk, posing a risk of hypoglycemia to the nursing infant. Women who choose to breast-feed should substitute insulin for the sulfonylurea.

PIOGLITAZONE

Preadministration Assessment

Therapeutic Goal

Pioglitazone is used in conjunction with caloric restriction and exercise to maintain glycemic control in patients with type 2 diabetes. Pioglitazone is not used for type 1 diabetes.

Identifying High-Risk Patients

Pioglitazone is *contraindicated* for patients with *severe* heart failure, and should be used with *caution* in those with *mild* heart failure or even heart failure risk factors. The drug is also *contraindicated* for patients with active bladder cancer or a history of bladder cancer. Exercise *caution* in patients taking insulin or drugs that inhibit or induce CYP2C8.

Baseline Data

Obtain a baseline value for serum alanine aminotransferase (ALT).

Implementation: Administration

Route

Oral.

Administration

Advise patients to take pioglitazone once daily, with or without food.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Heart Failure. Pioglitazone can cause heart failure secondary to renal retention of fluid. Accordingly, pioglitazone must be used with caution in patients with *mild* heart failure or heart failure risk factors, and must be avoided in those with *severe* failure. Inform patients about signs of heart failure (dyspnea, edema, weight gain, fatigue), and instruct them to consult the prescriber if these develop. If heart failure is diagnosed, pioglitazone should be discontinued or used in reduced dosage.

Liver Injury. Pioglitazone may pose a risk of liver injury. Accordingly, ALT should be determined at baseline and periodically thereafter (eg, every 3 to 6 months). If ALT levels rise to more than 3 times the upper limit of normal, or if jaundice develops, pioglitazone should be withdrawn. Inform patients about symptoms of liver injury (nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, jaundice), and instruct them to notify the prescriber if these develop.

Bladder Cancer. Pioglitazone may cause bladder cancer, especially with long-term, high-dose use. Avoid the drug in patients with active bladder cancer or a history of bladder cancer. Inform patients about signs of bladder cancer (eg, blood in urine, worsening urinary urgency, painful urination), and instruct them to contact their prescriber if these develop.

Fractures. Pioglitazone increases the risk of fractures in women (but not in men), especially with long-term, high-dose therapy. Advise women about measures to maintain bone health, including regular exercise, assuring adequate intake of calcium and vitamin D, and use of drugs for osteoporosis, if needed.

Hypoglycemia. Pioglitazone pose a risk of hypoglycemia when combined with insulin or drugs that inhibit pioglitazone metabolism. Use these combinations with caution. Inform patients about signs of hypoglycemia (palpitations, tachycardia, sweating, fatigue, excessive hunger), and instruct them to notify the prescriber if these occur.

Ovulation. Pioglitazone can cause ovulation in premenopausal anovulatory women, thereby posing a risk of unintended pregnancy. Inform women about this action, and educate them about contraceptive options.

Minimizing Adverse Interactions

Insulin. Like pioglitazone, insulin increases the risk of (1) hypoglycemia and (2) fluid retention and the associated risk of heart failure. Use the combination with caution.

Inhibitors and Inducers of CYP2C8. Strong inhibitors of CYP2C8 (eg, atorvastatin, ketoconazole) can increase pioglitazone levels and prolong its half-life, necessitating a reduction in pioglitazone dosage. Conversely, strong inducers of CYP2C8 (eg, rifampin, cimetidine) can reduce pio-

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

glitazone levels and shorten its half-life, necessitating an increase in pioglitazone dosage. Use caution when pioglitazone is combined with any of these drugs.

GLINIDES (MEGLITINIDES)

Repaglinide
Nateglinide

Preadministration Assessment

Therapeutic Goal

Glinides are used in conjunction with calorie restriction and exercise to maintain glycemic control in patients with type 2 diabetes. Glinides are not used for type 1 diabetes.

Identifying High-Risk Patients

Use with *caution* in patients with liver impairment and those taking gemfibrozil.

Implementation: Administration

Route

Oral.

Administration

Inform patients that dosing must be associated with a meal, and instruct them to take the drug 30 minutes or less before eating.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hypoglycemia. Inform patients about signs of hypoglycemia (palpitations, tachycardia, sweating, fatigue, excessive hunger), and instruct them to notify the prescriber if these occur. Treat severe hypoglycemia with IV glucose.

Minimizing Adverse Interactions

Gemfibrozil. Gemfibrozil slows metabolism of glinides, and thereby increases their levels and the risk of hypoglycemia. Avoid gemfibrozil if possible.

*Patient education information is highlighted as **blue text**.

Thyroid Physiology

Thyroid Function Tests

Thyroid Pathophysiology

Hypothyroidism

Hyperthyroidism

Thyroid Hormone Preparations

for Hypothyroidism

Levothyroxine (T_4)Liothyronine (T_3)

Other Thyroid Preparations

Drugs for Hyperthyroidism

Antithyroid Drugs: Thionamides

Radioactive Iodine (^{131}I)

Nonradioactive Iodine: Lugol's Solution

Beta Blockers

Thyroid hormones have profound effects on metabolism, cardiac function, growth, and development. These hormones stimulate the metabolic rate of most cells, and increase the force and rate of cardiac contraction. During infancy and childhood, thyroid hormones promote maturation; severe deficiency can produce extreme short stature and permanent mental impairment. Fortunately, most abnormalities of thyroid function can be effectively treated.

We begin our study of thyroid drugs by reviewing thyroid physiology. Next we review the pathophysiology of hypothyroid and hyperthyroid states. Finally, we discuss the agents used for thyroid disorders.

THYROID PHYSIOLOGY

Chemistry and Nomenclature

The thyroid gland produces two active hormones: triiodothyronine (T_3) and thyroxine (T_4 , tetraiodothyronine). As shown in Figure 58-1, these hormones have nearly identical structures. The only difference is that T_4 contains four atoms of iodine, whereas T_3 contains three. The biologic effects of T_3 and T_4 are qualitatively similar. However, when compared on a molar basis, T_3 is much more potent.

Preparations of T_3 and T_4 employed clinically, although synthetic, are identical in structure to the naturally occurring hormones. The generic name of synthetic T_3 is *liothyronine*, and the generic name of synthetic T_4 is *levothyroxine*. A fixed-ratio mixture of T_3 plus T_4 , known as *liotrix*, is also available.

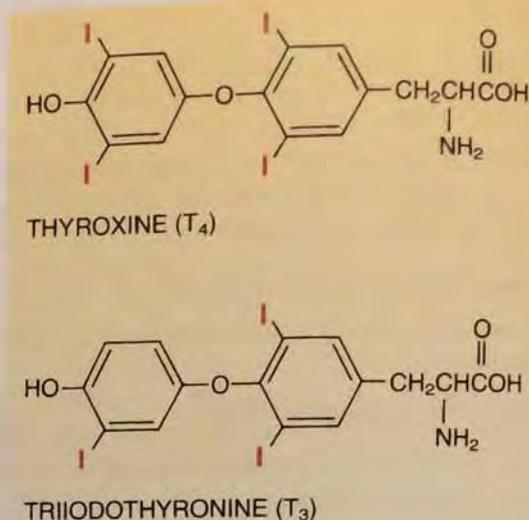


Figure 58-1 ■ Structural formulas of the thyroid hormones.

Synthesis and Fate of Thyroid Hormones

Synthesis. Synthesis of thyroid hormones takes place in four steps (Fig. 58-2). The circled numbers in the figure correspond with the steps below.

- **Step 1.** Formation of thyroid hormone begins with the active transport of *iodide* into the thyroid. Under normal conditions, this process produces concentrations of iodide within the thyroid that are 20 to 50 times greater than the concentration of iodide in plasma. When plasma iodide levels are extremely low, intrathyroid iodide content may reach levels that are more than 100 times greater than those in plasma.
- **Step 2.** Following uptake, iodide undergoes oxidation to *iodine*, the active form of iodide. Iodide oxidation is catalyzed by an enzyme called *peroxidase*.
- **Step 3.** In this step, activated iodine becomes incorporated into tyrosine residues that are bound to *thyroglobulin*, a large glycoprotein. As indicated in Figure 58-2, one tyrosine molecule may receive either one or two iodine atoms, resulting in the production of monoiodotyrosine (MIT) or diiodotyrosine (DIT), respectively.
- **Step 4.** In this final step, iodinated tyrosine molecules are coupled. Coupling of one DIT with one MIT forms T_3 (step 4A); coupling of one DIT with another DIT forms T_4 (step 4B).

Fate. Thyroid hormones are released from the thyroid gland by a proteolytic process. The amount of T_4 released is substantially greater than the amount of T_3 released. However, much of the T_4 that is released undergoes conversion to T_3 by enzymes in peripheral tissues. In fact, conversion of T_4 to T_3 accounts for the majority (about 80%) of the T_3 found in plasma.

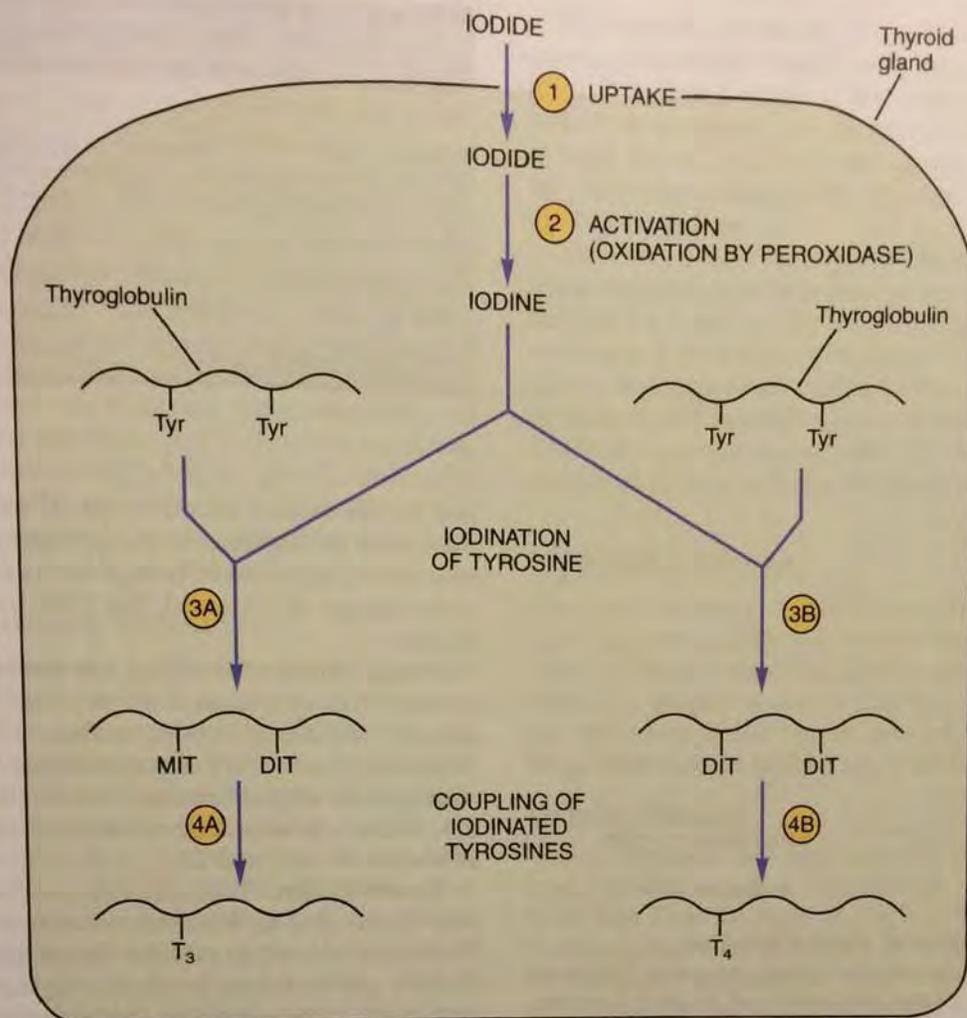


Figure 58-2 ■ Steps in thyroid hormone synthesis.

The reactions at each step (circled numbers) are explained in the text. (DIT = diiodotyrosine, MIT = monoiodotyrosine, T₃ = triiodothyronine, T₄ = thyroxine, Tyr = tyrosine.)

More than 99.5% of the T₃ and T₄ in plasma is bound to plasma proteins. Consequently, only a tiny fraction of circulating thyroid hormone is free to produce biologic effects.

Thyroid hormones are eliminated primarily by hepatic metabolism. Because T₃ and T₄ are extensively bound to plasma proteins, metabolism is slow. As a result, the half-lives of these hormones are prolonged—about 1 day for T₃ and 7 days for T₄.

Thyroid Hormone Actions

Thyroid hormones have three principal actions: (1) stimulation of energy use, (2) stimulation of the heart, and (3) promotion of growth and development. Stimulation of energy use elevates the basal metabolic rate, resulting in increased oxygen consumption and increased heat production. Stimulation of the heart increases both the rate and force of contraction, resulting in increased cardiac output and increased oxygen demand. Thyroid effects on growth and development are profound: Thyroid hormones are essential for normal development of the brain and other components of the nervous system, and they have a significant impact on maturation of skeletal muscle.

How do thyroid hormones produce their effects? By modulating the activity of specific genes. Furthermore, it appears that most, if not all, of the effects of thyroid hormones are

mediated by T₃, not by T₄. There is good evidence that T₃ penetrates to the cell nucleus and binds with high affinity to nuclear receptors, which in turn bind to specific DNA sequences. The result is modulation of gene transcription, causing production of proteins that mediate thyroid hormone effects. Although T₄ also binds with nuclear receptors, its affinity is low, and gene transcription is not altered. Hence it would seem that T₄ serves only as a source of T₃, having little or no physiologic effects of its own.

Regulation of Thyroid Function by the Hypothalamus and Anterior Pituitary

The functional relationship between the hypothalamus, anterior pituitary, and thyroid is depicted in Figure 58-3. As indicated, thyrotropin-releasing hormone (TRH), secreted by the hypothalamus, acts on the pituitary to cause secretion of thyrotropin (thyroid-stimulating hormone [TSH]). TSH then acts on the thyroid to stimulate all aspects of thyroid function: thyroid size is enlarged, iodine uptake is augmented, and synthesis and release of thyroid hormones are increased. In response to rising plasma levels of T₃ and T₄, further release of TSH is suppressed. The stimulatory effect of TSH on the thyroid, followed by the inhibitory effect of thyroid hormones on the pituitary, constitutes a negative feedback loop.

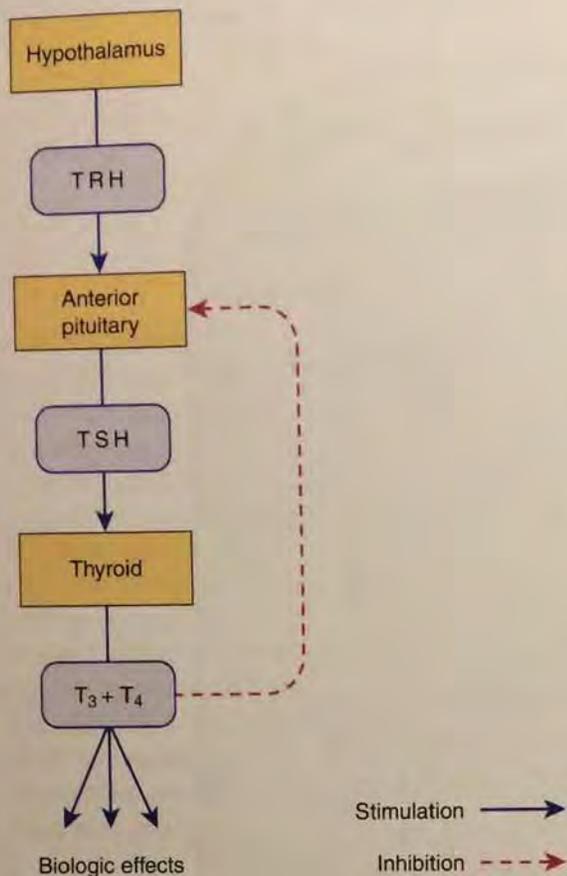


Figure 58-3 ■ Regulation of thyroid function.

TRH from the hypothalamus stimulates release of TSH from the pituitary. TSH stimulates all aspects of thyroid function, including release of T_3 and T_4 . T_3 and T_4 act on the pituitary to suppress further TSH release. (T_3 = triiodothyronine, T_4 = thyroxine, TRH = thyrotropin-releasing hormone, TSH = thyrotropin [thyroid-stimulating hormone].)

Effect of Iodine Deficiency on Thyroid Function

When iodine availability is diminished, production of thyroid hormones decreases. The ensuing drop in thyroid hormone levels promotes release of TSH, which acts on the thyroid to increase its size (causing goiter) and ability to concentrate iodine. If iodine deficiency is not too severe, the increased capacity for iodine uptake will restore normal production of T_3 and T_4 .

THYROID FUNCTION TESTS

Several laboratory tests can be used to evaluate thyroid function. Three are described below. Values indicating euthyroid (normal), hypothyroid, and hyperthyroid states are summarized in Table 58-1.

Serum TSH. Serum TSH determinations are used primarily for screening and diagnosis of hypothyroidism, and for monitoring replacement therapy in hypothyroid patients.

Measurement of serum TSH is the most sensitive method for diagnosing hypothyroidism. Why? Because the anterior pituitary is exquisitely sensitive to changes in thyroid hormone levels. As a result, very small reductions in serum T_3

TABLE 58-1 ■ Serum Values for Thyroid Function Tests

Thyroid Test	Serum Values		
	Normal	Hypothyroid	Hyperthyroid
Total T_4 (mcg/dL)	4.5–12.5	Under 4.5	Over 12.5
Free T_4 (ng/dL)	0.9–2	Under 0.9	Over 2
Total T_3 (ng/dL)	80–220	Under 80	Over 220
Free T_3 (pg/dL)	230–620	Under 230	Over 620
TSH (microunits/mL)	0.3–6	Over 6	Under 0.3

and T_4 can cause a dramatic rise in serum TSH. Therefore, even when the degree of hypothyroidism is minimal, it will be reflected by an abnormally high level of TSH. When replacement therapy is instituted, the TSH level should return to normal.

Serum TSH determinations can also be used to distinguish primary hypothyroidism from secondary hypothyroidism. In primary (thyroidal) hypothyroidism, TSH levels are *high*. However, in secondary hypothyroidism (hypothyroidism resulting from anterior pituitary dysfunction), TSH levels are low, normal, or even slightly elevated—despite the presence of low levels of T_3 and T_4 .

Serum T_4 Test. Testing can measure either *total T_4* (bound plus free) or *free T_4* . Measurement of free T_4 is preferred. The T_4 test can be used to monitor thyroid hormone replacement therapy, and to screen for thyroid dysfunction. However, in both cases, measurement of TSH is preferred.

Serum T_3 Test. As with T_4 , we can measure either total or free T_3 . Measurement of free T_3 is preferred. This test is useful for diagnosing hyperthyroidism. Why? Because, in this disorder, levels of T_3 often rise sooner and to a greater extent than do levels of T_4 . T_3 determinations can also be used to monitor thyroid hormone replacement therapy (all thyroid preparations should increase levels of T_3).

THYROID PATHOPHYSIOLOGY

Hypothyroidism

Hypothyroidism can occur at any age. In adults, mild deficiency of thyroid hormone is referred to simply as *hypothyroidism*. Severe deficiency is called *myxedema*. When hypothyroidism occurs in infants, the resulting condition is called *cretinism*.

Hypothyroidism in Adults

Clinical Presentation. Signs and symptoms of hypothyroidism depend on disease severity. With mild hypothyroidism, symptoms are subtle and may go unrecognized for what they are. In contrast, with moderate to severe disease, characteristic signs and symptoms emerge. The face is pale, puffy, and expressionless. The skin is cold and dry. The hair is brittle, and hair loss occurs. Heart rate and temperature are lowered. The patient may complain of lethargy, fatigue, and intolerance to cold. Mentation may be impaired. Thyroid enlargement (goiter) may occur if reduced levels of T_3 and T_4 promote excessive release of TSH.

Causes. Hypothyroidism in the adult is usually due to malfunction of the thyroid itself. In iodine-sufficient countries, the principal cause is *chronic autoimmune thyroiditis* (Hashimoto's thyroiditis). Other causes are insufficient iodine in the diet, surgical removal of the thyroid, and destruction of the thyroid by radioactive iodine. Adult hypothyroidism may also result from insufficient secretion of TSH and TRH.

Therapeutic Strategy. Hypothyroidism in adults requires replacement therapy with thyroid hormones. In almost all cases, treatment must continue lifelong. Today, the standard replacement regimen consists of *levothyroxine* (T_4) alone. Combined therapy with levothyroxine plus *liothyronine* (T_3) is an option. However, with only three exceptions, all studies to date indicate that combined T_3/T_4 offers no advantage over T_4 alone. (Remember, when we give T_4 , much of it is rapidly converted to T_3 , the active form of the hormone.) When replacement doses of T_4 are adequate, they can eliminate all signs and symptoms of thyroid deficiency.

Hypothyroidism During Pregnancy

Maternal hypothyroidism can result in permanent neuropsychologic deficits in the child. We have long known that *congenital* hypothyroidism can cause mental retardation and other developmental problems (see below under *Hypothyroidism in Infants*). However, it was not until 1999 that researchers demonstrated that *maternal* hypothyroidism—in the absence of fetal hypothyroidism—can decrease IQ and other aspects of neuropsychologic function in the child. The impact of maternal hypothyroidism is limited largely to the first trimester, a time during which the fetus is unable to produce thyroid hormones of its own. By the second trimester, the fetal thyroid gland is fully functional, and hence the fetus can supply its own hormones from then on. Therefore, to help ensure healthy fetal development, maternal hypothyroidism must be diagnosed and treated very early. Unfortunately, symptoms of hypothyroidism are often nonspecific (irritability, tiredness, poor concentration, etc.) or there may be no symptoms at all. Accordingly, some authorities now recommend routine screening for hypothyroidism as soon as pregnancy is confirmed. If hypothyroidism is diagnosed, replacement therapy should begin immediately.

When women taking thyroid supplements become pregnant, dosage requirements usually increase—often by as much as 50%. The need for increased dosage begins between weeks 4 and 8 of gestation, levels off around week 16, and then remains steady until parturition. To ensure adequate hormone levels, some authorities increase T_4 dosage by 30% as soon as pregnancy is confirmed. Further adjustments are based on serum TSH levels, which should be monitored closely.

Hypothyroidism in Infants

Clinical Presentation. Hypothyroidism in newborns may be permanent or transient. In either case, congenital hypothyroidism (cretinism) can cause mental retardation and derangement of growth. In the absence of thyroid hormones, the child develops a large and protruding tongue, potbelly, and dwarfish stature. Development of the nervous system, bones, teeth, and muscles is impaired.

Causes. Cretinism usually results from a failure in thyroid development. Other causes include autoimmune disease, severe iodine deficiency, TSH deficiency, and exposure to radioactive iodine *in utero*.

Therapeutic Strategy. Hypothyroidism in newborns requires replacement therapy with thyroid hormones. If treatment is initiated within a few days of birth, physical and mental development will be normal. However, if therapy is delayed beyond 3 to 4 weeks, some permanent retardation will be evident, although the physical effects of thyroid deficiency will reverse.

How long should replacement therapy last? In all children, treatment should continue for 3 years, after which it should be stopped for 4 weeks. The objective is to determine if thyroid deficiency is permanent or transient. If TSH rises, indicating thyroid hormone production is low, we know the deficiency is permanent, and hence replacement therapy should resume. If TSH and T_4 normalize, we know the deficiency was transient, and hence further replacement therapy is unnecessary.

Hyperthyroidism

There are two major forms of hyperthyroidism: *Graves' disease* and *toxic nodular goiter* (also known as *Plummer's disease*). Of the two disorders, Graves' disease is more common. Signs and symptoms of both disorders are similar. The principal difference is that Graves' disease may cause exophthalmos, whereas toxic nodular goiter does not.

Graves' Disease

Graves' disease is the most common cause of excessive thyroid hormone secretion. This disorder occurs most frequently in women 20 to 40 years of age. The incidence in females is 6 times greater than in males.

Clinical Presentation. Most clinical manifestations result from elevated levels of thyroid hormone. Heartbeat is rapid and strong, and dysrhythmias and angina may develop. The central nervous system is stimulated, resulting in nervousness, insomnia, rapid thought flow, and rapid speech. Skeletal muscles may weaken and atrophy. Metabolic rate is raised, resulting in increased heat production, increased body temperature, intolerance to heat, and skin that is warm and moist. Appetite is increased. However, despite increased food consumption, weight loss occurs if caloric intake fails to match the increase in metabolic rate. Collectively, the above signs and symptoms are referred to as *thyrotoxicosis*.

In addition to thyrotoxicosis, patients with Graves' disease often present with *exophthalmos* (protrusion of the eyeballs). The underlying cause is an immune-mediated infiltration of the extraocular muscles and orbital fat by lymphocytes, macrophages, plasma cells, mast cells, and mucopolysaccharides.

Cause. Thyroid stimulation in Graves' disease is caused by thyroid-stimulating immunoglobulins (TSIs), which are antibodies produced by an autoimmune process. TSIs increase thyroid activity by stimulating receptors for TSH on the thyroid gland. That is, TSIs mimic the effects of TSH on thyroid function. TSIs are not responsible for exophthalmos.

Treatment. Treatment for Graves' disease is directed at decreasing the production of thyroid hormones. Three modalities are employed: (1) surgical removal of thyroid tissue, (2) destruction of thyroid tissue with radioactive iodine, and (3) suppression of thyroid hormone synthesis with an antithyroid drug (methimazole or propylthiouracil). Radiation is the preferred treatment for adults, whereas antithyroid drugs are preferred for younger patients.

Beta blockers (eg, propranolol) and nonradioactive iodine may be used as adjunctive therapy. Beta blockers suppress tachycardia by blocking beta receptors on the heart. Nonradioactive iodine inhibits synthesis and release of thyroid hormones.

Since exophthalmos is not the result of hyperthyroidism *per se*, this condition is not improved by lowering thyroid hormone production. If exophthalmos is severe, it can be treated with surgery or with high doses of oral glucocorticoids.

Toxic Nodular Goiter (Plummer's Disease)

Toxic nodular goiter is the result of a thyroid adenoma. Clinical manifestations are much like those of Graves' disease, except exophthalmos is absent. Toxic nodular goiter is a persistent condition that rarely undergoes spontaneous remission. Treatment modalities are the same as for Graves' disease. However, if an antithyroid drug is used, symptoms return rapidly when the drug is withdrawn. Accordingly, surgery and radiation, which provide long-term control, are often preferred.

Thyrotoxic Crisis (Thyroid Storm)

Thyrotoxic crisis can occur in patients with severe thyrotoxicosis when they undergo major surgery or develop a severe intercurrent illness (eg, infection, sepsis). The syndrome is characterized by profound hyperthermia (105°F or even higher), severe tachycardia, restlessness, agitation, and tremor. Unconsciousness, coma, hypotension, and heart failure may ensue. These symptoms are produced by excessive levels of thyroid hormones.

Thyrotoxic crisis can be life threatening and requires immediate treatment. High doses of potassium iodide or strong iodine solution are given to suppress thyroid hormone release. Propylthiouracil is given to suppress thyroid hormone synthesis and peripheral conversion of T_4 to T_3 . A beta blocker is given to reduce heart rate. Additional measures include sedation, cooling, and giving glucocorticoids and IV fluids.

THYROID HORMONE PREPARATIONS FOR HYPOTHYROIDISM

Thyroid hormones are available as pure, synthetic compounds and as extracts of animal thyroid glands. All preparations have qualitatively similar effects. The synthetic preparations are more stable and better standardized than the animal gland

extracts. As a result, the synthetics are preferred to the natural products. Properties of thyroid hormone preparations are summarized in Table 58-2.

Levothyroxine (T_4)

Levothyroxine [Levothroid, Synthroid, others] is a synthetic preparation of thyroxine (T_4), a naturally occurring thyroid hormone. The structure of levothyroxine is identical to that of the natural hormone. Levothyroxine is the drug of choice for most patients who require thyroid hormone replacement. Consequently, levothyroxine will serve as our prototype for the thyroid hormone preparations.

Pharmacokinetics

Absorption. Absorption of oral levothyroxine is reduced by food. Accordingly, to minimize variability in blood levels, levothyroxine should be taken on an empty stomach in the morning, at least 30 to 60 minutes before breakfast.

Conversion to T_3 . Much of an administered dose of levothyroxine is converted to T_3 in the body. As a result, levothyroxine can produce nearly normal levels of both T_3 and T_4 . Hence, for most patients, there is no need to give T_3 along with levothyroxine.

Half-Life and Plasma Levels. Because levothyroxine is highly protein bound (about 99.97%), the hormone has a prolonged half-life (about 7 days). From a clinical perspective, this long half-life is good news and bad news. The good news is that hormone levels remain fairly steady, even with once-a-day dosing, which makes levothyroxine well suited for lifelong therapy. The bad news is that it takes about 1 month (four half-lives) for plasma levels of levothyroxine to reach plateau (steady state). As a result, onset of full effects is delayed.

Therapeutic Uses

Levothyroxine is indicated for all forms of hypothyroidism, regardless of cause. The drug is used for cretinism, myxedema coma, simple goiter, and primary hypothyroidism in adults and children. Levothyroxine is also used to treat hypothyroidism resulting from insufficient TSH (secondary to pituitary malfunction) and from insufficient TRH (secondary to hypothalamic malfunction). In addition, levothyroxine is used to maintain proper levels of thyroid hormones following thyroid surgery, irradiation, and treatment with antithyroid drugs.

TABLE 58-2 • Thyroid Hormone Preparations

Generic Name	Trade Names	Dosage Forms	Approximate Equivalent Dosage*	Description
Levothyroxine	Levothroid, Levoxyl, Synthroid, Thyro-Tabs	Tablets, injection	50–60 mcg	Synthetic preparation of T_4 identical to the naturally occurring hormone
Liothyronine	Cytomel, Triostat	Tablets, injection	15–37 mcg	Synthetic preparation of T_3 identical to the naturally occurring hormone
Liotrix	Thyrolar	Tablets	60 mcg	Synthetic T_4 plus synthetic T_3 in a 4:1 fixed ratio
Thyroid	Armour Thyroid, Bio-Thyroid, Nature-Thyroid, Thyroid USP, Westhroid	Tablets, capsules	60 mg	Desiccated animal thyroid glands (rarely used today)

*Approximate dosage needed to produce equivalent effects.

Levothyroxine and other thyroid hormones should not be taken to treat obesity. These hormones will accelerate metabolism and promote weight reduction only if the dosage is high enough to establish a pathologic (hyperthyroid) state.

Adverse Effects

When administered in appropriate dosage, levothyroxine rarely causes adverse effects. With an acute overdose, *thyrotoxicosis* may result. Signs and symptoms include tachycardia, angina, tremor, nervousness, insomnia, hyperthermia, heat intolerance, and sweating. The patient should be informed about these signs and instructed to notify the prescriber if they develop. Chronic overdosage is associated with accelerated bone loss and increased risk of atrial fibrillation, especially in the elderly. Loss of bone increases the risk of fractures.

Drug Interactions

Drugs That Reduce Levothyroxine Absorption. Absorption of levothyroxine can be reduced by the following drugs:

- H₂-receptor blockers (eg, cimetidine [Tagamet])
- Proton pump inhibitors (eg, lansoprazole [Prevacid])
- Sucralfate [Carafate]
- Cholestyramine [Questran]
- Colestipol [Colestid]
- Aluminum-containing antacids (eg, Maalox, Mylanta)
- Calcium supplements (eg, Tums, Os-Cal)
- Iron supplements (eg, ferrous sulfate)
- Magnesium salts
- Orlistat [Xenical]

To ensure adequate absorption of levothyroxine, patients should separate administration of levothyroxine and these drugs by 4 hours. As noted above, food also reduces absorption.

Drugs That Accelerate Levothyroxine Metabolism.

Several drugs can accelerate the metabolism of levothyroxine. Among these are phenytoin [Dilantin], carbamazepine [Tegretol, Carbatrol], rifampin [Rifadin, Rimactane], sertraline [Zoloft], and phenobarbital. Accordingly, in order to maintain adequate levothyroxine levels, patients taking these drugs may need to increase their levothyroxine dosage.

Warfarin. Levothyroxine accelerates the degradation of vitamin K–dependent clotting factors. As a result, effects of warfarin (an anticoagulant) are enhanced. If thyroid hormone replacement therapy is started in a patient taking warfarin, the dosage of warfarin may need to be reduced.

Catecholamines. Thyroid hormones increase cardiac responsiveness to catecholamines (epinephrine, dopamine, dobutamine), thereby increasing the risk of catecholamine-induced dysrhythmias. Caution must be exercised when administering catecholamines to patients receiving levothyroxine and other thyroid preparations.

Other Interactions. Levothyroxine can increase requirements for *insulin* and *digoxin*. Hence, when converting patients from a hypothyroid to a euthyroid state, dosages of insulin and digoxin may need to be increased.

Are Levothyroxine Preparations Interchangeable?

Levothyroxine is available in several brand-name and generic formulations. Whether any of these are interchangeable is in dispute.

Levothyroxine has a narrow therapeutic range, and hence tight control of plasma drug levels is important. Otherwise,

symptoms of hypothyroidism or toxicity will develop. In order to maintain good control, all pills a patient takes must produce the same levothyroxine levels. Accordingly, if a patient switches from one product to another, the new product must be bioequivalent to the old one.

Whether or not any levothyroxine products—brand-name or generic—are truly equivalent is a point of contention. According to the Food and Drug Administration (FDA), certain formulations of levothyroxine are therapeutically equivalent to others. For example, the FDA maintains that generic levothyroxine made by Mylan is equivalent to two brand-name products: Levoxyl and Synthroid. However, three medical organizations—the American Association of Clinical Endocrinologists (AACE), The Endocrine Society (TES), and the American Thyroid Association (ATA)—*strongly* disagree, as expressed in a 2004 position statement. Why do they disagree? Because they believe the FDA's testing procedure was seriously flawed. First, the FDA only measured blood levels of levothyroxine; they did not measure serum TSH, the favored clinical test for assessing thyroid status. Second, and more important, testing was done in *normal* (euthyroid) volunteers. Hence, when blood levels of levothyroxine were measured, the values reflected the sum of endogenous thyroxine plus levothyroxine contributed by the drug—making it impossible to state with precision how much of the total was truly due to the drug. As a result, conclusions regarding the equivalence of levothyroxine products are questionable. Nonetheless, pharmacists may switch patients from one product to another, often without the knowledge of the patient or prescriber—a practice with the potential for causing toxicity or therapeutic failure.

Given the debate about whether certain levothyroxine products are clinically interchangeable, what should the clinician do? In their position statement, the AACE, TES, and ATA recommend the following:

- Maintain patients on the same brand-name levothyroxine product.
- If a switch *is* made (from one branded product to another, from a branded product to a generic product, or from one generic product to another), retest serum TSH in 6 weeks, and adjust the levothyroxine dosage as indicated.
- Advise patients to check with their prescriber before allowing a pharmacist to switch to a different levothyroxine product.

Dosage and Administration I: General Considerations

Routes of Administration. Levothyroxine is almost always administered by mouth. Oral doses should be taken once daily on an empty stomach (to enhance absorption). *Dosing is usually done in the morning, at least 30 to 60 minutes before breakfast.*

Intravenous administration is used for myxedema coma and for patients who cannot take levothyroxine orally. Intravenous doses are about 80% of the size of oral doses.

Evaluation. The goal of replacement therapy is to provide a dosage that compensates precisely for the existing thyroid deficit. This dosage is determined using a combination of clinical judgment and laboratory tests. When therapy is successful in adults, clinical evaluation should reveal a reversal of the signs and symptoms of thyroid deficiency—and an absence of signs of thyroid excess. Successful therapy of infants

is reflected in normalization of intellectual function and normalization of growth and development. Monthly determinations of height provide a good index of success.

Measurement of serum TSH is an important means of evaluation. Successful replacement therapy causes elevated TSH levels to fall. However, TSH will not normalize quickly, and often lags behind normalization of serum T_3 and T_4 . Hence, evaluation should not be done until 6 to 8 weeks after starting treatment. A TSH target of 0.5 to 2 microunits/mL is appropriate for most patients. Once an adequate replacement dosage is established, TSH levels will remain suppressed for the duration of treatment.

In some cases, serum T_4 must be used to evaluate therapy. Why? Because, in some patients, TSH secretion remains high even though levels of thyroid hormones have been restored to normal. When this happens, success is indicated by levels of T_4 in the normal to high-normal range—whether or not TSH values are normal.

Duration of Therapy. For most hypothyroid patients, replacement therapy must be continued for life. Treatment provides symptomatic relief but does not produce cure. Patients must be made fully aware of the chronic nature of their condition. In addition, they should be forewarned that, although therapy will cause symptoms to improve, these improvements do not constitute a reason to interrupt or discontinue drug use.

Dosage and Administration II: Specific Applications

Hypothyroidism in Adults. When calculated on a body weight basis, the average adult dosage is about 1.6 mcg/kg/day. Most patients under the age of 50 or so can be started on full replacement doses (100 to 125 mcg/day for a 70-kg adult). For older patients, dosage should be low initially and then gradually increased. A typical starting dosage is 25 to 50 mcg/day. For elderly patients with coronary heart disease, the starting dosage is even lower—between 12.5 and 25 mcg/day.

Myxedema Coma. Myxedema coma is a rare but serious condition that requires rapid treatment. Levothyroxine is administered IV in a dose of 200 to 500 mcg. If required, an additional dose of 100 to 300 mcg can be given 1 day later. Glucocorticoids (eg, hydrocortisone) are also required.

Cretinism. In cretinism, thyroid hormone dosage decreases with age. For infants less than 3 months old, the dosage is 10 to 15 mcg/kg/day; for children ages 3 to 6 months, 8 to 10 mcg/kg/day; for children ages 6 to 12 months, 6 to 8 mcg/kg/day; for children ages 1 to 5 years, 5 to 6 mcg/kg/day; and for children ages 5 to 12 years, 4 to 5 mcg/kg/day. In all cases, dosage is adjusted to normalize TSH and free T_4 .

Simple Goiter. In simple goiter, the thyroid is enlarged and levels of thyroid hormones are reduced. Thyroid enlargement is caused by TSH that has been released in response to low levels of thyroid hormones. When treating simple goiter, the goal is to provide full replacement doses of thyroid hormones, so as to suppress further TSH release. For many patients, this can be achieved with 100 to 200 mcg of levothyroxine daily.

Liothyronine (T_3)

Liothyronine [Cytomel, Triostat] is a synthetic preparation of triiodothyronine (T_3), a naturally occurring thyroid hormone. The structure of liothyronine is identical to that of thyroid-derived T_3 . Since liothyronine is the active form of levothyroxine, the effects of the two drugs are identical.

Contrasts with Levothyroxine. Liothyronine differs from levothyroxine in three important ways: (1) liothyronine has a shorter half-life and shorter duration of action, (2) liothyronine has a more rapid onset, and (3) liothyronine is more expensive. Because of its high price and relatively brief duration of action, liothyronine is less desirable than levothyroxine for long-term use. However, because its effects develop quickly, liothyronine may be superior to levothyroxine in situations that require speedy results, especially myxedema coma.

Evaluation. As with levothyroxine, the dosage of liothyronine is adjusted on the basis of clinical evaluation and laboratory data. Two laboratory tests are useful: free serum T_3 and serum TSH. Since liothyronine is not converted into T_4 , plasma levels of T_4 remain low. Hence, T_4 levels cannot be used to assess treatment.

Dosage and Administration. The usual route is oral, using Cytomel although dosing may also be done IV, using Triostat. Oral dosage is about 80% of the dosage of levothyroxine. Because of its short half-life, oral liothyronine is taken twice daily, in contrast to levothyroxine, which is taken once daily.

Other Thyroid Preparations

Liotrix

Liotrix [Thyrolar] is a mixture of synthetic T_4 plus synthetic T_3 in a 4:1 fixed ratio. (This ratio is similar to the ratio of these hormones in plasma.) The rationale for using liotrix is that the mixture can produce plasma levels of T_4 and T_3 similar to those that occur naturally. However, since levothyroxine alone produces the same ratio of T_4 to T_3 , liotrix offers no advantage over levothyroxine for most indications.

Thyroid (Desiccated)

Thyroid [Armour Thyroid, others] consists of desiccated animal thyroid glands. Standardization is based on content of iodine, levothyroxine, and liothyronine. The ratio of levothyroxine to liothyronine is not less than 5:1. Thyroid is available in tablets (15 to 300 mg) and capsules (7.5 to 240 mg). For practical purposes, thyroid is obsolete; Use is limited to patients who have been taking the preparation for years. Thyroid is rarely prescribed for patients starting therapy today.

DRUGS FOR HYPERTHYROIDISM

Antithyroid Drugs: Thionamides

The thionamide drugs—methimazole and propylthiouracil (PTU)—suppress synthesis of thyroid hormones. These agents can be used long term to treat hyperthyroidism, or short term as preparation for subtotal thyroidectomy or therapy with radioactive iodine. Methimazole and PTU are similar in most respects. Primary differences concern pharmacokinetics (Table 58-3) and adverse effects.

Methimazole

Methimazole [Tapazole, Northyx] is a first-line drug for hyperthyroidism. Benefits derive from inhibiting thyroid hormone synthesis. Methimazole is safer and more convenient than PTU, and hence is preferred for most patients—except women who are pregnant or breast-feeding, and perhaps patients who are in thyrotoxic crisis.

Mechanism of Action. Therapeutic effects result from blocking synthesis of thyroid hormones. Two mechanisms are involved. First, methimazole prevents the oxidation of iodide, thereby inhibiting incorporation of iodine into tyrosine. Second, methimazole prevents iodinated tyrosines from coupling. Both effects result from inhibiting peroxidase, the enzyme that catalyzes both reactions.

TABLE 58-3 ■ Pharmacokinetics of Methimazole and Propylthiouracil

	Methimazole	Propylthiouracil
Bioavailability	80–95%	80–95%
Plasma protein binding	0	75–80%
Levels in breast milk	Higher	Low
Transplacental passage	Higher	Low
Half-life	6–13 hr	1–2 hr
Dosing frequency		
Initial therapy	1–3 times a day	3 or 4 times a day
Maintenance therapy	Once a day	2 or 3 times a day

Please note that, although methimazole prevents thyroid hormone synthesis, it does not destroy existing stores of thyroid hormone. Hence, once therapy has begun, it may take 3 to 12 weeks to produce a euthyroid state.

Pharmacokinetics. Methimazole is well absorbed following oral dosing. Binding to plasma proteins is minimal. The drug readily crosses membranes, including those of the placenta. Levels in breast milk are sufficient to affect the nursing infant. The plasma half-life is 6 to 13 hours—long enough to permit once-a-day dosing.

Therapeutic Uses Methimazole has four applications in hyperthyroidism:

- It can be used as the sole form of therapy for Graves' disease.
- It can be employed as an adjunct to radiation therapy until the effects of radiation become manifest.
- It can be given to suppress thyroid hormone synthesis in preparation for thyroid gland surgery (subtotal thyroidectomy).
- It can be given to patients experiencing thyrotoxic crisis (although PTU is preferred).

Adverse Effects. Methimazole is generally well tolerated, but should be avoided by women who are pregnant or breast-feeding. Agranulocytosis is the most dangerous toxicity.

Agranulocytosis. Agranulocytosis is a serious condition characterized by a dramatic reduction in circulating granulocytes, a type of white blood cell needed to fight infection. The reaction is rare (about 3 cases per 10,000 patients) and usually develops during the first 2 months of therapy. Sore throat and fever may be the earliest indications, and patients should be instructed to report these immediately. Because agranulocytosis often develops rapidly, periodic blood counts cannot guarantee early detection. If agranulocytosis occurs, methimazole should be discontinued. Agranulocytosis will then reverse. Treatment with granulocyte colony-stimulating factor (filgrastim [Neupogen]) may accelerate recovery.

Hypothyroidism. When given in high doses, methimazole can convert the patient from a hyperthyroid state to a hypothyroid state. If this occurs, dosage should be reduced. Temporary treatment with thyroid hormone may be required.

Effects in Pregnancy. Methimazole can cause neonatal hypothyroidism, goiter, and even cretinism. Accordingly, the drug should be avoided during the first trimester. Use in the second and third trimesters is considered safe. Compared with methimazole, PTU crosses the placenta poorly, and hence risk to the fetus is low. Accordingly, if a thionamide is needed during the first trimester of pregnancy, PTU is the preferred drug.

Effects in Lactation. Methimazole achieves significant levels in breast milk, and is contraindicated during pregnancy. If a thionamide must be used, PTU should be selected.

Preparations, Dosage, and Administration. Methimazole is supplied in tablets (5, 10, 15, and 20 mg) for oral dosing. For treatment of Graves' disease, doses are high initially (eg, 30 to 40 mg once a day) and then decreased for maintenance (5 to 15 mg once a day). As a rule, treatment continues for 1 to 2 years. When methimazole is discontinued, some 30% to 40% of patients remain euthyroid, indicating remission. Others become hyperthyroid in 1 to 4 weeks, indicating relapse. If relapse occurs, another round of methimazole can be tried. Alternatively, the patient can opt for radiation therapy or surgery.

Propylthiouracil

Like methimazole, PTU suppresses synthesis of thyroid hormones, and can be used for Graves' disease and other hyperthyroid states. Propylthiouracil, a much older drug than methimazole, is now considered a second-line treatment.

Contrasts with Methimazole. Propylthiouracil is much like methimazole, but with four significant differences:

- First, and most important, PTU can cause severe liver injury, whereas methimazole does not.
- Second, PTU has a shorter half-life than methimazole (90 minutes vs. 6 to 13 hours), and hence requires 2 or 3 daily doses rather than one.
- Third, PTU crosses the placenta less readily than does methimazole, and achieves lower concentrations in breast milk.
- Fourth, PTU blocks conversion of T_4 to T_3 in the periphery, whereas methimazole does not.

Current Role in Treating Hyperthyroidism. Because PTU is more toxic than methimazole and requires more daily doses, methimazole is preferred for most patients. However, there are four groups for whom PTU is preferred. These are:

- Pregnant women, but only during the first trimester. (Methimazole is preferred during the second and third trimesters.)
- Women who are breast-feeding (but only if a thionamide is absolutely needed).
- Patients experiencing thyroid storm. (Because PTU can block conversion of T_4 to T_3 , it may be more effective than methimazole.)
- Patients who are intolerant of methimazole.

Pharmacokinetics. Propylthiouracil is rapidly absorbed following oral administration. Therapeutic actions begin within 30 minutes. Plasma protein binding is moderate (75% to 80%). The half-life is short (about 90 minutes), and hence PTU must be administered 2 or 3 times a day. Transplacental passage is low, as is entry into breast milk.

Adverse Effects. As with methimazole, adverse effects are relatively rare. Nonetheless, severe adverse effects can occur, especially liver injury and agranulocytosis. The most common undesired effect is rash. PTU may also cause nausea, arthralgia, headache, dizziness, and paresthesias.

Adverse Effects Shared with Methimazole. Like methimazole, PTU has caused rare cases of agranulocytosis, and can cause hypothyroidism if the dosage is too high. In addition, PTU can harm the developing fetus and the breast-feeding infant, although the risk is lower than with methimazole.

Liver Injury. Propylthiouracil has caused rare cases of severe liver injury. Transplants have been required, and deaths have occurred. Children are especially vulnerable. The incidence in children is 1 case in 2000, compared with 1 case in 10,000 for adults. Liver toxicity is unrelated to dosage or duration of treatment. Furthermore, onset is sudden and progression is rapid, and hence performing routine tests of liver function doesn't help. Patients should be forewarned of the potential for liver injury, and instructed to promptly report any signs, such as fatigue, weakness, abdominal pain, reduced appetite, dark urine, or yellowing of the eyes or skin. If these signs appear, PTU should be discontinued until hepatotoxicity has been ruled out.

Preparations, Dosage, and Administration. Propylthiouracil is available in 50-mg tablets for oral use. Because of its short half-life, PTU requires multiple daily doses.

Treatment of Graves' Disease. High doses (100 to 300 mg 3 times a day) are used initially. Lower doses (eg, 50 mg 3 times a day) are used for maintenance. As a rule, treatment continues for 1 to 2 years.

Radioactive Iodine (^{131}I)

Physical Properties

Iodine-131 (formerly available as Iodotope) is a radioactive isotope of stable iodine that emits a combination of beta particles and gamma rays. Radioactive decay of ^{131}I takes place rapidly, with a half-life of 8 days. Hence, after 56 days (seven half-lives), less than 1% of the radioactivity in a dose of ^{131}I remains.

Use in Graves' Disease

Iodine-131 can be used to destroy thyroid tissue in patients with hyperthyroidism. The objective is to produce clinical remission without causing complete destruction of the gland.

Unfortunately, delayed hypothyroidism, due to excessive thyroid damage, is a frequent complication.

Effect on the Thyroid. Like stable iodine, ^{131}I is concentrated in the thyroid gland. Destruction of thyroid tissue is produced primarily by emission of beta particles. (The gamma rays from ^{131}I are relatively harmless.) Because beta particles have a very limited ability to penetrate any type of physical barrier, they do not travel outside the thyroid. Hence, damage to surrounding tissue is minimal.

Reduction of thyroid function is gradual. Initial effects become apparent in days or weeks. Full effects develop in 2 to 3 months.

Not all patients respond satisfactorily to a single treatment. About 66% of patients with Graves' disease are cured with a single exposure to ^{131}I . Others require two or more treatments.

Advantages and Disadvantages of ^{131}I Therapy. The advantages of ^{131}I treatment are considerable: (1) low cost; (2) patients are spared the risks, discomfort, and expense of thyroid surgery; (3) death from ^{131}I treatment is extremely rare; and (4) no tissue other than the thyroid is injured (patients should be reassured of this).

Treatment with ^{131}I is not without drawbacks. First, the effect of treatment is delayed, taking several months to become maximal. Second, and more important, treatment is associated with a significant incidence of delayed hypothyroidism. Hypothyroidism results from excessive dosage and occurs in up to 90% of patients within the first year following ^{131}I exposure.

Who Should Be Treated and Who Should Not. Patients over the age of 30 may be candidates for ^{131}I therapy. Iodine-131 also is indicated for patients who have not responded adequately to antithyroid drugs or to subtotal thyroidectomy.

As a rule, very young children are considered inappropriate candidates. The likelihood of delayed hypothyroidism is higher than in adults. Also, there is concern that administration of ^{131}I to young patients may carry a slight risk of cancer. It should be noted, however, that there is no evidence that the use of ^{131}I in Graves' disease has ever caused cancer of the thyroid or any other tissue. Although ^{131}I is generally avoided in young children, it is commonly used in postpubertal adolescents and young adults.

Iodine-131 is *contraindicated in pregnancy and lactation*. Exposure of the fetus to ^{131}I after the first trimester may damage the immature thyroid, and exposure to radiation at any point in fetal life carries a risk of generalized developmental harm. Accordingly, a negative pregnancy test is required before giving ^{131}I . Because ^{131}I enters breast milk, women receiving this agent should not breast-feed.

Dosage. Dosage of ^{131}I is determined by thyroid size and by the rate of thyroidal iodine uptake. For Graves' disease, the dosage usually ranges between 4 and 10 millicuries (mCi).

Use in Thyroid Cancer

Iodine-131 can be used to destroy malignant thyroid cells. However, since most forms of thyroid cancer do not accumulate iodine, only a small percentage of patients are candidates for ^{131}I therapy.

The doses of ^{131}I used to treat cancer are large, ranging from 50 to 150 mCi. These doses are much higher than those used in Graves' disease. Because high amounts of radioactivity are involved, body wastes must be disposed of properly. In addition, adverse effects from large doses of ^{131}I can

be severe: radiation sickness may occur; leukemia may be produced; and bone marrow function may be depressed, resulting in leukopenia, thrombocytopenia, and anemia. Fortunately, these severe effects are rare.

Diagnostic Use

Iodine-131 is employed to diagnose a variety of thyroid disorders, including hyperthyroidism, hypothyroidism, and goiter. Following ^{131}I administration, the thyroid is scanned for uptake of radioactivity; the amount and location of ^{131}I uptake reveal the extent of thyroid activity. Doses for diagnosis are minuscule (less than 1 microcurie for children and less than 10 microcuries for adults). These tracer doses pose virtually no threat to health. Please note that, although ^{131}I can be used for diagnosis, the preferred isotope is ^{123}I .

Preparations

Iodine-131 is supplied in capsules and solution for oral administration. Both preparations are odorless and tasteless. Capsules contain between 0.75 and 100 mCi of ^{131}I . Vials of oral solution contain between 3.5 and 150 mCi of ^{131}I .

Nonradioactive Iodine: Lugol's Solution

Description. Lugol's solution, also known as *strong iodine solution*, is a mixture containing 5% elemental iodine and 10% potassium iodide. The iodine undergoes reduction to iodide within the GI tract prior to absorption.

Mechanism of Action. When present in high concentrations, iodide has a paradoxical suppressant effect on the thyroid. Three mechanisms are involved. First, high concentrations of iodide decrease iodine uptake by the thyroid. Second, high concentrations of iodide inhibit thyroid hormone synthesis by suppressing both the iodination of tyrosine and the coupling of iodinated tyrosine residues. Third, high concentrations of iodine inhibit release of thyroid hormone into the blood. All three actions combine to decrease circulating levels of T_3 and T_4 .

Unfortunately, the effects of iodide on thyroid function cannot be sustained indefinitely. With long-term iodide administration, suppressant effects become weaker. Accordingly, iodide is rarely used alone for thyroid suppression.

Therapeutic Use. Strong iodine solution can be given to hyperthyroid individuals to suppress thyroid function in preparation for thyroidectomy. Initial effects develop within 24 hours. Peak effects develop in 10 to 15 days. In most cases, plasma levels of thyroid hormone are reduced with PTU before initiating strong iodine solution. Then iodine solution (along with more PTU) is administered for the last 10 days prior to surgery. In addition to its use prior to thyroidectomy, strong iodine solution is employed in thyrotoxic crisis and as an antiseptic (see Chapter 96).

Adverse Effects. Chronic ingestion of iodine can produce *iodism*. Signs and symptoms include a brassy taste, a burning sensation in the mouth and throat, soreness of the teeth and gums, frontal headache, coryza (nasal inflammation and sneezing), salivation, and various skin eruptions. All of these fade rapidly after iodine use stops.

Overdose. Iodine is corrosive, and hence overdose will injure the GI tract. Symptoms include abdominal pain, vomiting, and diarrhea. Swelling of the glottis may cause asphyxiation. Treatment consists of gastric lavage (to remove iodine from the stomach) and giving sodium thiosulfate (to reduce iodine to iodide).

Dosage and Administration. When employed to prepare hyperthyroid patients for thyroidectomy, strong iodine solution is administered in a dosage of 2 to 6 drops 3 times daily for 10 days immediately preceding surgery. Iodine solution should be mixed with juice or some other beverage to mask its unpleasant taste. The dosage for thyrotoxic crisis is 5 to 8 drops every 6 hours.

Beta Blockers

Propranolol [Inderal, InnoPran XL] and other beta blockers can suppress tachycardia and other symptoms of *Graves' disease*. Benefits derive from beta-adrenergic blockade, not from reducing levels of T_3 or T_4 . One advantage of beta blockers is that they work quickly, unlike PTU, methimazole, and ^{131}I . Dosages for hyperthyroidism are highly individualized.

Beta blockers are also beneficial in *thyrotoxic crisis*. In the absence of contraindications (eg, asthma, heart failure), all patients should receive one immediately. Administration may be oral or IV. The dosage for propranolol is 80 to 120 mg PO every 6 hours or 2 to 4 mg IV every 4 hours.

The basic pharmacology of beta blockers is discussed in Chapter 18.

KEY POINTS

- The thyroid gland produces two active hormones: triiodothyronine (T_3), which is highly active, and thyroxine (T_4 , tetraiodothyronine), which appears inactive.
- Thyroid hormones have three principal actions: stimulation of energy use, stimulation of the heart, and promotion of growth and development.
- Hormonal regulation of thyroid function occurs as follows: TRH from the hypothalamus causes the pituitary to release TSH, which causes the thyroid to make and release T_3 and T_4 , which then act on the pituitary to suppress further release of TSH.
- The four steps in thyroid hormone synthesis are (1) uptake of iodide by the thyroid, (2) conversion of iodide to iodine, (3) linking of iodine to tyrosine, and (4) coupling of two iodinated tyrosines to form T_3 or T_4 .
- Much of the T_4 released by the thyroid is converted to T_3 in the periphery.
- Low plasma levels of iodine stimulate synthesis of T_3 and T_4 .
- In iodine-sufficient areas, the major cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's thyroiditis).
- A goiter is an enlargement of the thyroid.
- Testing serum for elevated levels of TSH is the most sensitive way to diagnose hypothyroidism.
- Most patients with hypothyroidism require lifelong replacement therapy with thyroid hormones.
- Maternal hypothyroidism during the first trimester of pregnancy can result in permanent neuropsychologic deficits in the child.
- Levothyroxine (synthetic T_4) is the drug of choice for most patients who require thyroid hormone replacement.
- There is debate as to whether certain levothyroxine preparations are interchangeable. Until the debate is resolved, it would seem best for patients to use only one product, unless the switch is approved of and monitored by the prescriber.
- Levothyroxine should be taken on an empty stomach in the morning, at least 30 to 60 minutes before breakfast.
- Chronic overtreatment with levothyroxine can cause atrial fibrillation and bone loss, especially in the elderly.
- Many drugs, including cholestyramine [Questran], colestipol [Colestid], sucralfate [Carafate], H_2 -receptor blockers, proton pump inhibitors, aluminum-containing antacids, iron supplements, and calcium supplements can significantly reduce levothyroxine absorption. At least 4 hours should separate administration of levothyroxine and these drugs.
- Levothyroxine can intensify the anticoagulant effects of warfarin.
- Graves' disease is the most common cause of excessive thyroid hormone secretion.
- Graves' disease can be treated by surgical removal of thyroid tissue, destruction of thyroid tissue with radioactive iodine (^{131}I), or treatment with antithyroid drugs (methimazole or propylthiouracil).
- Methimazole, an antithyroid drug, benefits patients with hyperthyroidism by suppressing thyroid hormone synthesis.
- Full benefits of methimazole may take 3 to 12 weeks to develop.
- The most serious adverse effect of methimazole is agranulocytosis.
- Methimazole is contraindicated during breast-feeding, and should be avoided during the first trimester of pregnancy.
- Full effects of ^{131}I require 2 to 3 months to develop.
- Iodine-131 is contraindicated during pregnancy and lactation.
- Strong iodine solution (Lugol's solution) can be used to suppress thyroid hormone synthesis.

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Summary of Major Nursing Implications*

LEVOTHYROXINE (T_4)

Preadministration Assessment

Therapeutic Goal

Resolution of signs and symptoms of hypothyroidism and restoration of normal laboratory values for serum TSH and free T_4 .

Baseline Data

Obtain serum levels of TSH and free T_4 .

Implementation: Administration

Routes

Oral, IV.

Administration

Oral. Instruct the patient to take levothyroxine on an empty stomach in the morning, at least 30 to 60 minutes before breakfast.

Make certain the patient understands that replacement therapy must continue for life. Caution patients against discontinuing treatment without consulting the prescriber.

Intravenous. Intravenous administration is reserved for treating myxedema coma and for patients who cannot take levothyroxine orally.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Adults. Clinical evaluation should reveal reversal of signs of thyroid deficiency and an absence of signs of thyroid excess (eg, tachycardia). Laboratory tests should indicate normal plasma levels of TSH and T₄.

Infants. Clinical evaluation should reveal normalization of intellectual function, growth, and development. Monthly measurements of height provide a good index of thyroid sufficiency. Laboratory tests should show normal plasma levels of TSH and T₄. (*Note:* TSH levels may remain high in some children, despite adequate dosing.)

Minimizing Adverse Effects

Thyrotoxicosis. Overdose may cause thyrotoxicosis. Inform patients about symptoms of thyrotoxicosis (tachycardia, angina, tremor, nervousness, insomnia, hyperthermia, heat intolerance, sweating), and instruct them to notify the prescriber if these develop.

Atrial Fibrillation and Bone Loss. Chronic overtreatment with levothyroxine can cause atrial fibrillation and fractures (from bone loss), especially in the elderly. To prevent overtreatment, measure TSH levels at least once a year.

Minimizing Adverse Interactions

Drugs That Reduce Levothyroxine Absorption. Absorption of levothyroxine can be reduced by multiple drugs, including H₂-receptor blockers, proton pump inhibitors, cholestyramine, colestipol, sucralfate, aluminum-containing antacids, iron supplements, calcium supplements, magnesium salts, and orlistat. Instruct patients to separate administration of levothyroxine and these drugs by 4 hours.

Drugs That Accelerate Levothyroxine Metabolism. Several drugs, including carbamazepine, rifampin, phenytoin, phenobarbital, and sertraline, can accelerate metabolism of levothyroxine, and can thereby reduce its effects. An increase in levothyroxine dosage may be needed.

Warfarin. Levothyroxine can intensify the effects of warfarin. Warfarin dosage may need to be reduced.

Catecholamines. Thyroid hormones sensitize the heart to catecholamines (epinephrine, dopamine, dobutamine) and may thereby promote dysrhythmias. Exercise caution when catecholamines and levothyroxine are used together.

LIOTHYRONINE (T₃)

With the exceptions noted below, the nursing implications for liothyronine are the same as those for levothyroxine.

Evaluating Therapeutic Effects

Success is indicated by resolution of the signs and symptoms of hypothyroidism and by normalization of plasma T₃ and TSH levels. T₄ levels cannot be used to evaluate therapy.

METHIMAZOLE

Preadministration Assessment

Therapeutic Goals

Methimazole has four indications: (1) reduction of thyroid hormone production in Graves' disease, (2) control of hyperthyroidism until the effects of radiation on the thyroid become manifest, (3) suppression of thyroid hormone production prior to subtotal thyroidectomy, and (4) treatment of thyrotoxic crisis.

Baseline Data

Obtain serum levels of free T₃ and free T₄.

Identifying High-Risk Patients

Methimazole is *contraindicated* during breast-feeding, and should be *avoided* during the first trimester of pregnancy.

Implementation: Administration

Route

Oral.

Administration

Instruct the patient to take methimazole once daily, at the same time every day.

Ongoing Evaluation and Interventions

Summary of Monitoring

Evaluate treatment by monitoring for weight gain, decreased heart rate, and other indications that levels of thyroid hormone have declined. Laboratory tests should indicate a decrease in serum free T₃ and free T₄.

Minimizing Adverse Effects

Agranulocytosis. Inform patients about early signs of agranulocytosis (fever, sore throat), and instruct them to notify the prescriber if these develop. If follow-up blood tests reveal leukopenia, methimazole should be withdrawn. Giving granulocyte colony-stimulating factor may accelerate recovery.

Hypothyroidism. Methimazole may cause excessive reductions in thyroid hormone synthesis. If signs of hypothyroidism develop or if plasma levels of T₃ and T₄ become subnormal, methimazole dosage should be reduced. Supplemental thyroid hormone may be needed.

Effects in Pregnancy. When used during the first trimester, methimazole can cause neonatal hypothyroidism, goiter, and even cretinism. Use in the second and third trimesters is considered safe. If a thionamide is needed during the first trimester of pregnancy, PTU should be selected.

Effects in Lactation. Methimazole in breast milk can adversely affect the nursing infant, and hence the drug is contraindicated during lactation. If an antithyroid drug must be used, PTU should be selected.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

RADIOACTIVE IODINE (¹³¹I)

Use in Graves' Disease

Therapeutic Goal. Suppression of thyroid hormone production.

Identifying High-Risk Patients. Iodine-131 is *contraindicated* during pregnancy and lactation.

Dosage and Administration. Iodine-131 is administered in capsules or an oral liquid. The dosing objective is to reduce thyroid hormone production without causing complete thyroid destruction. The dosage for Graves' disease is 4 to 10 mCi.

Promoting Therapeutic Effects. Responses take 2 to 3 months to develop fully. Methimazole or propylthiouracil may be required during this interval.

Minimizing Adverse Effects. Excessive thyroid destruction can cause hypothyroidism. Patients who develop thyroid insufficiency need thyroid hormone supplements.

Use in Thyroid Cancer

High doses (50 to 150 mCi) are required. These doses can cause radiation sickness, leukemia, and bone marrow depression. Monitor for these effects. Body wastes will be contaminated with radioactivity and must be disposed of appropriately.

Diagnostic Use

Iodine-131 is used to diagnose hyperthyroidism, hypothyroidism, and goiter. Diagnostic doses are so small (less than 10 microcuries) as to be virtually harmless.

STRONG IODINE SOLUTION (LUGOL'S SOLUTION)

Preadministration Assessment

Therapeutic Goal

Suppression of thyroid hormone production in preparation for subtotal thyroidectomy. Also used to suppress thyroid hormone release in patients experiencing thyroid storm.

Baseline Data

Obtain tests of thyroid function.

Implementation: Administration

Route

Oral.

Administration

Advise patients to dilute strong iodine solution with fruit juice or some other beverage to increase palatability.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Mild Toxicity. Inform patients about symptoms of iodism (brassy taste, burning sensations in the mouth, soreness of gums and teeth), and instruct them to discontinue treatment and notify the prescriber if these occur. Symptoms fade upon drug withdrawal.

Severe Toxicity. Iodine solution can cause corrosive injury to the GI tract. Instruct patients to discontinue the drug and notify the prescriber immediately if severe abdominal distress develops. Treatment includes gastric lavage and giving sodium thiosulfate.

*Patient education information is highlighted as blue text.

Drugs Related to Hypothalamic and Pituitary Function

Overview of Hypothalamic and Pituitary Endocrinology

Growth Hormone

Physiology

Pathophysiology

Clinical Pharmacology

Mecasermin (Insulin-like Growth Factor-1)

Prolactin

Thyrotropin

Corticotropin

Gonadotropins

Antidiuretic Hormone (Vasopressin)

Antidiuretic Hormone (Vasopressin) Antagonists

Oxytocin

Drugs for Acromegaly

Drugs Related to Hypothalamic Function

The hypothalamus and pituitary are intimately related both anatomically and functionally. Working together, these structures help regulate practically all bodily processes. To achieve their widespread effects, the hypothalamus and pituitary employ at least 15 hormones and regulatory factors (Fig. 59-1). As you can imagine, the endocrinology of these structures is exceedingly complex. However, rather than discussing all relevant information in depth, we will focus on just three agents: growth hormone (GH), antidiuretic hormone (ADH), and prolactin. Additional hypothalamic and pituitary hormones of therapeutic interest are considered briefly here and discussed further in other chapters.

OVERVIEW OF HYPOTHALAMIC AND PITUITARY ENDOCRINOLOGY

Anatomic Considerations

The pituitary sits in a depression in the skull located just below the third ventricle of the brain; the hypothalamus is located immediately above (see Fig. 59-1). The pituitary has two divisions: the *anterior pituitary* (or adenohypophysis) and *posterior pituitary* (or neurohypophysis). Both divisions are under hypothalamic control. As indicated in Figure 59-1, the hypothalamus communicates with the anterior pituitary by way of release-regulating factors delivered through a system of portal blood vessels. In contrast, communication with the posterior pituitary is neuronal.

Hormones of the Anterior Pituitary

The anterior pituitary produces six major hormones. Production and release of these hormones is controlled largely by the hypothalamus. Functions of the anterior pituitary hormones are summarized briefly as follows:

- *Growth hormone* (GH) stimulates growth in practically all tissues and organs.
- *Corticotropin* (adrenocorticotrophic hormone [ACTH]) acts on the adrenal cortex to promote synthesis and release of adrenocortical hormones.
- *Thyrotropin* (thyroid-stimulating hormone [TSH]) acts on the thyroid gland to promote synthesis and release of thyroid hormones.
- *Follicle-stimulating hormone* (FSH) acts on the ovaries to promote follicular growth and development, and acts on the testes to promote spermatogenesis.
- *Luteinizing hormone* (LH) acts on the ovaries to promote ovulation and development of the corpus luteum, and acts on the testes to promote androgen production.
- *Prolactin* stimulates milk production after parturition.

Hormones of the Posterior Pituitary

The posterior pituitary has only two hormones: *oxytocin* and *antidiuretic hormone* (ADH). The principal function of oxytocin is to facilitate uterine contractions at term. ADH promotes renal conservation of water.

Although oxytocin and ADH are considered hormones of the posterior pituitary, these agents are actually synthesized in the hypothalamus. The cells that make oxytocin and ADH are called neurosecretory cells. As indicated in Figure 59-1, these cells originate in the hypothalamus and project their axons to the posterior pituitary. Oxytocin and ADH are produced within the bodies of these cells and then undergo transport down axons to the axon terminals for storage. When appropriate stimuli impinge upon the bodies of the neurosecretory cells, impulses are sent down the axon, causing hormone release.

Hypothalamic Release-Regulating Factors

The hypothalamus has the primary responsibility for regulating the release of hormones from the *anterior* pituitary. To accomplish this, the hypothalamus employs seven different release-regulating factors (see Fig. 59-1). Most of these factors *stimulate* the release of anterior pituitary hormones. However, two of these factors *inhibit* hormone release. As indicated in Figure 59-1, the hypothalamic release-regulating factors are delivered to the anterior pituitary via portal blood vessels. Although the hypothalamic releasing factors are of extreme *physiologic* importance, only five of them—growth

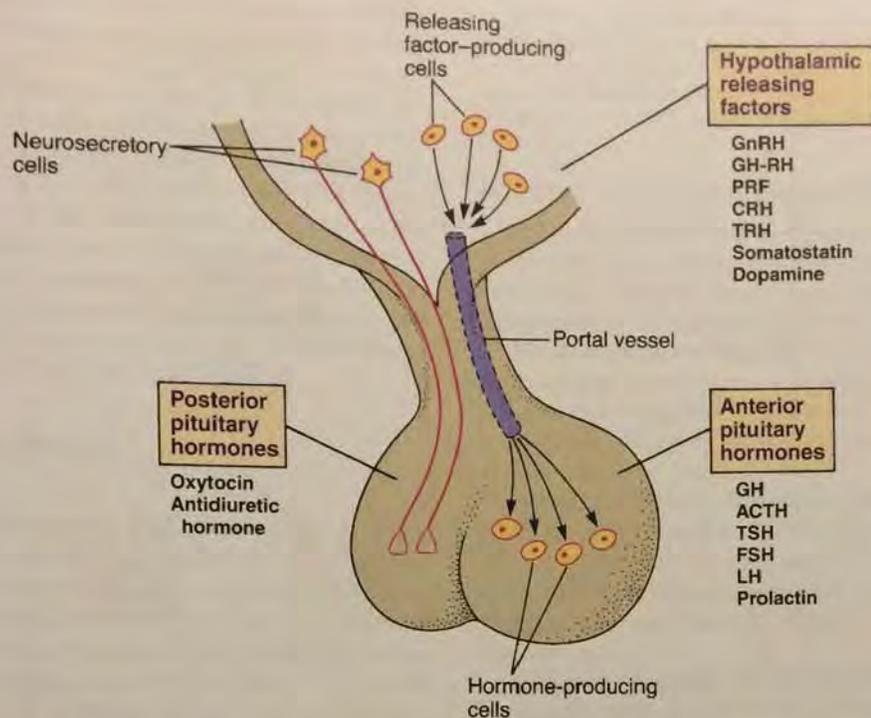


Figure 59-1 ■ Hormones and releasing factors of the hypothalamus and pituitary.

Hypothalamic releasing factors: GnRH = gonadotropin-releasing hormone, GH-RH = growth hormone-releasing hormone, PRF = prolactin-releasing factor, CRH = corticotropin-releasing hormone, TRH = thyrotropin-releasing hormone.

Anterior pituitary hormones: GH = growth hormone, ACTH = adrenocorticotropic hormone (corticotropin), TSH = thyroid-stimulating hormone, FSH = follicle-stimulating hormone, LH = luteinizing hormone.

hormone-releasing hormone, thyrotropin-releasing hormone, gonadotropin-releasing hormone, corticotropin-releasing hormone, and somatostatin—have clinical applications. These are the only hypothalamic release-regulating factors discussed in this chapter.

Feedback Regulation of the Hypothalamus and Anterior Pituitary

With few exceptions, the release of hypothalamic and anterior pituitary hormones is regulated by a *negative feedback loop*, as illustrated in Figure 59-2. In this example, the loop begins with the secretion of releasing-factor *X* from the hypothalamus. Factor *X* then acts on the anterior pituitary to stimulate release of hormone A. Hormone A then acts on its target gland to promote release of hormone B. Hormone B has two actions: (1) it produces its designated biologic effects and (2) it acts on the hypothalamus and pituitary to inhibit further release of factor *X* and hormone A. This feedback inhibition of the hypothalamus and pituitary suppresses further release of hormone B itself, thereby keeping levels of hormone B within an appropriate range.

GROWTH HORMONE

Growth hormone (GH) is a large polypeptide hormone (191 amino acids) produced by the anterior pituitary. As its name suggests, GH helps regulate growth. Childhood deficiency of GH results in *short stature*. Excessive GH results in *gigantism*

(when too much is present prior to puberty) and *acromegaly* (when too much is present during adulthood).

Physiology

Regulation of Release

The factors that regulate GH release are summarized in Figure 59-3. As indicated, the hypothalamus first releases growth hormone-releasing hormone (GH-RH), which stimulates release of GH from the pituitary. Growth hormone then acts on the liver and other tissues to cause release of *insulin-like growth factor-1* (IGF-1). IGF-1 has two actions: it (1) promotes growth and (2) acts on the hypothalamus and pituitary to suppress release of GH-RH and GH, thereby completing a negative feedback loop.

One additional hormone—*somatostatin*—helps regulate GH release. As shown in Figure 59-3, somatostatin, which is produced in the hypothalamus, acts on the pituitary to *inhibit* GH release.

Biologic Effects

Promotion of Growth. GH, acting through IGF-1, stimulates the growth of practically all organs and tissues. If administered to a GH-deficient child prior to epiphyseal closure, GH will increase bone length, producing a corresponding increase in height. The size and number of muscle cells is increased, resulting in enlargement of muscle mass, and the internal organs are stimulated to grow in proportion to overall body growth. The only structures that do not respond noticeably are the brain and eyes.

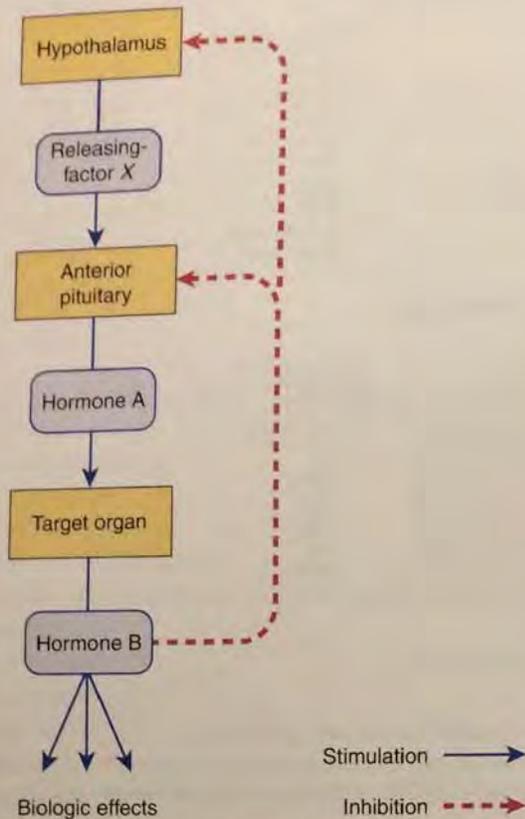


Figure 59-2 • Negative feedback regulation of the hypothalamus and anterior pituitary.

The feedback loop works as follows: Factor X stimulates the pituitary to release hormone A, which stimulates its target organ, causing release of hormone B. Hormone B then acts on the hypothalamus and pituitary to suppress further release of factor X and hormone A, thereby suppressing further release of hormone B itself.

Promotion of Protein Synthesis. For growth to occur, cells must increase production of protein. GH facilitates this process by increasing amino acid uptake and utilization. Since amino acids have substantial nitrogen content, increased protein synthesis results in net nitrogen retention, which is reflected in reduced urinary nitrogen excretion. Increased amino acid utilization also causes blood urea nitrogen to fall.

Effect on Carbohydrate Metabolism. Growth hormone reduces glucose utilization, causing a tendency for plasma levels of glucose to rise. When GH is administered to nondiabetics, elevation of blood glucose stimulates release of insulin, thereby maintaining glucose levels within a normal range. In contrast, when GH is administered to patients with type 1 diabetes, insulin cannot be released. As a result, the hyperglycemic action of GH goes unopposed, allowing plasma glucose levels to rise, sometimes dramatically.

Pathophysiology

Growth Hormone Deficiency

Pediatric. Growth hormone is essential for normal growth of children, and hence GH deficiency results in *short stature*. Growth is retarded to an equal extent in all parts of the body, and hence the child, although short, has normal proportions.

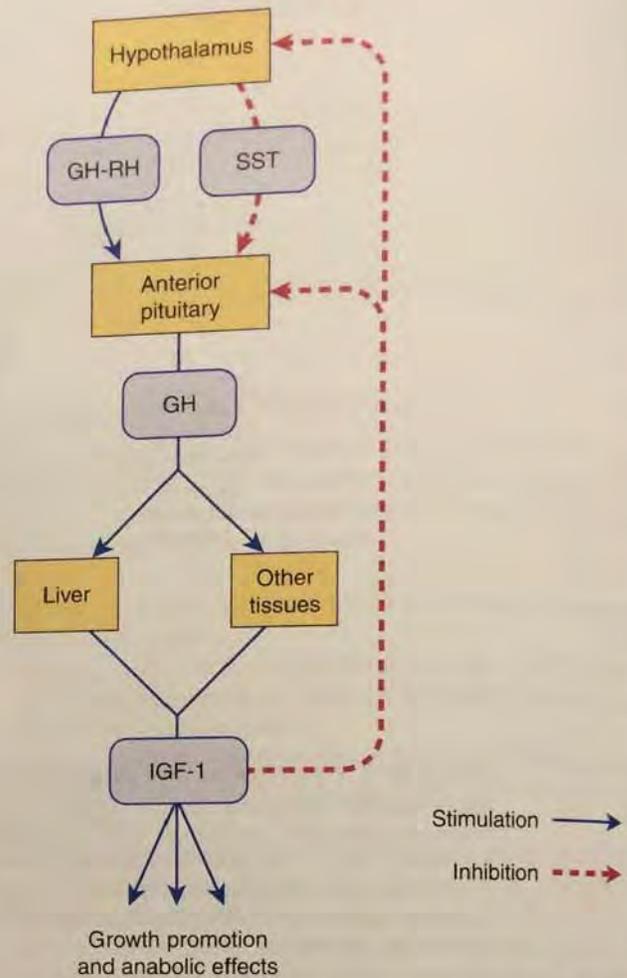


Figure 59-3 • Regulation of growth hormone release.

(GH = growth hormone, GH-RH = growth hormone-releasing hormone, IGF-1 = insulin-like growth factor-1; SST = somatostatin.)

Mental function is not impaired. The only treatment for GH deficiency is replacement therapy with human GH itself (see below under *Therapeutic Uses*).

Adult. In adults, GH deficiency causes a syndrome characterized by reduced muscle mass, reduced exercise capacity, increased mortality from cardiovascular causes, and impaired psychosocial function. Onset of GH deficiency may begin in childhood or later in life.

Growth Hormone Excess

Consequences. When GH excess occurs in children, the resulting syndrome is called *gigantism*, and when the excess occurs in adults, the syndrome is called *acromegaly*. The pathophysiology of both syndromes is similar. The principal difference is that GH excess causes children to grow very tall—as much as 7 to 9 feet—owing to stimulation of long bones prior to epiphyseal closure. In adults, effects on bone growth result in coarse facial features, splayed teeth, and large hands and feet. However, because the epiphyses have already closed, height is not increased. Other manifestations, seen in adults and children, include headache, profuse sweating, soft tissue swelling, cardiomegaly, hypertension, arthralgias, and diabetes. Levels of IGF-1 are elevated in all patients. In almost all cases, the cause of GH excess is a pituitary adenoma.

Treatment Overview. Treatment of gigantism requires surgical removal of the pituitary. In contrast, acromegaly may be treated with three modalities: surgery, radiation, or drugs. Surgical excision of the pituitary adenoma is the preferred initial treatment. Radiation therapy may be used as primary treatment or as an adjunct to surgery. When used as primary treatment, radiation takes 10 to 20 years to produce a full response.

Drugs are generally reserved for patients with large tumors or residual disease despite tumor excision and/or radiation therapy. Three drugs are available: octreotide [Sandostatin, Sandostatin LAR Depot], lanreotide [Somatuline Depot], and pegvisomant [Somavert]. The pharmacology of these agents is discussed later under *Drugs for Acromegaly*.

Clinical Pharmacology

Therapeutic Uses

Pediatric Growth Hormone Deficiency. Prior to 2003, pediatric indications for GH were limited to children with documented GH deficiency. For these children, treatment should begin early in life and must stop prior to epiphyseal closure. To ensure timely termination of treatment, epiphyseal status should be assessed annually. When treatment is started early, adult height may be increased by as much as 6 inches. To monitor treatment, height and weight should be measured monthly. Therapy should continue until a satisfactory adult height has been achieved, until epiphyseal closure occurs, or until a response can no longer be elicited. Efficacy of therapy declines as the patient grows older and is usually lost entirely by age 20 to 24 years. If treatment fails to promote growth, GH should be discontinued and the diagnosis of GH deficiency re-evaluated. Growth hormone replacement is very expensive, costing between \$20,000 and \$40,000 a year.

Pediatric Non-Growth-Hormone-Deficient (NGHD) Short Stature. In 2003, the Food and Drug Administration approved GH for treating children with NGHD short stature. These children have normal levels of GH but are nonetheless very short. To qualify for treatment, children must be 2.25 standard deviations below the mean height for their sex and age, which makes them among the shortest 1.2% of their peers. In clinical trials, children who received 6 to 7 injections a week for 4 to 6 years grew an extra 1 to 3 inches, although some did not respond at all. As with treatment of GH-deficient children, the cost is very high.

Pediatric Short Stature Associated with Prader-Willi Syndrome. Prader-Willi syndrome (PWS) is a complex genetic disorder characterized by short stature, mental impairment, incomplete sexual development, behavior problems, low muscle tone, and the urge to eat constantly, which promotes obesity. Growth hormone is indicated to increase the height of PWS patients, but only if GH deficiency has been documented. However, owing to a risk of sudden death, GH must be avoided in PWS patients who are severely obese, have severe respiratory impairment, or have a history of upper airway obstruction or sleep apnea.

Growth Hormone Deficiency in Adults. In adults with GH deficiency—be it childhood-onset or adult-onset—replacement therapy can increase lean body mass, decrease adipose mass, and increase lumbar spine density. Unfortunately, GH also increases systolic blood pressure and fasting blood glucose. Furthermore, although GH increases muscle mass, it does not increase strength.

Other Uses. In addition to the uses noted above, GH is approved for pediatric growth failure associated with chronic renal insufficiency, cachexia or wasting in patients with AIDS, short-bowel syndrome, and short stature associated with Turner's syndrome or Noonan's syndrome. Individual GH preparations that are approved for these indications are listed in Table 59-1.

Adverse Effects and Interactions

Hyperglycemia. GH is diabetogenic. When used in patients with pre-existing diabetes, significant hyperglycemia may result. Glucose levels should be monitored and insulin dosage should be adjusted accordingly.

Neutralizing Antibodies. Over the course of treatment, patients may develop neutralizing antibodies that bind with GH and thereby render the hormone inactive. If these antibodies develop, treatment with mecasermin (recombinant IGF-1) may be effective (see below).

Fatality in PWS Patients. Fatalities have occurred in PWS patients treated with GH. Major risk factors are severe obesity, upper airway obstruction, sleep apnea, and respiratory infection. Growth hormone is contraindicated in PWS patients who are severely obese or have severe respiratory impairment.

Interaction with Glucocorticoids. Glucocorticoids can oppose the growth-promoting effects of GH. Glucocorticoid replacement doses must be carefully adjusted to avoid growth inhibition.

Preparations, Dosage, and Administration

Preparations: Somatropin. Growth hormone for clinical use is available as *somatropin* [Humatrope, Nutropin, others], a molecule produced by recombinant DNA technology. The structure and actions of somatropin are identical to those of GH produced by the human pituitary. At this time, 9 preparations of somatropin are available. As indicated in Table 59-1, they differ with respect to approved indications and dosages.

Administration. Administration is parenteral—IM or subQ. Subcutaneous administration is preferred because it is less painful than IM while being just as safe and effective. Subcutaneous administration can be done using either a traditional syringe and needle, or a pre-filled injection device. To avoid local tissue atrophy, the injection site should be rotated.

MECASERMIN (INSULIN-LIKE GROWTH FACTOR-1)

Mecasermin [Increlex], produced by recombinant DNA technology, is identical to naturally occurring IGF-1, the compound that mediates the effects of GH. Mecasermin is approved for long-term therapy of growth failure in children with severe primary deficiency of IGF-1, a rare condition seen in about 10,000 children worldwide. The drug may also be used in children with GH deficiency who can no longer be treated with GH itself, owing to development of neutralizing antibodies. In children with GH deficiency who are still responsive to GH, treatment with GH is preferred to IGF-1. Mecasermin should not be used after epiphyseal closure or by children with secondary forms of IGF-1 deficiency.

Mecasermin can cause a variety of adverse effects. The most common is hypoglycemia, which develops in nearly 50% of patients, usually during the first weeks of treatment. Hypertrophy of the tonsils develops in 15% of patients, and can be managed by tonsillectomy if needed. Other adverse effects include intracranial hypertension, vomiting, arthralgia, otitis media, elevation of serum aminotransferases and lipids, and overgrowth of fat, facial bones, and the kidneys. Like all other foreign proteins, mecasermin can trigger allergic reactions, both local and systemic.

Mecasermin is supplied in solution (10 mg/mL) in 40-mL multi-use vials. Administration is by subQ injection. The initial dosage is 40 to 80 mcg/kg

Trade Name	Approved Indications	Dosage
Genotropin, Genotropin-Miniquick	GFAW pediatric GH deficiency Pediatric NGHD short stature GFAW Prader-Willi syndrome GFAW Turner's syndrome Adult GH deficiency	0.16–0.24 mg/kg/wk subQ, divided into 6 or 7 equal daily doses Up to 0.47 mg/kg/wk subQ, divided into 6 or 7 equal daily doses 0.24 mg/kg/wk subQ, divided into 6 or 7 equal daily doses 0.33 mg/kg/wk subQ, divided into 6 or 7 equal daily doses 0.04–0.08 mg/kg/wk subQ, divided into 7 equal daily doses
Humatrope, HumatroPen	GFAW pediatric GH deficiency Pediatric NGHD short stature GFAW Turner's syndrome	0.18 mg/kg/wk subQ or IM, divided into either (a) 6 equal daily doses or (b) 3 equal doses administered every other day Up to 0.37 mg/kg/wk subQ, divided into 6 or 7 equal daily doses 0.375 mg/kg/wk (max) subQ, divided into either (a) 7 equal daily doses or (b) 3 equal doses administered every other day 0.006–0.0125 mg/kg/day subQ
Norditropin	Adult GH deficiency GFAW pediatric GH deficiency GFAW Turner's syndrome GFAW Noonan's syndrome Adult GH deficiency	0.024–0.034 mg/kg subQ 6–7 days/wk 0.067 mg/kg/day subQ Up to 0.066 mg/kg/day subQ 0.004–0.016 mg/kg/day subQ
Nutropin, Nutropin AQ	GFAW pediatric GH deficiency Pediatric NGHD short stature GFAW chronic renal insufficiency GFAW Turner's syndrome Adult GH deficiency	0.3 mg/kg/wk subQ, divided into 7 equal daily doses 0.3 mg/kg/wk subQ, divided into 7 equal daily doses 0.35 mg/kg/wk subQ, divided into 7 equal daily doses
Omnitrope	GFAW pediatric GH deficiency Adult GH deficiency	0.375 mg/kg/wk subQ, divided into 3–7 equal daily doses 0.006 mg/kg/day subQ initially, increased to 0.025 mg/kg/day (max) in patients under 35 yr, or to 0.0125 mg/kg/day (max) in patients over 35 yr
Saizen	GFAW pediatric GH deficiency Adult GH deficiency	0.1–0.24 mg/kg/wk subQ, divided into 6 or 7 equal daily doses 0.04–0.08 mg/kg/wk subQ, divided into 7 equal daily doses
Serostim	Cachexia or wasting in AIDS	0.06 mg/kg subQ or IM 3 days/wk 0.005 mg/kg/day subQ initially, increased to no more than 0.01 mg/kg/day after 4 wk
Tev-Tropin	GFAW pediatric GH deficiency	4–6 mg subQ daily at bedtime (dose depends on patient's weight). For adults under 35 kg, dosage is 0.1 mg/kg subQ once daily at bedtime
Zorbtive	Short-bowel syndrome	0.1 mg/kg subQ 3 times a week 0.1 mg/kg subQ daily for 4 wk

AIDS = acquired immunodeficiency syndrome, GFAW = growth failure associated with, GH = growth hormone, NGHD = non-growth-hormone-deficient.

twice daily. If treatment is well tolerated for at least 1 week, the dosage may be increased by 40 mcg/kg/dose up to a maximum of 120 mcg/kg twice daily. Higher doses, which have not been evaluated, will increase the risk of hypoglycemia. To minimize hypoglycemia, all injections should be made about 20 minutes before or after eating. If hypoglycemia develops despite adequate food intake, the dosage should be reduced. If the patient is unable to eat when a dose is scheduled, that dose should be withheld; subsequent doses should not be increased to make up for the dose that was missed. Treatment is expensive: A regimen of 120 mcg/kg twice daily costs about \$29,000 a year.

PROLACTIN

Prolactin is a polypeptide hormone produced by the anterior pituitary. The principal function of prolactin is stimulation of milk production after parturition. Prolactin deficiency is generally without symptoms, except for disturbance of lactation. In contrast, overproduction of prolactin causes multiple adverse effects.

Regulation of Release

Regulation of prolactin release is predominantly *inhibitory*. Under the influence of dopamine released from the hypothalamus, release of prolactin by the pituitary is *suppressed*. When release of dopamine declines, release of prolactin is allowed to

increase. Another hypothalamic factor, known as prolactin-releasing factor (PRF), *promotes* prolactin release. However, the stimulatory influence of PRF is usually dominated by dopamine-mediated inhibition. The most powerful stimulus to prolactin release is suckling, an action that presumably suppresses release of dopamine from the hypothalamus.

Prolactin Hypersecretion

Excessive secretion of prolactin produces adverse effects in males and females. Women may experience amenorrhea, galactorrhea (excessive milk flow), and infertility. In men, libido and potency are reduced; galactorrhea occurs on occasion. Puberty may be delayed in boys and girls. Causes of prolactin hypersecretion include pituitary adenoma, injury to the hypothalamus, and certain drugs (eg, antipsychotic drugs, estrogens).

Suppressing Prolactin Release with Dopamine Agonists

Excessive secretion of prolactin can be reduced with two dopamine agonists: cabergoline and bromocriptine. These drugs bind with dopamine receptors in the pituitary, and thereby exert the same inhibitory influence on prolactin release as does dopamine released from the hypothalamus. Cabergoline is better tolerated than bromocriptine, and dosing is more

convenient. As a result, cabergoline is generally preferred. The pharmacology of both drugs and their use in hyperprolactinemia is discussed in Chapter 63 (Drug Therapy of Infertility). The use of cabergoline and bromocriptine (and other dopamine agonists) in Parkinson's disease is discussed in Chapter 21.

THYROTROPIN

Thyrotropin (thyroid-stimulating hormone [TSH]) is produced by the anterior pituitary. The physiologic role of thyrotropin is stimulation of thyroid gland function. Specifically, thyrotropin promotes (1) thyroidal uptake of iodine, (2) synthesis and release of thyroid hormones, and (3) thyroid growth. Clinical application of thyrotropin is limited to diagnostic evaluation of patients with thyroid cancer.

ADRENOCORTICOTROPIC HORMONE

Adrenocorticotrophic hormone (ACTH) is a polypeptide hormone produced by the anterior pituitary. This hormone acts on the adrenal cortex to stimulate production and release of adrenocortical hormones (eg, cortisol, aldosterone). The principal use of ACTH is diagnosis of adrenocortical dysfunction. A synthetic analog of ACTH, called cosyntropin, is used for this purpose, as discussed in Chapter 60 (Drugs for Disorders of the Adrenal Cortex).

GONADOTROPINS

The anterior pituitary produces two gonadotropic hormones: *follicle-stimulating hormone* (FSH) and *luteinizing hormone* (LH). (Note: LH is also known as *interstitial cell-stimulating hormone*, a term that is not widely used.) LH and FSH are produced by the pituitaries of males and females and serve to regulate gonadal function in both sexes. In women, FSH acts on the ovaries to promote follicular growth and development. In men, FSH supports sperm production. The role of LH in women is to promote ovulation and formation of the corpus luteum. In men, LH stimulates testosterone synthesis by Leydig cells of the testicular interstitium. Plasma levels of LH and FSH are relatively stable in males. In females, levels of both hormones vary with the phase of the menstrual cycle. The physiology of LH and FSH in females is discussed further in Chapter 61.

LH and FSH are employed clinically to treat infertility in men and women. In women, fertility is increased by promoting follicular development and ovulation. In men, fertility is increased through enhanced spermatogenesis.

Four preparations of gonadotropins are used clinically: menotropins, urofollitropin, follitropin alfa, and follitropin beta. Menotropins [Pergonal] is a 50:50 mixture of LH and FSH. Urofollitropin [Bravelle] is primarily FSH. Follitropin alfa [Gonal-F] and follitropin beta [Follistim AQ] are human FSH preparations produced by recombinant DNA technology. The use of gonadotropins to treat infertility is discussed in Chapter 63.

ANTIDIURETIC HORMONE (VASOPRESSIN)

Antidiuretic hormone, also known as *vasopressin*, is a nine-peptide hormone that acts on the kidney to cause reabsorption (conservation) of water. Deficiency of ADH produces *hypothalamic diabetes insipidus*, a condition in which large volumes of dilute urine are produced.

Physiology

Actions. ADH promotes *renal conservation of water*. How? ADH acts on the collecting ducts of the kidney to increase their permeability to water, which results in increased *water reabsorption*. Because water is withdrawn from the tubular urine (back into the extracellular space), urine that entered the collecting ducts in a relatively dilute state becomes highly concentrated by the time it leaves.

In addition to its renal actions, ADH can stimulate *contraction of vascular smooth muscle and smooth muscle of the GI tract*. Because of its ability to cause vasoconstriction, ADH is also known as *vasopressin*. It should be noted that the plasma levels of ADH required to cause smooth muscle contraction are higher than those that occur physiologically.

Production, Storage, and Release. ADH is produced in neurosecretory cells of the hypothalamus, transported down their axons, and then stored in their terminals until released. Release is regulated by the hypothalamus—the brain center responsible for maintaining body fluids at their proper osmolality. When the hypothalamus senses that osmolality has risen too high, it instructs the posterior pituitary to release ADH. The resultant increase in water reabsorption dilutes body fluids, causing osmolality to decline. Release of ADH can also be stimulated by hypotension and by reduced plasma volume.

Pathophysiology: Hypothalamic Diabetes Insipidus

Hypothalamic diabetes insipidus is a syndrome caused by partial or complete deficiency of ADH. The syndrome is characterized by polydipsia (excessive thirst) and excretion of large volumes of dilute urine. Deficiency of ADH may be inherited or may result from head trauma, neurosurgery, cancer, and other causes. The best treatment is replacement therapy with ADH. (In contrast to hypothalamic diabetes insipidus, *nephrogenic diabetes insipidus* results from a failure of the kidney to produce concentrated urine despite adequate levels of ADH.)

Antidiuretic Hormone Preparations

Two preparations with ADH activity are available: *vasopressin* [Pitressin Synthetic, Pressyn AR⁺] and *desmopressin* [DDAVP, Stimate]. Vasopressin is identical in structure to naturally occurring ADH; desmopressin is a structural analog of natural ADH. The preparations differ with respect to route of administration, duration of action, and therapeutic applications (Table 59-2). They also differ in their ability to cause vasoconstriction.

Adverse Effects

Water Intoxication. Excessive water retention can cause water intoxication. Early signs include drowsiness, listlessness, and headache. Severe intoxication progresses to convulsions and terminal coma. Patients experiencing early symptoms should notify their prescriber. Treatment includes diuretic therapy and restricting fluid intake.

A major cause of intoxication is failure to reduce water intake once ADH therapy has begun. Since treatment prevents continued fluid loss, failure to decrease fluid intake will result in water buildup. Hence, at the onset of treatment, patients should be instructed to reduce their accustomed intake of fluid.

The risk of water intoxication is also increased by renal impairment. Accordingly, if creatinine clearance is below 50 mL/min, ADH should not be used.

Excessive Vasoconstriction. Because of its powerful vasoconstrictor actions, *vasopressin* can cause severe adverse cardiovascular effects. (Desmopressin is a weak pressor agent, and hence does not adversely affect hemodynamics.) By constricting arteries of the heart, *vasopressin* can cause angina

TABLE 59-2 ■ ADH Preparations

Generic Name [Trade Name]	Routes	Duration of Antidiuretic Action (hr)	Therapeutic Uses	Usual Maintenance Dosage
Desmopressin [DDAVP, Stimate]	Intranasal, subQ, IV, PO	8–20	Diabetes insipidus	Adults: 0.1 mL (10 mcg) intranasally 2 times/day or 0.25–0.5 mL subQ or IV twice daily or 0.1–1.2 mg PO daily in 2 or 3 doses Children: 0.05–0.3 mL intranasally daily either as a single dose or in 2 doses 0.2–0.6 mg PO at bedtime (intranasal therapy of enuresis is contraindicated) See Chapter 54
Vasopressin [Pitressin Synthetic, Pressyn AR♦]	IM, subQ*	2–8	Nocturnal enuresis Hemophilia Diabetes insipidus Postoperative abdominal distention Abdominal radiography (to dispel gas shadows) Cardiac resuscitation	5–10 units IM or subQ 2–3 times/day 5 units IM initially; then 10 units IM every 3–4 hr 10 units 2 hr before and again 30 min before the procedure 40 units

*Sometimes administered intranasally or IV.

pectoris and even myocardial infarction—especially in patients with coronary insufficiency. In addition, vasopressin may cause gangrene by decreasing blood flow in the periphery. Because it can reduce cardiac perfusion, vasopressin must be used with extreme caution in patients with coronary artery disease. This warning does not apply to desmopressin. Despite its potential for adverse effects on cardiac circulation, vasopressin can be lifesaving in people experiencing cardiac arrest (see below).

Therapeutic Uses

Diabetes Insipidus. Diabetes insipidus may be treated with either desmopressin or vasopressin. However, *desmopressin* is the agent of choice. Why? Because desmopressin has a long duration of action, is easy to administer (by mouth or intranasal spray), and lacks significant side effects, especially vasoconstriction. The response to treatment is rapid, and urine volume quickly drops to normal. Because desmopressin is expensive, and because excessive dosing can result in water intoxication, the smallest effective dosage should be employed.

Cardiac Arrest. For patients in cardiac arrest, vasopressin can be used to enhance cardiopulmonary resuscitation (CPR). Benefits derive from vasopressin-induced vasoconstriction, which, in people receiving CPR, increases blood flow to the heart and brain, improves neurologic outcome, and increases the chances of successful resuscitation.

Other Uses. *Vasopressin* is indicated for postoperative abdominal distention and preparation for abdominal radiography.

Desmopressin is indicated for nocturnal enuresis (bedwetting), hemophilia A, and von Willebrand’s disease. The drug decreases enuresis by reducing urine production, and helps patients with hemophilia A and von Willebrand’s disease by promoting release of clotting factor VIII (see Chapter 54).

ANTIDIURETIC HORMONE (VASOPRESSIN) ANTAGONISTS

Antidiuretic hormone antagonists, also known as vasopressin antagonists, block the effects of ADH (vasopressin) in renal collecting ducts. By doing so,

they increase the excretion of free water. Two vasopressin antagonists are available: conivaptan and tolvaptan. These drugs, also known as *vaptans*, have only one indication: treatment of hyponatremia in euvolemic or hypervolemic patients. The principal difference between the two drugs concerns route of administration: conivaptan is administered IV, whereas tolvaptan is administered PO.

Conivaptan

Conivaptan [Vaprisol], approved in 2006, is indicated for short-term IV therapy of hyponatremia in euvolemic and hypervolemic hospitalized patients. How does the drug work? In patients with euvolemic or hypervolemic hyponatremia, levels of circulating vasopressin are usually high, causing retention of water by the kidney. Conivaptan blocks vasopressin V₂ receptors in renal collecting ducts, and thereby promotes “aquaresis” (renal excretion of free water), leaving sodium behind for reabsorption into the blood. As a result, the concentration of sodium in blood rises, thereby correcting the hyponatremia.

The most common adverse effects are infusion-site reactions, seen in 32% to 51% of patients. Other common reactions include hypokalemia (10% to 22%), orthostatic hypotension (6% to 14%), headache (8% to 10%), fever (5% to 11%), constipation (6% to 8%), diarrhea (7%), and vomiting (5% to 7%). If blood sodium rises too rapidly (more than 12 mEq/L/24 hr), neurons can undergo *osmotic demyelination*, resulting in serious neurologic deficits (eg, difficulty swallowing, inability to speak, affective changes, seizures, coma, and death). Accordingly, blood sodium should be monitored often and, if the rise is too fast, conivaptan should be interrupted.

Conivaptan is both a substrate for and inhibitor of CYP3A4 (the 3A4 isozyme of cytochrome P450). Accordingly, the drug must not be combined with strong inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, ritonavir), owing to a risk of conivaptan toxicity. Combined use with drugs that are substrates for CYP3A4 should be done with caution.

Conivaptan is supplied in dilute solution (0.2 mg/mL) and concentrated solution (5 mg/mL) for IV administration. The concentrated solution must be diluted prior to use. Dosing consists of an initial IV infusion (20 mg over 30 minutes) followed by a more prolonged infusion (20 mg over 24 hours). A maximum of three additional infusions (20 or 40 mg over 24 hours each) may be done as needed.

Tolvaptan

Tolvaptan [Samsca], approved in 2009, is an oral vasopressin antagonist indicated for reducing hypernatremia in patients with euvolemic or hypervolemic hypernatremia, including those with heart failure, cirrhosis, or the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. This new vaptan represents an oral alternative to IV conivaptan. Like conivaptan, tolvaptan blocks vasopressin V₂ receptors in renal collecting ducts, and thereby increases renal excretion of free water, causing the sodium concentration in blood to rise. Although tolvaptan is administered PO, patients must still be hospitalized during initial therapy.

The most common adverse effects are thirst (16%), dry mouth (13%), polyuria (11%), weakness (9%), constipation (7%), and hyperglycemia (6%). As with conivaptan, osmotic demyelination can occur if blood sodium rises too rapidly. Accordingly, to prevent neuronal injury, the rate of rise in blood sodium must not exceed 12 mEq/L/24 hr.

Drug interactions with tolvaptan are complex. Tolvaptan is metabolized by CYP3A4, and hence must not be combined with strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole, ritonavir), owing to a risk of tolvaptan toxicity. Combined use with moderately strong CYP3A4 inhibitors (eg, diltiazem, grapefruit juice) should also be avoided. Combined use with a CYP3A4 inducer (eg, phenytoin, rifampin, St. John's wort) might reduce benefits of tolvaptan, possibly necessitating an increase in dosage. Tolvaptan is both a substrate for and inhibitor of P-glycoprotein, a transporter protein that, among other things, enhances renal excretion of drugs. By inhibiting P-glycoprotein, tolvaptan can raise levels of digoxin by 30%, thereby increasing the risk of digoxin toxicity.

Tolvaptan [Samsca] is supplied in tablets (15 and 30 mg) for oral dosing, with or without food. Treatment must be started in a hospital in order to (1) monitor the therapeutic response and (2) avoid osmotic demyelination caused by too rapid elevation of blood sodium. Dosing begins at 15 mg once daily. After at least 24 hours, the dosage can be raised to 30 mg once daily. If needed, the dosage can be further raised to a maximum of 60 mg once daily.

OXYTOCIN

Oxytocin is produced by neurosecretory cells of the hypothalamus and is then transported down the axons of these cells for storage in the posterior pituitary. Oxytocin has two physiologic roles: (1) promotion of uterine contractions during labor and (2) stimulation of milk ejection during breast-feeding. The principal therapeutic application of the drug is induction of labor near term. The physiology, pharmacology, and applications of oxytocin are discussed in Chapter 64.

DRUGS FOR ACROMEGALY

As discussed above, acromegaly results from excessive production of GH by a pituitary tumor, and can be treated with three modalities: surgical excision of the pituitary, irradiation of the pituitary, and drug therapy. As a rule, drugs are reserved for patients who did not respond adequately to surgery and/or radiation, or for whom these modalities are not options. Two types of drugs are available: somatostatin analogs and GH receptor antagonists. Drug therapy is both prolonged and expensive.

Somatostatin Analogs. The somatostatin analogs—octreotide and lanreotide—are our most effective drugs for suppressing GH release. Benefits derive from mimicking the suppressant actions of somatostatin on the pituitary (see Fig. 59-3). The somatostatin analogs can be used as primary therapy for acromegaly or as an adjunct to surgery and/or radiation. In both cases, the objective is to normalize levels of GH and IGF-1.

Octreotide is available in two formulations: an immediate-release product, sold as *Sandostatin*, and a sustained-release product, sold as *Sandostatin LAR Depot*. The usual maintenance dosage is 100 mcg subQ 3 times a day (for Sandostatin) or 10 to 30 mg IM once a month (for Sandostatin LAR Depot). Gastrointestinal side effects (nausea, cramps, diarrhea, flatulence) are common initially, but subside in 1 to 2 weeks. Within a year, cholesterol gallstones develop in about 25% of patients, although they are usually asymptomatic.

Lanreotide [Somatuline Depot] is supplied in single-use, pre-filled syringes (60, 90, and 120 mg) for deep subQ injection into the buttocks. Dosages range from 60 to 120 mg every 4 weeks. The most common side effect is diarrhea, which develops in 31% to 48% of patients. Other common reactions include gallstones, bradycardia, injection-site reactions, and hypo- or hyperglycemia.

Pegvisomant, a Growth Hormone Receptor Antagonist. Pegvisomant [Somavert], a GH receptor antagonist, may be our most effective drug for acromegaly. The goal of therapy is to normalize serum levels of IGF-1. In clinical trials, treatment for 12 months or longer greatly reduced symptoms and normalized IGF-1 levels in nearly all patients (97%). Pegvisomant is generally well tolerated. The most common side effects are injection-site reactions, nausea, diarrhea, chest pain, and flu-like symptoms. In a few patients, serum levels of hepatic transaminases rise, indicating liver injury. Monitoring of hepatic function is recommended. The only known drug interaction is an apparent reduction in pegvisomant effects by opioid analgesics. Why this occurs is a mystery. Pegvisomant is available as a powder (10, 15, and 20 mg) that must be reconstituted with sterile water prior to use. Administration is by subQ injection. Treatment consists of an initial 40-mg loading dose (given by the prescriber), followed by 10-mg doses injected once daily by the patient. Every 4 to 6 weeks, the level of IGF-1 is measured, and dosage is increased by 5 mg (if the IGF-1 level is still above normal) or decreased by 5 mg (if the IGF-1 level is below normal). Treatment should continue indefinitely, which can be hugely expensive—ranging from \$50,000 to \$100,000 a year.

DRUGS RELATED TO HYPOTHALAMIC FUNCTION

Of the seven regulatory factors found in the hypothalamus, only three—gonadotropin-releasing hormone (GnRH), corticotropin-releasing hormone (CRH), and somatostatin—have clinical applications. GnRH and its synthetic analogs are used to treat prostate cancer and endometriosis, and to induce ovulation. CRH is used to diagnose adrenal disorders. As discussed above, somatostatin is used for acromegaly.

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone (GnRH) is produced by the hypothalamus and promotes release of gonadotropins (LH and FSH) from the pituitary. Four drugs that mimic GnRH—the GnRH agonists—are available: *leuprolide*, *goserelin*, *nafarelin*, and *gonadorelin*. Leuprolide and goserelin are discussed in Chapter 103 (Anticancer Drugs II). Nafarelin is discussed in Chapter 63 (Drug Therapy of Infertility). Gonadorelin is used to evaluate anterior pituitary function.

KEY POINTS

- Release of hormones from the anterior pituitary is stimulated by releasing factors from the hypothalamus and inhibited by negative feedback loops.
- The growth-promoting actions of growth hormone (GH) are mediated by insulin-like growth factor-1 (IGF-1).
- Pediatric GH deficiency causes short stature.
- Adult GH deficiency causes reduced muscle mass, reduced exercise capacity, increased mortality from cardiovascular causes, and impaired psychosocial function.
- Pediatric GH excess causes gigantism.
- Adult GH excess causes acromegaly.
- Among pediatric patients, GH is approved for growth promotion in children who are GH deficient, and in children who are very short despite having normal GH levels.
- Exogenous glucocorticoids can inhibit responses to GH.
- GH can elevate glucose levels in patients with diabetes.
- Acromegaly can be treated with three drugs: pegvisomant (a GH receptor antagonist) and two analogs of somatostatin—octreotide and lanreotide—that suppress GH release.
- Prolactin stimulates milk production after delivery.
- Excessive production of prolactin can be suppressed with cabergoline and bromocriptine, drugs that mimic the inhibitory action of hypothalamic dopamine on the pituitary.
- Antidiuretic hormone (ADH) acts on the kidney to cause reabsorption (conservation) of water.
- ADH deficiency results in hypothalamic diabetes insipidus.

- Hypothalamic diabetes insipidus can be treated by replacement therapy with desmopressin, a synthetic form of ADH.
- When initiating ADH replacement therapy, warn the patient to decrease water intake, because failure to do so can cause water intoxication.
- Vasopressin, a drug identical to natural ADH, can cause profound vasoconstriction.

- By promoting vasoconstriction, vasopressin can be lifesaving in patients with cardiac arrest.

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Summary of Major Nursing Implications*

SOMATROPIN (HUMAN GROWTH HORMONE)

The nursing implications summarized here apply only to the use of GH in *pediatric* patients.

Preadministration Assessment

Therapeutic Goal

Normalization of growth and development in children with (1) proven GH deficiency and (2) very short stature despite normal GH levels.

Baseline Data

Assess developmental status (height, weight, etc.) and obtain laboratory data on thyroid function and GH levels.

Identifying High-Risk Patients

GH is *contraindicated* during and after epiphyseal closure, and in children with PWS who are severely obese or have severe respiratory impairment.

Use with *caution* in children with diabetes mellitus and hypothyroidism.

Implementation: Administration

Routes

SubQ (preferred) or IM.

Administration

Provide the following administration instructions:

- For powdered preparations, reconstitute with the appropriate volume of diluent. *Mix gently; do not shake.*
- Do not inject if the preparation is cloudy or contains particulate matter.
- Rotate the injection site to avoid localized tissue atrophy.

Ongoing Evaluation and Interventions

Evaluating Treatment

Monitor height and weight monthly. Continue therapy until a satisfactory adult height has been achieved, until epiphyseal closure occurs, or until a response can no longer be elicited (usually by age 20 to 24).

If no stimulation of growth occurs, discontinue treatment and re-evaluate the diagnosis of GH deficiency.

Minimizing Adverse Effects and Interactions

Hyperglycemia. GH can elevate plasma glucose levels in diabetics. Increase insulin dosage as needed.

Hypothyroidism. GH may suppress thyroid function. Assess thyroid function before treatment and periodically thereafter. If levels of thyroid hormone fall, institute replacement therapy.

Fatality in PWS Patients. Owing to a risk of death, do not give GH to pediatric patients with PWS who are severely obese or have severe respiratory impairment.

Interaction with Glucocorticoids. Glucocorticoids can oppose the growth-stimulating effects of GH. Carefully adjust glucocorticoid replacement dosage to avoid growth inhibition.

Neutralizing Antibodies. Antibodies that neutralize exogenous GH can develop over the course of treatment. If this happens, mecasermin (recombinant IGF-1) may be an effective alternative to GH.

ANTIDIURETIC HORMONE

Desmopressin
Vasopressin

The nursing implications summarized here apply only to the use of ADH preparations for *hypothalamic diabetes insipidus*.

Preadministration Assessment

Therapeutic Goal

Normalization of urinary water excretion in patients with hypothalamic diabetes insipidus.

Baseline Data

Determine creatinine clearance and fluid and electrolyte status.

Identifying High-Risk Patients

Use *vasopressin* with *caution* in patients with coronary artery disease and other vascular diseases.

Implementation: Administration

Routes

Desmopressin. Intranasal, PO, subQ, IV.
Vasopressin. IM, subQ.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Administration

Teach the patient the technique for intranasal administration. To promote adherence, make certain the patient understands that treatment is lifelong.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Teach the patient to monitor and record daily intake and output of fluid. If ADH dosage is correct, urine volume should rapidly drop to normal.

Minimizing Adverse Effects

Water Intoxication. Excessive retention of water can produce water intoxication—most often at the beginning of therapy. **Instruct patients to decrease their accustomed fluid**

intake at the start of treatment. Inform patients about early signs of water intoxication (drowsiness, listlessness, headache), and instruct them to notify the prescriber if these occur. Treatment includes fluid restriction and diuretic therapy. Avoid ADH in patients with creatinine clearance below 50 mL/min.

Cardiovascular Effects. *Vasopressin*, but not desmopressin, is a powerful vasoconstrictor. Excessive vasoconstriction can produce angina pectoris, myocardial infarction, and gangrene (from extravasation of IV vasopressin). Use vasopressin with caution, especially in patients with coronary insufficiency.

*Patient education information is highlighted as blue text.

Drugs for Disorders of the Adrenal Cortex

- Physiology of the Adrenocortical Hormones
 - Glucocorticoids
 - Mineralocorticoids
 - Adrenal Androgens
- Pathophysiology of the Adrenocortical Hormones
 - Adrenal Hormone Excess
 - Adrenal Hormone Insufficiency
- Agents for Replacement Therapy
in Adrenocortical Insufficiency
 - Hydrocortisone
 - Dexamethasone, Prednisone, and Cortisone
 - Fludrocortisone
- Agents for Diagnosing Adrenocortical Disorders
 - Cosyntropin
 - Dexamethasone

The hormones of the adrenal cortex affect multiple physiologic processes, including maintenance of glucose availability, regulation of water and electrolyte balance, development of sexual characteristics, and life-preserving responses to stress. As you might guess, when production of adrenal hormones goes awry, the consequences can be profound. The two most familiar forms of adrenocortical dysfunction are *Cushing's syndrome*, caused by adrenal hormone excess, and *Addison's disease*, caused by adrenal hormone deficiency.

In approaching the drugs for treating disorders of the adrenal cortex, we begin by reviewing adrenocortical endocrinology. After that, we discuss the disease states associated with adrenal hormone excess and adrenal hormone insufficiency. Having established this background, we discuss the agents used for diagnosis and treatment of adrenocortical disorders.

PHYSIOLOGY OF THE ADRENOCORTICAL HORMONES

The adrenal cortex produces three classes of steroid hormones: *glucocorticoids*, *mineralocorticoids*, and *androgens*. Glucocorticoids influence carbohydrate metabolism and other processes; mineralocorticoids modulate salt and water balance; and adrenal androgens contribute to expression of sexual characteristics. When referring to either the glucocorticoids or the mineralocorticoids, three terms may be used: *corticosteroids*, *adrenocorticoids*, or simply *corticoids*. These terms are not used in reference to adrenal androgens.

Glucocorticoids

Glucocorticoids are so named because they increase the availability of glucose. Of the several glucocorticoids produced by the adrenal cortex, *cortisol* is the most important. The structural formula of cortisol is shown in Figure 60-1.

When considering the glucocorticoids, we need to distinguish between *physiologic effects* and *pharmacologic effects*. *Physiologic effects* occur at low levels of glucocorticoids (ie, the levels produced by release of glucocorticoids from healthy adrenals, or by administering glucocorticoids in low doses). *Pharmacologic effects* occur at high levels of glucocorticoids. These levels are achieved when glucocorticoids are administered in the large doses required to treat disorders unrelated to adrenocortical function (eg, allergic reactions, asthma, inflammation, cancer). Pharmacologic levels can also be reached when production of endogenous glucocorticoids is excessive, as occurs in Cushing's disease. In this chapter, we focus on the *physiologic* role of glucocorticoids. The use of high-dose glucocorticoids for nonendocrine purposes is discussed in Chapter 72.

Physiologic Effects

Carbohydrate Metabolism. Supplying the brain with glucose is essential for survival. Glucocorticoids help meet this need. Specifically, they promote glucose availability in four ways: (1) stimulation of gluconeogenesis, (2) reduction of peripheral glucose utilization, (3) inhibition of glucose uptake by muscle and adipose tissue, and (4) promotion of glucose storage (in the form of glycogen). All four actions increase glucose availability during fasting, and thereby help ensure the brain will not be deprived of its primary source of energy.

The effects of glucocorticoids on carbohydrate metabolism are opposite to those of insulin. That is, whereas insulin lowers plasma levels of glucose, glucocorticoids raise them. When present chronically in high concentrations, glucocorticoids produce symptoms much like those of diabetes.

Protein Metabolism. Glucocorticoids promote protein catabolism (breakdown). This action, which is opposite to that of insulin, provides amino acids for glucose synthesis. If present at high levels for a prolonged time, glucocorticoids will cause muscle wasting, thinning of the skin, and negative nitrogen balance.

Fat Metabolism. Glucocorticoids promote lipolysis (fat breakdown). When present at high levels for an extended time, as occurs in Cushing's syndrome, glucocorticoids cause fat redistribution, giving the patient a potbelly, "moon face," and "buffalo hump" on the back.

Cardiovascular System. Glucocorticoids are required to maintain the functional integrity of the vascular system.

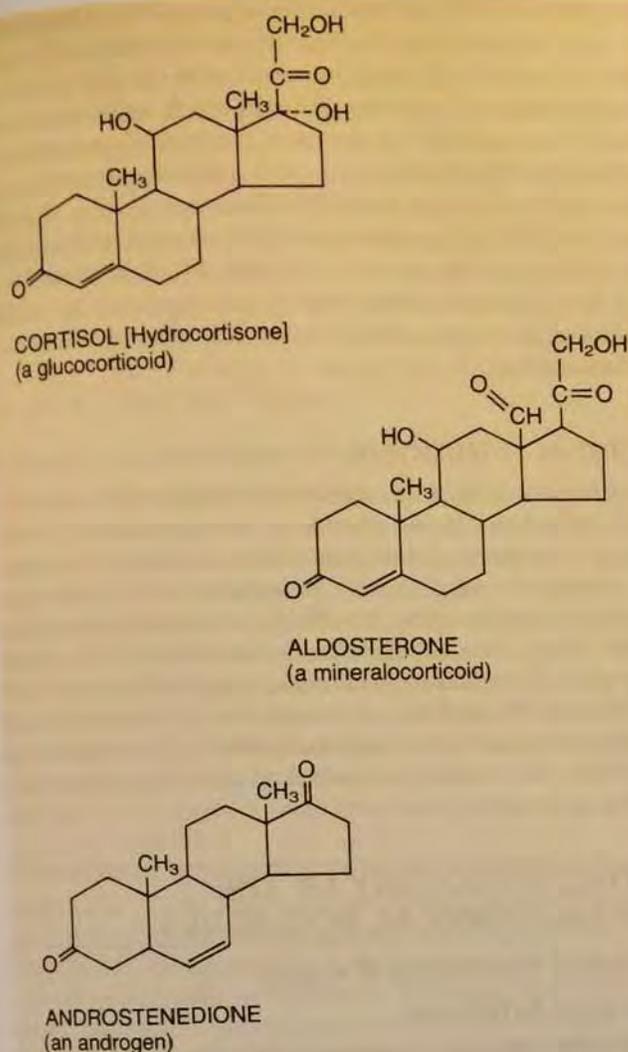


Figure 60-1 ■ Structural formulas of representative adrenocortical hormones.

When levels of glucocorticoids are depressed, capillary permeability is increased, the ability of vessels to constrict is reduced, and blood pressure falls.

Glucocorticoids have multiple effects on blood cells. These hormones increase red blood cell counts and hemoglobin levels. Of the white blood cells, only counts of polymorphonuclear leukocytes increase. In contrast, counts of lymphocytes, eosinophils, basophils, and monocytes decrease.

Skeletal Muscle. Glucocorticoids support function of striated muscle, primarily by maintaining circulatory competence. In the absence of sufficient levels of glucocorticoids, muscle perfusion decreases, causing work capacity to decrease as well.

Central Nervous System. Glucocorticoids affect mood, central nervous system (CNS) excitability, and the electroencephalogram. Glucocorticoid insufficiency is associated with depression, lethargy, and irritability. Rarely, outright psychosis occurs. In contrast, when present in excess, glucocorticoids can produce generalized excitation and euphoria.

Stress. In response to stress (eg, anxiety, exercise, trauma, infection, surgery), the adrenal cortex secretes increased amounts of glucocorticoids, and the adrenal medulla secretes increased amounts of epinephrine. Working together, glu-

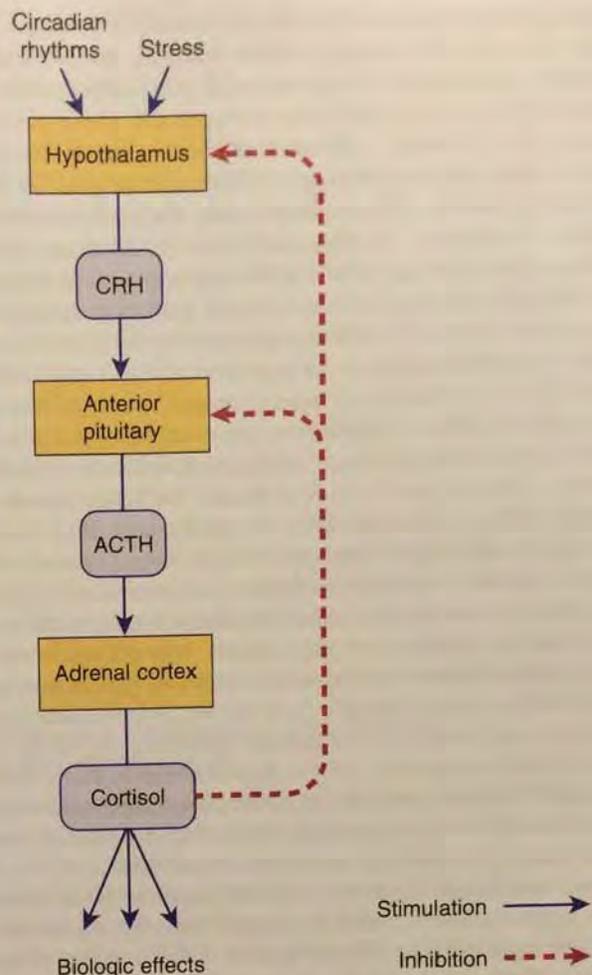


Figure 60-2 ■ Negative feedback regulation of glucocorticoid synthesis and secretion.

(ACTH = adrenocorticotropic hormone, CRH = corticotropin-releasing hormone.)

corticoids and epinephrine serve to maintain blood pressure and blood glucose content. If glucocorticoid levels are inadequate, hypotension and hypoglycemia can occur. If the stress is extreme (eg, trauma, surgery, severe infection), glucocorticoid deficiency can result in circulatory collapse and death. Accordingly, it is imperative that patients with adrenal insufficiency receive glucocorticoid supplements when severe stress occurs.

Respiratory System in Neonates. During labor and delivery, the adrenals of the full-term fetus release a burst of glucocorticoids. Within hours, these steroids act on the lungs to accelerate their maturation. In the preterm infant, the adrenals produce only small amounts of glucocorticoids. As a result, preterm infants experience a high incidence of respiratory distress syndrome.

Regulation of Synthesis and Secretion

Adrenal storage of glucocorticoids is minimal. Accordingly, the amount of glucocorticoid released from the adrenals per unit time closely approximates the amount being made.

Glucocorticoid synthesis and release are regulated by a negative feedback loop (Fig. 60-2). The loop begins with release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH acts on the anterior pituitary to promote

release of adrenocorticotrophic hormone (ACTH), which stimulates the zona fasciculata of the adrenal cortex, causing synthesis and release of cortisol and other glucocorticoids. Following release, cortisol acts in two ways: (1) it promotes its designated biologic effects and (2) it acts on the hypothalamus and pituitary to suppress further release of CRH and ACTH. Hence, as cortisol levels rise, they act to suppress further stimulation of glucocorticoid production, thereby keeping glucocorticoid levels within an appropriate range.

The hypothalamic-pituitary-adrenal system is activated by signals from the CNS. These signals turn the system on by causing the hypothalamus to release CRH. As indicated in Figure 60-2, two modes of activation are involved. One provides a basal level of stimulation; the other increases stimulation at times of stress. Basal stimulation follows a circadian rhythm: Cortisol levels are lowest near bedtime, rise during sleep, reach a peak just before waking, and then decline through the day. (Note that this cycle is linked to one's *sleep pattern*, and not to the clock. Hence, for some people, cortisol may peak in the morning, and for others it may peak in the afternoon or evening, depending on when they normally sleep.) When stress occurs, glucocorticoid production goes up. Stressful events that can activate the loop include injury, infection, and surgery. The signals generated by stress produce intense stimulation of the hypothalamus. The resultant release of CRH and ACTH can cause plasma levels of cortisol to increase 10-fold. Because stress is such a powerful stimulus, it overrides feedback inhibition by cortisol.

How much cortisol do the adrenals produce? Basal production ranges between 5 and 10 mg/m²/day (the equivalent of 20 to 30 mg/day of hydrocortisone or 5 to 7 mg/day of prednisone). When severe stress occurs, production increases 5- to 10-fold—to a maximum of 100 mg/m²/day.

Mineralocorticoids

The mineralocorticoids influence renal processing of sodium, potassium, and hydrogen. In addition, they have direct effects on the heart and blood vessels. Of the mineralocorticoids made by the adrenal cortex, *aldosterone* is the most important.

Physiologic Effects. Renal Actions. Aldosterone promotes sodium and potassium hemostasis, and helps maintain intravascular volume. Specifically, the hormone acts on the collecting ducts of the nephron to promote sodium reabsorption in exchange for secretion of potassium and hydrogen. The total amount of hydrogen and potassium lost equals the amount of sodium reabsorbed. You should note that, as sodium is reabsorbed, water is reabsorbed along with it. In the absence of aldosterone, renal excretion of sodium and water is greatly increased, whereas excretion of potassium and hydrogen is reduced. As a result, aldosterone insufficiency causes hyponatremia, hyperkalemia, acidosis, cellular dehydration, and reduction of extracellular fluid volume. Left uncorrected, the condition can lead to renal failure, circulatory collapse, and death.

Cardiovascular Actions. In addition to its effects on the kidneys, aldosterone acts on the heart and blood vessels as well. When aldosterone levels are high, cardiovascular effects are *harmful*, increasing the risk of heart failure and hypertension. Specific cardiovascular effects include (1) promotion of myocardial remodeling (which can impair pumping); (2) promotion of myocardial fibrosis (which increases the risk of

dysrhythmias); (3) activation of the sympathetic nervous system and suppression of norepinephrine uptake in the heart (both of which can promote dysrhythmias and ischemia); (4) promotion of vascular fibrosis (which decreases arterial compliance); and (5) disruption of the baroreceptor reflex.

Control of Secretion. Secretion of aldosterone is regulated by the renin-angiotensin-aldosterone system (RAAS), not by ACTH. The mechanisms by which the RAAS regulates aldosterone are discussed in Chapter 44. It is important to note that, because aldosterone is not regulated by ACTH, conditions that alter secretion of ACTH do not alter secretion of aldosterone.

Adrenal Androgens

The adrenal cortex produces several steroids that have androgenic properties. *Androstenedione* is representative. Under normal conditions, physiologic effects of adrenal androgens are minimal. In adult males, the influence of adrenal androgens is overshadowed by the effects of testosterone produced by the testes. In adult females, a metabolite of the adrenal androgens—testosterone—contributes to development of sexual hair and maintenance of normal libido. Although adrenal androgens normally have very little effect, when production is excessive, as occurs in congenital adrenal hyperplasia, virilization can result.

PATHOPHYSIOLOGY OF THE ADRENOCORTICAL HORMONES

Adrenal Hormone Excess Cushing's Syndrome

Causes. Signs and symptoms of Cushing's syndrome result from excess levels of circulating glucocorticoids. Principal causes are (1) hypersecretion of ACTH by pituitary adenomas (Cushing's disease), (2) hypersecretion of glucocorticoids by adrenal adenomas and carcinomas, and (3) administering glucocorticoids in the large doses used to treat arthritis and other nonendocrine disorders (see Chapter 72).

Clinical Presentation. Cushing's syndrome is characterized by obesity, hyperglycemia, glycosuria, hypertension, fluid and electrolyte disturbances, osteoporosis, muscle weakness, myopathy, hirsutism, menstrual irregularities, and decreased resistance to infection. The skin is weakened, resulting in striae (stretch marks) and increased susceptibility to injury. Fat undergoes redistribution to the abdomen, face, and upper back, giving the patient a characteristic potbelly, "moon face," and "buffalo hump." Psychiatric changes are common.

Treatment. Treatment is directed at the cause. The treatment of choice for adrenal adenoma and carcinoma is surgical removal of the diseased adrenal gland. If bilateral adrenalectomy is required, replacement therapy with glucocorticoids and mineralocorticoids will be needed. For patients with inoperable adrenal carcinoma, treatment with *mitotane* may be indicated. Mitotane is an anticancer drug that produces selective destruction of adrenocortical cells. The pharmacology of mitotane is discussed in Chapter 102.

When Cushing's syndrome is caused by pituitary adenoma, surgery is the preferred intervention. Partial removal of the pituitary often lowers ACTH secretion to safe levels, while leaving other pituitary functions intact. If partial adrenalectomy is

unsuccessful, the remainder of the pituitary may be removed. As an alternative, pituitary irradiation may be employed.

The role of drugs in treating Cushing's syndrome is limited. Specifically, drugs are employed only as adjuncts to radiation and surgery—not as the primary intervention. Benefits derive from suppressing corticosteroid synthesis. The most effective agent is *ketoconazole* [Nizoral], an antifungal drug that also blocks glucocorticoid synthesis. The dosage for suppression of steroid synthesis is 600 to 800 mg/day—much higher than doses employed for antifungal therapy. At these doses, ketoconazole can cause significant liver dysfunction. The basic pharmacology of ketoconazole is discussed in Chapter 92 (Antifungal Agents).

Primary Hyperaldosteronism

Clinical Presentation, Causes, and Diagnosis. Hyperaldosteronism (excessive secretion of aldosterone) causes hypokalemia, metabolic alkalosis, and hypertension, and can increase the risk of heart failure. Muscle weakness and changes in the electrocardiogram develop secondary to hypokalemia. Hyperaldosteronism is frequently caused by an aldosterone-producing adrenal adenoma. The condition may also result from bilateral adrenal hyperplasia. Primary hyperaldosteronism can be diagnosed by determining the ratio of plasma aldosterone concentration to plasma renin activity (as discussed in Chapter 44, renin is an enzyme that plays a critical role in the RAAS).

Treatment. Management of hyperaldosteronism depends on the cause. When an adrenal adenoma is responsible, surgical resection of the adrenal gland is usually curative. When bilateral adrenal hyperplasia is the cause, an *aldosterone antagonist* is the preferred treatment. The antagonist employed most frequently is *spironolactone*, a drug we normally think of as a potassium-sparing diuretic. Under the influence of spironolactone, potassium levels may normalize in 2 weeks. To achieve full control of hypertension, an additional diuretic may be required. The basic pharmacology of spironolactone is discussed in Chapter 41 (Diuretics). Alternatives to spironolactone include *amiloride* (another potassium-sparing diuretic [see Chapter 41]) and *epplerenone* (a highly selective aldosterone antagonist [see Chapter 44]).

Adrenal Hormone Insufficiency

General Therapeutic Considerations

Chronic adrenal hormone insufficiency can result from multiple causes, including destruction of the adrenals, inborn deficiencies of the enzymes required for corticosteroid synthesis, and reduced secretion of ACTH and CRH. Regardless of the cause, chronic adrenal insufficiency requires lifelong replacement therapy with appropriate corticosteroids. All patients require a *glucocorticoid*. Some may require a *mineralocorticoid* as well. Of the glucocorticoids available, *hydrocortisone*, *prednisone*, and *dexamethasone* are drugs of choice. When a mineralocorticoid is indicated, *fludrocortisone* is the drug of choice.

Replacement therapy should mimic normal patterns of corticosteroid secretion. Since levels of glucocorticoids normally peak in the morning, the usual practice is to take the entire daily dose immediately after waking up. An alternative is to divide the daily dose, giving two-thirds in the morning and one-third in the afternoon. Mineralocorticoids can be administered once

a day. Doses of glucocorticoids and mineralocorticoids should approximate the amounts normally secreted by the adrenals. It is important to note that, when glucocorticoids are employed for replacement therapy, doses are much smaller than the doses employed for nonendocrine disorders.

At times of stress, patients must increase their glucocorticoid dosage. I cannot overemphasize the importance of doing so: *Failure to increase the dosage can be fatal.* Recall that healthy adrenals increase their output of glucocorticoids in response to stress. For patients with adrenal insufficiency, the extra glucocorticoids that would normally be supplied by the adrenals must instead be supplied through supplemental dosing. Dosing guidelines related to specific medical conditions and surgical procedures are summarized in Table 60-1. For mild or febrile illness, the “3 by 3 rule” applies: Take 3 times the usual dosage for 3 days.

To ensure availability of glucocorticoids in emergencies, patients should carry an adequate supply at all times. This supply should include an injectable preparation plus an oral preparation. Furthermore, the patient should wear some form of identification (eg, Medic Alert bracelet) to inform emergency personnel about his or her glucocorticoid needs.

Primary Adrenocortical Insufficiency (Addison's Disease)

Causes. Primary adrenocortical insufficiency (PAI), also known as Addison's disease, is a condition in which the adrenal glands are damaged, and hence are unable to make corticosteroids. Most cases (80%) are caused by autoimmune destruction of adrenal tissue. Another 15% are caused by tuberculosis and other infections. Other causes include adrenal hemorrhage, cancers, and certain drugs (eg, ketoconazole, rifampin).

Clinical Presentation. Symptoms can range from mild (anorexia, nausea, weight loss) to severe (hypotensive crisis). In most patients, PAI follows a chronic course. Patients typically present with nonspecific symptoms: nausea, vomiting, diarrhea, anorexia, weakness, emaciation, and abdominal pain. Hyperkalemia, hyponatremia, and hypotension are present as well. These symptoms result from a deficiency of glucocorticoids and mineralocorticoids that occurs secondary to adrenal atrophy. In addition, patients may develop hyperpigmentation of the skin and mucous membranes. The cause is excessive production of ACTH in attempts to restore depressed levels of glucocorticoids. Severe symptoms of acute adrenal crisis are discussed separately below.

Treatment. Replacement therapy with adrenocorticoids is required. *Hydrocortisone*, which has both glucocorticoid and mineralocorticoid activity, is a drug of choice. If additional mineralocorticoid activity is needed, *fludrocortisone*, the only mineralocorticoid available, can be added to the regimen.

Secondary and Tertiary Adrenocortical Insufficiency

Secondary adrenocortical insufficiency results from decreased secretion of ACTH, while tertiary insufficiency results from decreased secretion of CRH. In both cases, adrenal secretion of glucocorticoids is diminished, whereas secretion of mineralocorticoids is usually normal. Glucocorticoid insufficiency produces a characteristic set of symptoms: hypoglycemia, malaise, loss of appetite, and reduced capacity to respond to

TABLE 60-1 ■ Guidelines for Giving Supplemental Doses of Glucocorticoids at Times of Stress Related to Medical Conditions and Surgical Procedures

Medical Condition or Surgical Procedure	Supplemental Glucocorticoid Dosage
Minor Inguinal hernia repair Colonoscopy Mild febrile illness Mild to moderate nausea/vomiting Gastroenteritis	25 mg of hydrocortisone (or 5 mg of methylprednisolone) IV on day of procedure
Moderate Open cholecystectomy Hemicolectomy Significant febrile illness Pneumonia Severe gastroenteritis	50–75 mg of hydrocortisone (or 10–15 mg of methylprednisolone) IV on day of procedure Taper quickly over 1–2 days to usual replacement dose
Severe Major cardiothoracic surgery Whipple procedure Liver resection Pancreatitis	100–150 mg of hydrocortisone (or 20–30 mg of methylprednisolone) IV on day of procedure Rapidly taper to usual replacement dose over next 1–2 days
Critically Ill Sepsis-induced hypotension or shock	50–100 mg of hydrocortisone IV every 6–8 hr (or 0.18 mg/kg/hr as continuous infusion) <i>plus</i> 50 mg of fludrocortisone until shock resolves, which may take several days to a week or more Then gradually taper to usual replacement dose, following vital signs and serum sodium

Adapted from Coursin DB, Wood KE: Corticosteroid supplementation for adrenal insufficiency. *JAMA* 287:236–240, 2002.

stress. For secondary and tertiary insufficiency, treatment consists of replacement therapy with a glucocorticoid (eg, hydrocortisone). Rarely, a mineralocorticoid is needed too.

Acute Adrenal Insufficiency (Adrenal Crisis)

Clinical Presentation. Acute adrenal insufficiency is characterized by hypotension, dehydration, weakness, lethargy, and GI symptoms (eg, vomiting, diarrhea). Left untreated, the syndrome progresses to shock and then death.

Causes. Adrenal crisis may be brought on by adrenal failure, pituitary failure, or failure to provide patients receiving replacement therapy with adequate doses of corticosteroids. Adrenal crisis may also be triggered by abrupt withdrawal from chronic, high-dose glucocorticoid therapy.

Treatment. Patients require rapid replacement of fluid, salt, and glucocorticoids. They also need glucose for energy. These needs are met by injecting 100 mg of hydrocortisone (as an IV bolus) followed by IV infusion of normal saline with dextrose. Additional hydrocortisone is given by infusion at a rate of 100 mg every 8 hours.

Congenital Adrenal Hyperplasia

Clinical Presentation and Causes. Congenital adrenal hyperplasia (CAH) results from an inborn deficiency of enzymes needed for glucocorticoid synthesis, most commonly *21-alpha-hydroxylase*. The ability to make glucocorticoids is reduced, but not eliminated. In an attempt to enhance glucocor-

ticoid synthesis, the pituitary releases large amounts of ACTH, which act on the adrenal to cause growth of adrenal tissue (hyperplasia) and increased synthesis of glucocorticoids and androgens. Synthesis of mineralocorticoids changes very little. Frequently, stimulation of glucocorticoid synthesis may be sufficient to normalize levels of cortisol. Unfortunately, the amounts of ACTH required for normalization are so large that synthesis of adrenal androgens becomes excessive. In girls, increased androgen levels cause masculinization of the external genitalia, but the ovaries, uterus, and fallopian tubes are not affected. Increased androgen levels in boys may cause precocious penile enlargement. In children of both sexes, linear growth is accelerated. However, because androgens cause premature closure of the epiphyses, adult height is usually diminished. CAH affects 1 of every 10,000 to 20,000 infants.

Treatment. The objective is to ensure adequate levels of glucocorticoids while preventing excessive production of adrenal androgens. This goal is achieved through lifelong glucocorticoid replacement. *Hydrocortisone*, *dexamethasone*, and *prednisone* are preferred agents. By supplying glucocorticoids exogenously, we can suppress secretion of ACTH. As a result, the adrenals are no longer stimulated to produce excessive quantities of androgens. As a rule, ACTH suppression can be achieved with daily doses of hydrocortisone equivalent to twice the amount secreted by normal adrenals. To assess treatment, children should be monitored every 3 months for growth rate and signs of virilization.

Screening. In 2010, The Endocrine Society recommended universal screening of newborns for 21-alpha-hydroxylase deficiency. If the test is positive, follow-up testing should be done to confirm a CAH diagnosis. These recommendations were endorsed by several professional organizations, including the American Academy of Pediatrics, the Pediatric Endocrine Society, the Society for Pediatric Urology, and the CARES Foundation.

AGENTS FOR REPLACEMENT THERAPY IN ADRENOCORTICAL INSUFFICIENCY

Patients with adrenocortical insufficiency require replacement therapy with corticosteroids. A glucocorticoid is always required; some patients require a mineralocorticoid too. The principal glucocorticoids employed are *hydrocortisone*, *dexamethasone*, and *prednisone*. *Fludrocortisone* is the only mineralocorticoid available.

Please note that classification of a drug as a "glucocorticoid" or "mineralocorticoid" may be an oversimplification. That is, a drug that we classify as a glucocorticoid may also exhibit salt-retaining (mineralocorticoid) activity. Conversely, a drug that we classify as a mineralocorticoid may also display typical glucocorticoid activity.

Hydrocortisone

Hydrocortisone is a synthetic steroid with a structure identical to that of cortisol, the principal glucocorticoid produced by the adrenal cortex (see Fig. 60-1). Hydrocortisone is a preferred drug for adrenocortical insufficiency and will serve as our prototype of the glucocorticoids employed clinically. Please note that, despite being classified as a glucocorticoid, hydrocortisone also has mineralocorticoid actions.

Therapeutic Uses

Replacement Therapy. Hydrocortisone is a preferred drug for all forms of adrenocortical insufficiency. Oral hydrocortisone is ideal for chronic replacement therapy. Parenteral administration is used for acute adrenal insufficiency and to supplement oral doses at times of stress. Because of its mineralocorticoid actions, hydrocortisone may suffice as sole therapy for adrenal insufficiency, even when salt loss is a symptom.

Nonendocrine Applications. Hydrocortisone and other glucocorticoids are used to treat a broad spectrum of nonendocrine disorders, ranging from allergic reactions to inflammation to cancer. The doses required are considerably higher than those employed for replacement therapy. The use of glucocorticoids for nonendocrine diseases is discussed in Chapter 72.

Adverse Effects

When given in the low doses required for replacement therapy, hydrocortisone and other glucocorticoids are devoid of adverse effects. In contrast, when taken chronically in the large doses employed to treat nonendocrine disorders, glucocorticoids are highly toxic. The adverse effects of chronic, high-dose therapy include adrenal suppression and production of Cushing's syndrome. These and other adverse effects are discussed in Chapter 72.

Preparations, Dosage, and Administration

Dosages presented here are for oral and parenteral therapy of adrenal insufficiency. Dosages for nonendocrine disorders are presented in Chapter 72.

Oral Therapy. *Hydrocortisone base* [Hydrocortone, Cortef \clubsuit] is available in tablets (5, 10, and 15 mg) for oral therapy of chronic adrenal insufficiency. The total daily dose is 12 to 15 mg/m². For adults, this translates to 22 to 25 mg/day. To mimic normal cortisol secretion, patients can take the entire daily dose in the morning, immediately after waking. If this schedule results in afternoon or evening fatigue, patients may split the dosage, taking two-thirds in the morning and one-third around 4:00 in the afternoon.

Parenteral Therapy. *Hydrocortisone sodium succinate* [A-Hydrocort, Solu-Cortef] is available in single-use vials (100, 250, 500, and 100 mg) for IM or IV administration. For emergency treatment, IV doses of 50 to 100 mg are employed (see Table 60-1). When IV injections can't be used, IM doses of 100 to 250 mg may be given instead.

Dexamethasone, Prednisone, and Cortisone

Like hydrocortisone, prednisone and dexamethasone are preferred drugs for oral therapy of chronic adrenal insufficiency. The total daily dosage is 0.25 to 0.75 mg for dexamethasone, and 5 to 10 mg for prednisone. In addition to its use for replacement therapy, dexamethasone is used to diagnose adrenal dysfunction (see below).

Cortisone is a prodrug that undergoes conversion to hydrocortisone (its active form) in the body. The drug has both glucocorticoid and mineralocorticoid activity. For management of chronic adrenal insufficiency, the total daily oral dosage is 12 to 15 mg/m².

Fludrocortisone

Fludrocortisone [Florinef] is a potent mineralocorticoid that also possesses significant glucocorticoid activity. Fludrocortisone is the only mineralocorticoid available and is the drug of choice for chronic mineralocorticoid replacement.

Therapeutic Uses. Fludrocortisone is a preferred drug for treating primary adrenal insufficiency, primary hypoadosteronism, and congenital adrenal hyperplasia (when salt wasting is a feature of the syndrome). In most cases, fludrocortisone must be used in combination with a glucocorticoid (eg, hydrocortisone).

Adverse Effects. Adverse effects are a direct consequence of mineralocorticoid actions. When dosage is too high, salt and water are retained in excess, while excessive amounts of potassium are lost. These effects on salt and water can result in expansion of blood volume, hypertension, edema, cardiac enlargement, and hypokalemia. Patients should be monitored for weight gain, elevation of blood pressure, and hypokalemia. If these changes occur, fludrocortisone should be temporarily withdrawn. Fluid and electrolyte imbalance should resolve spontaneously in a few days.

Preparations, Dosage, and Administration. Fludrocortisone acetate is available in 0.1-mg tablets for oral dosing. The dosage is 0.1 mg/day. If excessive salt retention occurs, the dose should be cut to 0.05 mg/day.

AGENTS FOR DIAGNOSING ADRENOCORTICAL DISORDERS

Cosyntropin

Cosyntropin [Cortrosyn], a synthetic analog of ACTH, acts on the adrenal cortex to stimulate synthesis and secretion of cortisol and other adrenal corticosteroids. The drug is used to diagnose adrenal insufficiency. In the usual test, patients are given a 250-mcg dose of cosyntropin, injected IM or IV. Plasma cortisol is measured just before the injection and then 30 or 60 minutes later. If cortisol rises to above 20 mcg/dL, the adrenal response is considered normal, and hence primary adrenal insufficiency

can be ruled out. If cortisol fails to rise significantly, a diagnosis of primary adrenal insufficiency can be made.

Dexamethasone

Dexamethasone is a synthetic steroid that has pronounced glucocorticoid properties and very little mineralocorticoid activity. The drug is used for replacement therapy, treating nonendocrine disorders, and diagnosing Cushing's syndrome.

Overnight Dexamethasone Suppression Test

The overnight dexamethasone suppression test is used to diagnose Cushing's syndrome. The test is performed by administering 1 mg of dexamethasone at 11:00 PM followed by measurement of plasma cortisol levels at 8:00 the following morning. In normal individuals, dexamethasone acts on the pituitary to suppress release of ACTH, thereby suppressing synthesis and release of cortisol. If the patient has Cushing's syndrome, little or no suppression of cortisol production will occur.

Prolonged Dexamethasone Suppression Test

Once Cushing's syndrome has been diagnosed, the prolonged dexamethasone suppression test can be used to determine if excessive ACTH release or primary adrenal dysfunction is the cause. The test is performed as follows: (1) baseline measurement of urinary 17-hydroxycorticosteroids is made (these compounds provide an index of adrenal corticosteroid production); (2) dexamethasone is administered in 2-mg doses every 6 hours for 48 hours; and (3) 24-hour urine is collected and assessed for 17-hydroxycorticosteroids. If primary adrenal dysfunction is responsible for the symptoms of Cushing's syndrome, no suppression of 17-hydroxycorticosteroid production will occur. In contrast, if excessive ACTH release underlies Cushing's syndrome, prolonged administration of dexamethasone should produce some suppression of ACTH secretion, and therefore should cause a small but measurable reduction in urinary 17-hydroxycorticosteroids.

It should be noted that the dexamethasone suppression test is not the best method for determining the underlying cause of Cushing's syndrome. The preferred procedure is to measure plasma ACTH and cortisol content directly. If plasma cortisol levels are high and ACTH levels are normal, adrenal dysfunction is responsible for the observed signs. If levels of both ACTH and cortisol are high, excessive ACTH secretion is the likely cause.

KEY POINTS

- The adrenal cortex produces three classes of steroid hormones: glucocorticoids, mineralocorticoids, and androgens.
- Glucocorticoids influence the metabolism of carbohydrates, proteins, and fats. In addition, they affect skeletal muscle, the cardiovascular system, and the CNS. At times of stress, glucocorticoids are essential for survival.
- Synthesis and release of glucocorticoids is regulated by a negative feedback loop involving CRH from the hypothalamus, ACTH from the pituitary, and cortisol from the adrenal cortex.
- Aldosterone, the major mineralocorticoid, acts on the kidney to promote retention of sodium and water and excretion of potassium and hydrogen. Aldosterone also acts directly on the heart and blood vessels, causing harm when its levels are high.
- Glucocorticoid excess causes Cushing's syndrome.
- The principal treatment for Cushing's syndrome is surgical removal of the adrenals (if adrenal adenoma or carcinoma is the cause) or part of the pituitary (if pituitary adenoma is the cause).
- Ketoconazole can be used to suppress synthesis of adrenal steroids in patients with Cushing's syndrome. However, this drug is employed only as an adjunct to surgery or radiation.
- Adrenal insufficiency causes Addison's disease.
- Adrenal insufficiency is treated by replacement therapy with glucocorticoids (eg, hydrocortisone). Fludrocortisone, a pure mineralocorticoid, may be added if the mineralocorticoid actions of hydrocortisone are inadequate.
- Glucocorticoid replacement therapy may be done by (1) giving the entire daily dose in the morning or by (2) splitting the daily dose, giving two-thirds in the morning and one-third in the afternoon.
- In patients with adrenal insufficiency, it is essential to increase glucocorticoid doses at times of stress (eg, surgery, infection, trauma). Failure to do so may be fatal.
- When used in the low (physiologic) doses needed for replacement therapy, glucocorticoids have no adverse effects. In contrast, when used chronically in the high (pharmacologic) doses needed to treat nonendocrine diseases (eg, arthritis), glucocorticoids can cause severe adverse effects (see Chapter 72).
- Cosyntropin, which acts like ACTH, is only used for diagnosis of adrenal insufficiency—not for treatment.

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Summary of Major Nursing Implications*

GLUCOCORTICOIDS: HYDROCORTISONE AND CORTISONE

The nursing implications summarized here apply only to the use of glucocorticoids for *replacement therapy*. Nursing implications that apply to use of glucocorticoids for *nonendocrine disorders* are summarized in Chapter 72.

Use in Addison's Disease

Administration. Instruct patients to follow the prescribed dosing schedule. Primary options are (1) take the entire daily dose in the morning upon waking or (2) divide the daily dose, taking two-thirds upon waking and one-third in the afternoon.

Make certain the patient understands that replacement therapy must continue lifelong.

Emergency Preparedness. Warn patients that dosage must be increased at times of stress (eg, infection, surgery, trauma). For mild or febrile illness, the "3 by 3 rule" applies: Take 3 times the usual dosage for 3 days. Advise the patient to carry an emergency supply of glucocorticoids—oral and injectable—at all times. Advise patients to wear identification (eg, Medic Alert bracelet) to inform emergency medical personnel of their glucocorticoid requirements.

Monitoring. Determine electrolyte and glucocorticoid levels at baseline and periodically thereafter.

Use in Congenital Adrenal Hyperplasia

To assess therapy, monitor the child at 3-month intervals for signs of excess androgen production (eg, excessive growth rate, virilization in girls, precocious penile enlargement in boys). Suppression of these effects indicates success.

*Patient education information is highlighted as **blue text**.

Minimizing Adverse Effects

Excessive doses can produce symptoms of Cushing's syndrome. Observe the patient for signs of Cushing's syndrome and notify the prescriber if these develop.

FLUDROCORTISONE (A MINERALOCORTICOID)

Route

Oral.

Minimizing Adverse Effects

Excessive doses cause retention of sodium and water and excessive excretion of potassium, resulting in expansion of blood volume, hypertension, cardiac enlargement, edema, and hypokalemia. Evaluate patients periodically for clinical status and electrolyte levels. **Inform patients about signs of salt and water retention (eg, unusual weight gain, swelling of the feet or lower legs) and hypokalemia (eg, muscle weakness, irregular heartbeat), and instruct them to notify the prescriber if these occur.** Treatment consists of temporary withdrawal of fludrocortisone, after which fluid and electrolyte balance should normalize within days.

Estrogens and Progestins: Basic Pharmacology and Noncontraceptive Applications

The Menstrual Cycle

Estrogens

Biosynthesis and Elimination

Mechanism of Action

Physiologic and Pharmacologic Effects

Clinical Pharmacology

Selective Estrogen Receptor Modulators (SERMs)

Progestins

Biosynthesis

Mechanism of Action

Physiologic and Pharmacologic Effects

Clinical Pharmacology

Menopausal Hormone Therapy

Landmark Studies: WHI and HERS

Benefits and Risks of Hormone Therapy

Warnings

Recommendations on Hormone Therapy Use

Safety in Younger Women Who Don't Have
a Uterus

Discontinuing Hormone Therapy

Open Questions

Drug Products for Hormone Therapy

THE MENSTRUAL CYCLE

Because much of the clinical pharmacology of the estrogens and progestins is related to their actions during the menstrual cycle, understanding the menstrual cycle is central to understanding these hormones. Accordingly, we begin by reviewing the menstrual cycle. The anatomic and hormonal changes that take place during the cycle are summarized in Figure 61-1. As indicated, the first half of the cycle (days 1 through 14) is called the *follicular phase*, and the second half is called the *luteal phase*. One full cycle typically takes 28 days.

Ovarian and Uterine Events. The menstrual cycle consists of a coordinated series of ovarian and uterine events. In the ovary, the following sequence occurs: (1) several ovarian follicles ripen; (2) one of the ripe follicles ruptures, causing ovulation; (3) the ruptured follicle evolves into a corpus luteum; and (4) if fertilization does not occur, the corpus luteum atrophies. As these ovarian events are taking place, parallel events take place in the uterus: (1) while ovarian follicles ripen, the endometrium prepares for nidation (implantation of a fertilized ovum) by increasing in thickness and vascularity; (2) following ovulation, the uterus continues its preparation by increasing secretory activity; and (3) if nidation fails to occur, the thickened endometrium breaks down, causing menstruation, and the cycle begins anew.

The Roles of Estrogens and Progesterone. The uterine changes that occur during the cycle are brought about under the influence of estrogens and progesterone produced by the ovaries. During the first half of the cycle, estrogens are secreted by the maturing ovarian follicles. As suggested by Figure 61-1, these estrogens act on the uterus to cause proliferation of the endometrium. At midcycle, one of the ovarian follicles ruptures and then evolves into a corpus luteum. For most of the second half of the cycle, estrogens and progesterone are produced by the newly formed corpus luteum. These hormones maintain the endometrium in its hypertrophied state. At the end of the cycle, the corpus luteum atrophies, causing production of estrogens and progesterone to decline. In response to the diminished supply of ovarian hormones, the endometrium breaks down.

The Role of Pituitary Hormones. Two anterior pituitary hormones—follicle-stimulating hormone (FSH) and luteinizing hormone (LH)—play central roles in regulating the menstrual cycle. During the first half of the cycle, FSH acts on the developing ovarian follicles, causing them to mature and secrete estrogens. The resultant rise in estrogen levels exerts a negative feedback influence on the pituitary, thereby suppressing further FSH release. At midcycle, LH levels rise

Box 61-1. Premenstrual Syndrome (PMS)

Estrogens and progestins are hormones with multiple actions. They promote female maturation, and help regulate the ongoing activity of female reproductive organs. In addition, they affect bone mineralization and lipid metabolism. The principal endogenous estrogen is estradiol. The principal endogenous progestational hormone is progesterone. Both hormones are produced by the ovaries. During pregnancy, large amounts are produced by the placenta. In addition, small amounts of estrogens and progestins are produced in peripheral tissues.

Clinical applications of the female sex hormones fall into two major categories: contraceptive and noncontraceptive applications. In this chapter, we focus on noncontraceptive uses. Contraception is discussed in Chapter 62. The principal noncontraceptive application of estrogens and progestins is menopausal hormone therapy (HT): estrogens are given to manage hot flashes and other menopausal symptoms; progestins are given to oppose estrogen-mediated stimulation of the endometrium.

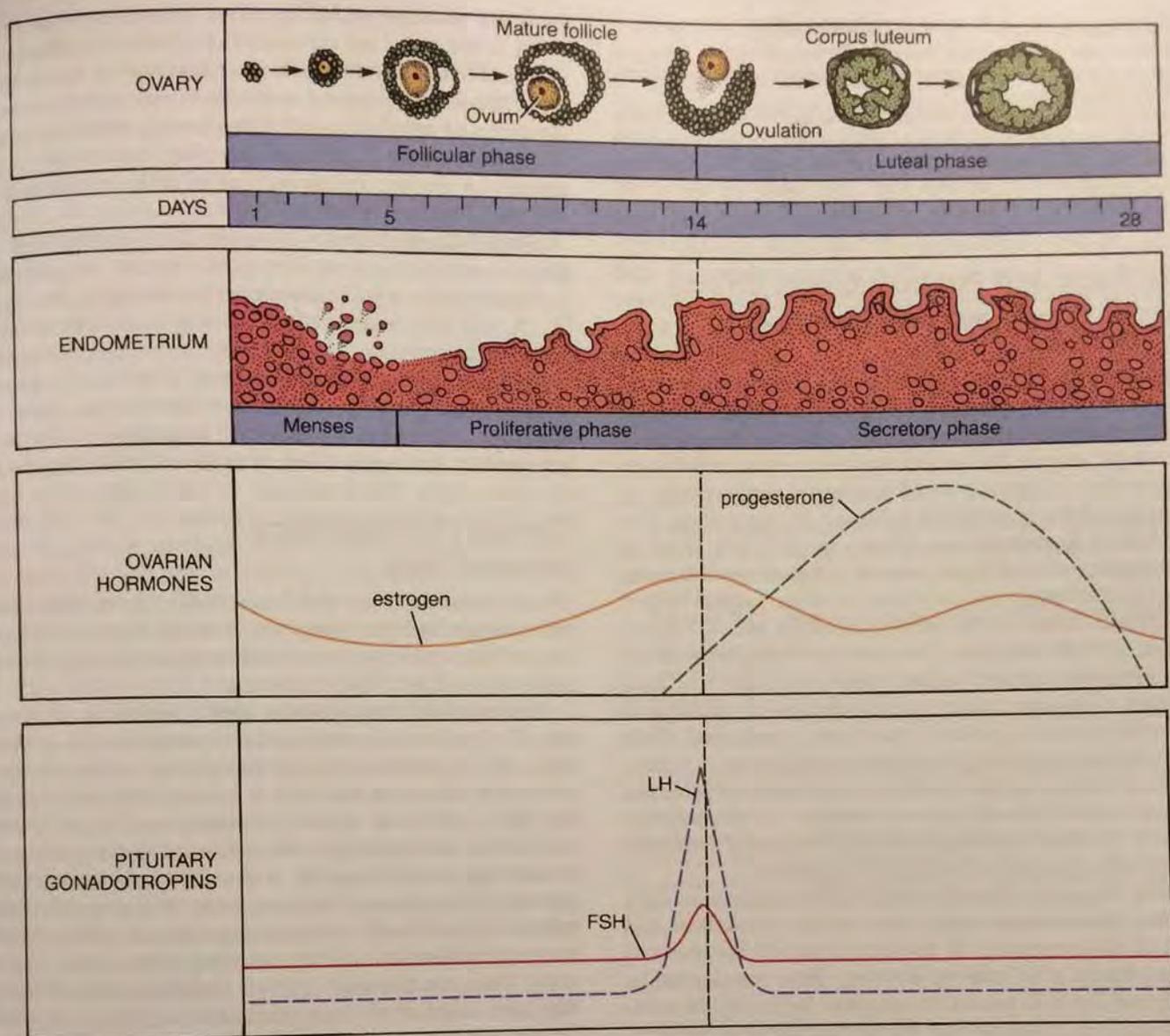


Figure 61-1 ■ The menstrual cycle: anatomic and hormonal changes. (FSH = follicle-stimulating hormone, LH = luteinizing hormone.)

abruptly (see Fig. 61-1). This LH surge causes the dominant follicle to swell rapidly, burst, and release its ovum. Following ovulation, the ruptured follicle becomes a corpus luteum and, under the influence of LH, begins to secrete progesterone.

From the foregoing, it is clear that precisely timed alterations in the secretion of FSH and LH are responsible for coordinating the structural and secretory changes that occur throughout the menstrual cycle. The mechanisms that regulate secretion of FSH and LH are complex and beyond the scope of this book.

ESTROGENS

Biosynthesis and Elimination

Females. In premenopausal women, the ovary is the principal source of estrogen. During the follicular phase of the menstrual cycle, estrogens are synthesized by ovarian follicles; during the luteal phase, estrogens are synthesized by the corpus luteum. The major estrogen produced by the ovaries is *estra-*

diol. In the periphery, some of the estradiol secreted by the ovaries is converted into *estrone* and *estriol*, hormones that are less potent than estradiol itself. Estrogens are eliminated by a combination of hepatic metabolism and urinary excretion.

During pregnancy, large quantities of estrogens are produced by the placenta. Excretion of these hormones results in high levels of estrogens in the urine. (The urine of pregnant mares is extremely rich in estrogens and serves as a commercial source of these hormones.)

Males. Estrogen production is not limited to females. In the human male, small amounts of testosterone are converted into estradiol and estrone by the testes. Enzymatic conversion of testosterone in peripheral tissues (eg, liver, fat, skeletal muscle) results in additional estrogen production.

Mechanism of Action

Like other steroidal hormones (eg, testosterone, cortisol), estrogen acts primarily through receptors in the cell nucleus, not on the cell surface. Hence, to produce its effects, estrogen must diffuse into cells, migrate to the nucleus, and then bind with an estrogen receptor (ER). The estrogen-ER complex then binds with an *estrogen response element* on a target gene, thereby altering the

rate of gene transcription. It is important to note that not all ERs are found in the nucleus. Some ERs are found on cell membranes. Activating these surface receptors produces a rapid response—more rapid than can be produced by activating nuclear receptors.

There are two forms of ERs, termed *ER alpha* and *ER beta*. *ER alpha* is highly expressed in the vagina, uterus, ovaries, mammary glands, vascular epithelium, and hypothalamus. *ER beta* is expressed in the ovary and prostate, and to a lesser extent in the lungs, brain, bones, and blood vessels. Some cells have both types of ER receptor.

Physiologic and Pharmacologic Effects

Effects on Primary and Secondary Sex Characteristics of Females

Estrogens support the development and maintenance of the female reproductive tract and secondary sex characteristics. These hormones are required for the growth and maturation of the uterus, vagina, fallopian tubes, and breasts. In addition, estrogens direct pigmentation of the nipples and genitalia.

Estrogens have a profound influence on physiologic processes related to reproduction. During the follicular phase of the menstrual cycle, estrogens promote (1) ductal growth in the breast, (2) thickening and cornification of the vaginal epithelium, (3) proliferation of the uterine epithelium, and (4) copious secretion of thickened mucus from endocervical glands. In addition, estrogens increase vaginal acidity (by promoting local deposition of glycogen, which is then acted upon by lactobacilli and corynebacteria to produce lactic acid). At the end of the menstrual cycle, a decline in estrogen levels can bring on menstruation. However, it is the fall in progesterone levels at the end of the cycle that normally causes breakdown of the endometrium and resultant menstrual bleeding. Following menstruation, estrogens promote endometrial restoration.

During pregnancy, the placenta produces estrogen in large amounts. This estrogen stimulates uterine blood flow and growth of uterine muscle. In addition, it acts on the breast to continue ductal proliferation. However, final transformation of the breast for milk production requires the combined influence of estrogen, progesterone, and human placental lactogen.

Metabolic Actions

Estrogens can affect various nonreproductive tissues. Important among these are bone, blood vessels, the heart, liver, and central nervous system (CNS).

Bone. Estrogens have a positive effect on bone mass. Under normal conditions, bone undergoes continuous remodeling, a process in which bone mineral is resorbed and deposited in equal amounts. The principal effect of estrogens on the process is to block bone resorption, although estrogens may also promote mineral deposition.

During puberty, the long bones grow rapidly under the combined influence of growth hormone, adrenal androgens, and low levels of ovarian estrogens. When estrogen levels grow high enough, they promote epiphyseal closure, and thereby bring linear growth to a stop.

After menopause, more bone is resorbed than is deposited, and hence bone mass declines. Why does this occur? Because the braking influence of estrogen on bone resorption is gone. Although estrogen therapy can help preserve bone mass, other drugs—raloxifene, bisphosphonates, calcitonin, and teriparatide—are safer, and hence are preferred (see Chapter 75).

Cholesterol. Estrogens have favorable effects on cholesterol levels: levels of low-density lipoprotein (LDL) chole-

sterol are reduced, while levels of high-density lipoprotein (HDL) cholesterol are elevated. These beneficial effects result from actions in the liver. There is speculation, but no proof, that effects on cholesterol metabolism may contribute the low incidence of myocardial infarction in premenopausal women.

Estrogens alter cholesterol excretion. Specifically, they increase the amount of cholesterol in bile and decrease the amount of bile acids in bile.

Blood Coagulation. Estrogens both promote and suppress blood coagulation. Estrogens promote coagulation by (1) increasing levels of coagulation factors (eg, factors II, VII, IX, X, and XII) and by (2) decreasing levels of factors that suppress coagulation (eg, antithrombin). Estrogens suppress coagulation by increasing the activity of factors that promote breakdown of fibrin, a protein that reinforces blood clots. The net effect—increased or decreased coagulation—may be determined by a hereditary defect in one of these targets.

Clinical Pharmacology

Adverse Effects

The principal concerns with estrogen therapy are the potential for endometrial hyperplasia, endometrial cancer, breast cancer, and cardiovascular events. Most other adverse effects are more of a nuisance than a concern.

Endometrial Hyperplasia and Carcinoma. Prolonged use of estrogens *alone* by postmenopausal women is associated with an increased risk of endometrial carcinoma. However, when estrogens are used in combination with a progestin, there is little or no risk of uterine cancer. Why? When used alone, estrogens act on the endometrium to cause proliferation and hyperplasia. In a few cases, hyperplasia progresses to carcinoma. Concurrent use of a progestin greatly reduces cancer risk by antagonizing estrogen-mediated endometrial proliferation and by reversing hyperplasia. Accordingly, whenever estrogen is given to postmenopausal women who have an intact uterus, a progestin should be given as well. During the first 3 to 6 months of treatment, about 30% of women experience benign, irregular bleeding. If bleeding persists, or if it starts after prolonged therapy, the possibility of endometrial carcinoma should be evaluated.

Breast Cancer. Does estrogen increase the risk of breast cancer? Yes—but primarily in *postmenopausal* women who are using estrogen *combined* with a progestin. In *younger* women, and in women using estrogen *without* a progestin, the risk, if any, is very low. Results of the Women's Health Initiative (WHI) indicate that treatment of postmenopausal women with estrogen plus a progestin produces a small increase in the risk of breast cancer—but treatment with estrogen alone carries little or no risk (see below under *Menopausal Hormone Therapy*). In contrast, the Women's Contraceptive and Reproductive Experience study has shown that, for most younger women, use of estrogen plus a progestin for contraception does *not* increase breast cancer risk (see Chapter 62). How can we explain these contradictory results? The best explanation is that risk is a function of age—being relatively high in older women and very low in younger women. In either population—old or young—the risk of breast cancer from estrogen *alone* has not been firmly established. Of note, after the results of the WHI were published, there was a dramatic decline in postmenopausal estrogen use, followed by a significant decline in the incidence of breast cancer. This observation

reinforces the conclusion that postmenopausal hormone therapy increases breast cancer risk.

How does estrogen increase breast cancer risk? Estrogen does not *cause* breast cancer—it only *promotes* the growth of a cancer that already exists, and then only if the cancer is estrogen receptor-positive. Accordingly, estrogen-dependent breast cancer must be ruled out before initiating estrogen treatment. Furthermore, because all women are at potential risk for breast cancer, and because estrogens may slightly increase that risk, women taking estrogens should have a yearly breast exam by a health professional. For women older than 40, an annual mammogram is recommended.

Ovarian Cancer. In postmenopausal women, therapy with estrogen alone or estrogen combined with a progestin may increase the risk of ovarian cancer. Details are presented below under *Menopausal Hormone Therapy*.

Cardiovascular Events. In *postmenopausal* women, estrogen, used either alone or combined with a progestin, increases the risk of venous thromboembolism (VTE) and stroke. In addition, estrogen *alone* increases the risk of coronary heart disease and myocardial infarction, but only in women over age 60. The risk of VTE is greatest during the first years of treatment, and is greater with oral dosing than with transdermal or intravaginal dosing. These effects are discussed further under *Menopausal Hormone Therapy*.

In *premenopausal* women, use of combination estrogen/progestin oral contraceptives increases the risk of VTE. Although the risk is dose dependent, even low-dose formulations cause an estimated 15 to 30 cases per 100,000 woman-years of use. The cardiovascular risk associated with oral contraceptives is discussed further in Chapter 62.

Nausea. Nausea is the most frequent undesired response to the estrogens. Fortunately, nausea diminishes with continued use, and is rarely so severe as to necessitate treatment cessation. Nausea can be minimized by administering estrogens with food, initiating therapy at low doses, and, when appropriate, using a topical estrogen formulation (eg, gel, spray, patch, vaginal ring).

Adverse Effects from Use During Pregnancy. Most estrogens are safe when used during pregnancy. However, there is one important exception: diethylstilbestrol (DES), a nonsteroidal estrogen. Between 1948 and 1971, DES was used extensively during pregnancy to prevent miscarriage. Sadly, DES use caused clear cell adenocarcinoma (CCA) of the vagina in many women who were exposed to DES during fetal life. What about other estrogens? Studies have shown that there is no risk of birth defects when pregnancy occurs inadvertently while a woman is taking an estrogen-based oral contraceptive. These data suggest that fetal harm associated with DES does not apply to other estrogens. DES is no longer available in the United States.

Other Adverse Effects. Estrogens have been associated with gallbladder disease, jaundice, headache, and *chloasma* (patchy brown facial pigmentation that may develop in pregnancy). Use during menopause may produce or uncover gallbladder disease. Jaundice may develop in women with pre-existing liver dysfunction, especially those who experienced cholestatic jaundice of pregnancy. Estrogens can increase the risk of headache, especially migraine.

Therapeutic Uses

Estrogens have contraceptive and noncontraceptive applications. In this chapter, discussion is limited to the noncontraceptive applications. Use of estrogens for contraception is discussed in Chapter 62.

Menopausal Hormone Therapy. Hormone therapy in postmenopausal women is the most common noncontraceptive use of estrogens. This use is discussed separately below.

Female Hypogonadism. In the absence of ovarian estrogens, pubertal transformation will not take place. Causes of estrogen deficiency include primary ovarian failure, hypopituitarism, bilateral oophorectomy (removal of both ovaries), and Turner's syndrome (a genetic disorder that impairs gonadal function). In girls with estrogen insufficiency, puberty can be induced by giving exogenous estrogens. This treatment promotes breast development, maturation of the reproductive organs, and development of pubic and axillary hair. To simulate normal patterns of estrogen secretion, the regimen should consist of continuous low-dose therapy (for about a year) followed by cyclic administration of estrogen in higher doses.

Acne. Estrogens, in the form of oral contraceptives, can help control acne. Treatment is limited to females at least 15 years old who want contraception. The use of estrogen for acne is discussed in Chapter 105.

Routes of Administration

Oral. Owing to convenience, the oral route is used more than any other. The most active estrogenic compound—estradiol—is available alone and in combination with progestins. Estrogen itself is available in conjugated and esterified forms.

Transdermal. Transdermal estradiol is available in four formulations:

- Emulsion [Estrasorb]
- Spray [Evamist]
- Gels [EstroGel, Elestrin, Divigel]
- Patches [Alora, Climara, Estraderm, Estradot, Menostar, Vivelle, Vivelle-Dot, Oesclim★]

The emulsion is applied once daily to the top of both thighs and the back of both calves. The spray is applied once daily to the forearm, never to the breasts or pubic area. The gel is applied once daily to one arm, from the shoulder to the wrist. The patches are applied to the skin of the trunk (but not the breasts), allowing estrogen to be absorbed through the skin and then directly into the bloodstream. Rates of estrogen absorption with transdermal formulations range from 14 to 60 mcg/24 hr, depending on the product employed.

Compared with oral formulations, the transdermal formulations have four advantages:

- The total dose of estrogen is greatly reduced (because the liver is bypassed).
- There is less nausea and vomiting.
- Blood levels of estrogen fluctuate less.
- There is a lower risk of deep vein thrombosis, pulmonary embolism, and stroke.

Intravaginal. Estrogens for intravaginal administration are available as tablets, creams, and vaginal rings. The tablets [Vagifem], creams [Estrace Vaginal, Premarin Vaginal, Ogen Vaginal], and one of the two available vaginal rings [Estring] are used only for local effects, primarily treatment of vulval and vaginal atrophy associated with menopause. The other vaginal ring [Femring] is used for systemic effects (eg, control of hot flashes and night sweats) as well as local effects (eg, treatment of vulval and vaginal atrophy).

Parenteral. Although estrogens are formulated for IV and IM administration, use of these routes is rare. Intravenous administration is generally limited to acute, emergency control of heavy uterine bleeding.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

SERMs are drugs that activate estrogen receptors in some tissues and block them in others. These drugs were developed in an effort to provide the benefits of estrogen (eg, protection against osteoporosis, maintenance of the urogenital tract, reduction of LDL cholesterol) while avoiding its drawbacks (eg, promotion of breast cancer, uterine cancer, and thromboembolism). Three SERMs are available: tamoxifen [Nolvadex], toremifene [Fareston], and raloxifene [Evista]. None of these

offers all of the benefits of estrogen, and none avoids all of the drawbacks.

Tamoxifen was the first SERM to be widely used. By blocking estrogen receptors, tamoxifen (and its active metabolite, endoxifen) can inhibit cell growth in the breast. As a result, the drug is used extensively to prevent and treat breast cancer. Unfortunately, blockade of estrogen receptors also produces hot flashes. By activating estrogen receptors, tamoxifen protects against osteoporosis and has a favorable effect on serum lipids. However, receptor activation also increases the risk of endometrial cancer and thromboembolism. The pharmacology of tamoxifen and toremifene (a close relative of tamoxifen) is discussed at length in Chapter 103.

Raloxifene is very similar to tamoxifen. The principal difference is that raloxifene does not activate estrogen receptors in the endometrium, and hence does not pose a risk of uterine cancer. Like tamoxifen, raloxifene protects against breast cancer and osteoporosis, promotes thromboembolism, and induces hot flashes. Raloxifene is approved only for prevention and treatment of osteoporosis, and for prevention of breast cancer in high-risk women. Raloxifene is discussed at length in Chapter 75.

PROGESTINS

Progestins are compounds that have actions like those of progesterone, the principal endogenous progestational hormone. As their name implies, the progestins act prior to gestation to prepare the uterus for implantation of a fertilized ovum. In addition, progestins help maintain the uterus throughout pregnancy.

Biosynthesis

Progesterone is produced by the ovaries and the placenta. Ovarian production occurs during the second half of the menstrual cycle. During this period, progesterone is synthesized by the corpus luteum, in response to LH released from the anterior pituitary. If implantation of a fertilized ovum does not occur, progesterone production by the corpus luteum ceases, and menstrual flow begins. However, if implantation does take place, the developing trophoblast will produce its own luteotropic hormone—human chorionic gonadotropin (hCG)—that will stimulate the corpus luteum to continue making progesterone. For the first 7 weeks of gestation, the placenta depends entirely on progesterone from the corpus luteum. However, between weeks 7 and 10, production of progesterone is shared between the corpus luteum and placenta. After 10 weeks of gestation, progesterone made by the placenta is sufficient to support pregnancy, and hence ovarian progesterone production declines. Placental synthesis of progesterone and estrogen continues throughout the pregnancy.

Mechanism of Action

As with estrogen, receptors for progesterone are found in the cell nucleus. Hence, to produce an effect, progesterone must diffuse across the cell membrane, migrate to the nucleus, and then bind with a progesterone receptor (PR). The progesterone-PR complex then binds with a progesterone regulatory element on a target gene, thereby rapidly increasing gene transcription. As with estrogen, there are two types of receptors for progesterone, designated PR-A and PR-B. In general, the stimulatory actions of progesterone are mediated by PR-B, whereas inhibitory actions are mediated by PR-A.

Physiologic and Pharmacologic Effects

Effects During the Menstrual Cycle. Progesterone secreted during the second half of the menstrual cycle converts the endometrium from a proliferative state into a secretory state. If implantation does not occur, progesterone production by the corpus luteum declines. The resultant fall in progesterone levels is the principal stimulus for the onset of menstruation.

In addition to affecting the endometrium, progesterone affects the endocervical glands, breasts, body temperature, respiration, and mood. Under the influence of progesterone, secretions from endocervical glands become scant and viscous. (In contrast, estrogen makes these secretions profuse and watery.) In addition, progesterone causes the epithelium of the breast to divide and grow. Actions in the CNS may cause depression and sleepiness. By increasing the sensitivity of the respiratory center to CO_2 , progesterone causes the partial pressure of carbon dioxide (pCO_2) in blood to fall. At midcycle, when ovulation occurs, progesterone raises body temperature by 0.6°C (1°F).

Effects During Pregnancy. As noted, progesterone levels increase during pregnancy. These high levels suppress contraction of uterine smooth muscle, and thereby help sustain pregnancy. Unfortunately, progesterone also suppresses contraction of GI smooth muscle, which leads to prolonged transit time and constipation. In the breast, progesterone promotes growth and proliferation of alveolar tubules (acini), the structures that produce milk. Metabolic effects include suppression of arterial pCO_2 , altered serum bicarbonate content, and elevation of serum pH. Lastly, progesterone may help suppress the maternal immune system, thereby preventing immune attack on the fetus.

Other Effects. Pharmacologic doses of progesterone can suppress release of pituitary gonadotropins (LH and FSH). This prevents follicular maturation and ovulation. Also, individual progestin preparations display varying degrees of estrogenic, androgenic, and anabolic activity.

Clinical Pharmacology

Adverse Effects

Teratogenic Effects. High-dose therapy during the first 4 months of pregnancy has been associated with an increased incidence of birth defects (limb reductions, heart defects, masculinization of the female fetus). Accordingly, use of progestins during early pregnancy is not recommended.

Gynecologic Effects. When used continuously for birth control, progestins greatly decrease production of cervical mucus and cause involution of the endometrial layer. Effects on the endometrium lead to spotting, breakthrough bleeding, and irregular menses.

Breast Cancer. Progestins, in combination with estrogen, increase the risk of breast cancer in postmenopausal women (see below under *Menopausal Hormone Therapy*).

Other Adverse Effects. Common side effects are breast tenderness, bloating, and depression.

Therapeutic Uses

Discussion in this chapter is limited to the noncontraceptive uses of progestins. Use for contraception is considered in Chapter 62.

Menopausal Hormone Therapy. The primary noncontraceptive use of progestins is to counteract the adverse effects of estrogen on the endometrium in women undergoing HT. This application is discussed below.

Dysfunctional Uterine Bleeding. This condition, characterized by heavy irregular bleeding, occurs when progesterone levels are insufficient to balance the stimulatory influence of estrogen on the endometrium. In the

BOX 61-1 ■ SPECIAL INTEREST TOPIC

PREMENSTRUAL SYNDROME (PMS)

PMS consists of a constellation of psychologic and physical symptoms that consistently and predictably develop during the luteal phase of the menstrual cycle, and then resolve around the onset of menses. Common psychologic symptoms include irritability, depression, mood lability, crying spells, and social withdrawal. Common physical symptoms include breast tenderness, abdominal bloating, and increased appetite, especially for carbohydrates. Additional symptoms are listed in the table below. The psychologic symptoms are much more disabling than the physical symptoms. PMS is among the most common disorders in women of reproductive age.

Common Symptoms of PMS

Somatic Symptoms	Emotional Symptoms	Cognitive Symptoms
<ul style="list-style-type: none"> • Breast tenderness • Abdominal bloating • Ankle edema • Weight gain • Headache • Backache • Constipation or diarrhea 	<ul style="list-style-type: none"> • Irritability • Depression • Mood swings • Hypersensitivity to trivial events • Loneliness and social withdrawal 	<ul style="list-style-type: none"> • Impaired memory • Confusion • Difficulty concentrating

Etiology

Although PMS is clearly of neuroendocrine origin, the exact cause has not been established. At one time, abnormal hormone levels were suspected. However, we now know that hormone levels in women who experience PMS are identical to those in women who do not. Hence abnormal levels can't be the cause. Nonetheless, because symptoms are synchronized with the menstrual cycle, it would seem that hormones are in some way involved—even if levels are normal. One reasonable hypothesis is that women who experience PMS are sensitive to hormonal changes in a way that other women are not. Because of this altered sensitivity, normal hormonal changes are able to trigger PMS. Current evidence points to altered responsiveness in the brain. In particular, the ability of selective serotonin reuptake inhibitors (SSRIs) to relieve psychologic symptoms—as well as some physical symptoms—suggests an abnormality in circuits that use serotonin as their transmitter.

Diagnosis

To make a diagnosis of PMS, symptoms must be *intense* and *intermittent*. That is, symptoms should be prominent in the luteal phase of the menstrual cycle, and minimal or absent in the follicular phase. Practically all women experience some PMS-like symptoms in the late luteal phase. However, in the majority of women, symptoms are relatively mild, and hence do not constitute PMS. Only 20% to 30% of women have symptoms that are strong enough to be considered PMS. An even smaller number—3% to 5%—have symptoms that constitute *premenstrual dysphoric disorder* (PMDD), an especially severe form of PMS described in the American Psychi-

atric Association's *Diagnostic and Statistical Manual of Mental Disorders*.

Timing of symptoms is critical. On days 4 through 12 of the menstrual cycle, symptoms should be absent—or at least no greater than would be expected in the population at large. Symptoms should begin following ovulation (around day 14 of the cycle), become most intense in the fourth week of the cycle (late luteal phase), and then stop before or shortly after onset of menstruation. To make a diagnosis, total symptom severity in the fourth week must be at least twice the intensity of any symptoms present in the second week. Daily charting of symptoms for at least three menstrual cycles is needed to establish whether symptoms occur in the appropriate pattern and are of sufficient intensity to permit a diagnosis of PMS or PMDD.

When diagnosing PMS, it is essential to rule out conditions whose symptoms can intensify in the late luteal phase or menstrual phase, a phenomenon known as “menstrual magnification.” Common conditions subject to menstrual magnification include depression, migraine headaches, chronic fatigue syndrome, and irritable bowel syndrome. The differential diagnosis is relatively easy to make, in that, unlike PMS, these disorders are symptomatic *throughout* the cycle—they simply can become more intense as menstruation approaches.

Treatment Guidelines

In 2000, the American College of Obstetricians and Gynecologists (ACOG) issued guidelines for the diagnosis and treatment of PMS (“Clinical Management Guidelines for Premenstrual Syndrome,” *ACOG Practice Bulletin* No. 15). For women with a positive diagnosis of PMS, the guidelines recommend stepwise intervention, beginning with lifestyle changes and then progressing to drug therapy if needed.

For women with mild symptoms, lifestyle changes may provide relief. Regular aerobic exercise can reduce depressive symptoms and has numerous other health benefits. Eating foods rich in complex carbohydrates can enhance mood and reduce food cravings. Getting enough sleep can also help. In addition, small clinical trials have shown that dietary supplements (200 to 400 mg of magnesium/day and 1200 mg of calcium/day) can improve symptom scores.

If lifestyle changes fail to suppress symptoms, drug therapy may be needed. Two types of drugs are recommended: SSRIs and ovulation suppressants. SSRIs are the initial drugs of choice, especially for women with severe PMS. According to the guidelines, ovulation suppressants should be used only if SSRIs are inadequate.

Agents that are *ineffective* should be avoided. Among these are progesterone and various supplements, including black cohosh, red clover, dong quai, and evening primrose oil. Progesterone has been used for years on the theory that it may produce a favorable hormonal balance. However, we now know that progesterone is no more effective than placebo, and in fact may exacerbate some symptoms (bloating, breast tenderness, and emotional lability).

Continued

Selective Serotonin Reuptake Inhibitors

SSRIs such as fluoxetine [Prozac, Sarafem] and sertraline [Zoloft] are the most effective treatment for the psychologic symptoms of PMS or PMDD, and hence are considered first-line therapy. These drugs, which were developed as antidepressants (see Chapter 32), can significantly reduce depression, anger, irritability, tension, dysphoria, fatigue, and confusion. Success rates range from 50% to 75%. Moreover, benefits develop quickly—within 2 to 3 days, compared with 2 to 4 weeks when SSRIs are used for depression. Why were SSRIs ever tried for PMS? Because the psychologic symptoms of PMS are much like those of depression. Interestingly, although SSRIs are most effective at reducing affective symptoms of PMS, they can also reduce physical symptoms, such as breast tenderness, bloating, and headaches.

In clinical trials, about 15% of women discontinued treatment because of side effects. The most prominent are sexual dysfunction (anorgasmia and decreased libido), sleep disturbances (insomnia or hypersomnia), and GI distress (nausea and diarrhea). If side effects are intolerable, dosage can be reduced.

Most research on using SSRIs for PMS has been conducted with either fluoxetine or sertraline. However, other SSRIs—paroxetine [Paxil], fluvoxamine [Luvox], citalopram [Celexa], and escitalopram [Lexapro]—are probably effective too. Hence, if a patient fails to respond to fluoxetine or sertraline, a trial with a different SSRI may be merited. It should be noted that, although the SSRIs are highly effective in PMS, none of these drugs is approved for PMS. However, three SSRIs—fluoxetine, sertraline, and paroxetine—are approved for PMDD.

With fluoxetine, sertraline, and paroxetine, dosing may be done either (1) every day throughout the menstrual cycle or (2) just during the luteal phase, the time when symptoms are present. With the second option, dosing is begun on day 14 of the cycle and stopped on day 2 of the following cycle (ie, the day after menstruation begins). The intermittent schedule has two obvious advantages: it's cheaper than continuous dosing and side effects are minimized. Hence, unless a woman has depression in addition to PMS, intermittent dosing may be preferred. Specific dosages for three SSRIs are as follows:

- **Fluoxetine**—The usual dosage is 20 mg/day, given continuously or just during the luteal phase.
- **Sertraline**—The usual dosage is 50 to 150 mg/day, given continuously or just during the luteal phase.
- **Paroxetine**—The usual dosage is 12.5 to 25 mg/day, given continuously or just during the luteal phase.

Ovulation Suppressants

Two classes of drugs—gonadotropin-releasing hormone (GnRH) agonists and oral contraceptives (OCs)—can suppress ovulation, and may thereby suppress both menstrual cycling and associated symptoms of PMS. Of note, these drugs reduce physical symptoms better than psychologic symptoms. Ovula-

tion suppressants are considered second-line drugs for PMS, and hence should be used only if first-line agents are ineffective or intolerable.

GnRH agonists (eg, leuprolide) can reduce physical and psychologic symptoms of PMS. Treatment can relieve breast tenderness, bloating, depression, nervous tension, anxiety, and loss of control. These agents act by suppressing release of LH and FSH from the pituitary, and thereby cause levels of estrogen and progesterone to fall to postmenopausal concentrations. Unfortunately, although GnRH agonists are effective, these drugs are expensive. In addition, with prolonged treatment (more than 6 months), there is a risk of osteoporosis (owing to loss of estrogen). The risk of osteoporosis can be overcome by giving supplemental estrogen and progestin. Nonetheless, because of the expense and need for supplemental estrogen and progestin, use of GnRH agonists is limited.

Oral contraceptives can reduce physical symptoms of PMS (eg, bloating, breast tenderness), but are generally less effective at reducing emotional symptoms. However, in 2005, investigators reported that Yasmin—an OC composed of 30 mcg ethinyl estradiol plus 3 mg drospirenone—could reduce emotional symptoms as effectively as SSRIs. Two years later, a similar combination OC (20 mcg ethinyl estradiol plus 3 mg drospirenone), sold as YAZ, became the only OC actually approved for PMDD.

Other Remedies

Calcium supplements (1000 to 1200 mg/day) have been shown to reduce symptoms of mild to moderate PMS. In one study, 2 to 3 months of daily calcium therapy decreased depression and mood swings by 45% (vs. 28% with placebo), generalized aches and pains by 54% (vs. a 15% increase with placebo), food cravings by 54% (vs. 35% with placebo), and water retention by 36% (vs. 24% with placebo). Calcium did not reduce fatigue or insomnia. These data are the first clear indication that a dietary supplement can significantly reduce symptoms of PMS. Moreover, the required dosage is low—about equal to the recommended dietary intake for preventing osteoporosis (1300 mg/day for teenagers and 1000 mg/day for women ages 19 to 40). Hence, women now have two good reasons for ensuring adequate calcium intake: alleviation of PMS and protection against osteoporosis.

Spiro lactone, a diuretic and aldosterone antagonist, can counteract water retention and can thereby relieve bloating and water weight gain. In addition, several well-controlled trials have shown the drug can relieve affective symptoms as well. For women with PMS, the usual dose is 100 mg/day during the luteal phase of the menstrual cycle. Of note, spiro lactone is similar to drospirenone, the progestin in YAZ, an OC discussed above.

Analgesics, such as ibuprofen and naproxen, have no effect on mood, but can reduce headache, dysmenorrhea, cramps, and muscle and joint pain.

absence of sufficient progesterone, estrogen puts the endometrium in a state of continuous proliferation. Since progesterone is unavailable to induce monthly endometrial breakdown, the excessively proliferative endometrium undergoes spontaneous sloughing at irregular intervals. The result is periodic episodes of severe menstrual bleeding. Dysfunctional uterine bleeding is typically associated with anovulatory cycles. The disorder occurs most com-

monly in adolescents and women approaching menopause. Obese women and those with polycystic ovary syndrome are also susceptible.

Treatment has two objectives: the initial goal is cessation of hemorrhage, the long-term goal is to establish a regular monthly cycle. Excessive bleeding can be stopped by administering a progestin for 10 to 14 days. When dosing is stopped, withdrawal bleeding takes place. Bleeding is likely to be profuse

and associated with cramping. Giving an oral contraceptive twice daily for 5 to 7 days can help stabilize the endometrium and thereby reduce bleeding duration.

Cyclic therapy is employed to establish a regular monthly cycle. In one regimen, oral dosing is started 10 to 14 days after the onset of each menstrual period and continued for the next 10 days. Alternatively, a progestin can be given for the first 10 days of each month. Both approaches can promote regular endometrial breakdown and menstruation.

Amenorrhea. Progestins can induce menstrual flow in selected women who are experiencing amenorrhea. If endogenous estrogen levels are adequate, treatment with a progestin for 5 to 10 days will be followed by withdrawal bleeding when the progestin is stopped. If estrogen levels are low, it may be necessary to induce endometrial proliferation with an estrogen prior to giving the progestin.

Infertility. Progestins are used to support an early pregnancy in women with corpus luteum deficiency syndrome and in women undergoing *in vitro* fertilization (IVF).

Prematurity Prevention. One progestin—*hydroxyprogesterone acetate* [Makena]—is approved for preventing preterm birth in women with a singleton pregnancy and a history of preterm delivery. This use is discussed in Chapter 64.

Endometrial Carcinoma and Hyperplasia. Progestins can provide palliation in women with metastatic endometrial carcinoma, but these drugs do not prolong life. Several months of treatment may be required for a response. The progestins employed are *medroxyprogesterone acetate* (MPA) and *megestrol acetate*. MPA is given once weekly by IM injection; megestrol acetate is administered daily by mouth.

Endometrial hyperplasia, a potentially precancerous condition, can be suppressed with progestins. Benefits derive from counteracting the proliferative effects of estrogen. Treatment options include oral therapy with megestrol acetate [Megace] or medroxyprogesterone acetate [Provera], and local delivery of a levonorgestrel using the Mirena IUD.

Preparations and Routes

Progestins are available in oral, IM, subQ, intravaginal, intrauterine, and transdermal formulations. Older oral progestins include *medroxyprogesterone acetate* [Provera], *norethindrone* [Micronor, Nor-QD, others], *norethindrone acetate* [Aygestin], *megestrol acetate* [Megace], *levonorgestrel* [Plan B, Next Choice], and a micronized formulation of *progesterone* [Prometrium]. Newer oral progestins—*norgestimate* and *drospirenone*—are available in fixed-dose combinations with estradiol sold as Prefest and Angeliq, respectively. Intramuscular progestins are *medroxyprogesterone acetate* [Depo-Provera] and *progesterone* (in oil). *Medroxyprogesterone acetate* is also available in a formulation for subQ injection [Depo-subQ Provera 104]. *Micronized progesterone* for intravaginal use is available as progesterone gel [Crinone] and a vaginal insert [Endometrin]. Transdermal products are limited to *norethindrone* (formulated with estradiol under the name *CombiPatch*) and *levonorgestrel* (formulated with estradiol under the name *ClimaraPro*). A second-generation progestin—*etonogestrel*—used for contraception is available by itself as a subQ implant [Nexplanon] and combined with estradiol in a vaginal ring [NuvaRing].

MENOPAUSAL HORMONE THERAPY

Menopausal hormone therapy (HT), formerly known as *hormone replacement therapy* (HRT), consists of low doses of estrogen (with or without a progestin) taken to compensate for the loss of estrogen that occurs during menopause. Why is estrogen lost? Because ovarian follicles, which are the primary source of estrogen, decline as women grow older. Menopause typically begins around age 50, but can begin as early as 48 and as late as 55. During the initial phase, the menstrual cycle becomes irregular, anovulatory cycles may occur, and periods of amenorrhea may alternate with menses. Eventually, ovulation and menstruation cease entirely. Production of ovarian estrogens decreases gradually, coming to a complete stop several years after menstruation has ceased.

Loss of estrogen has multiple effects. Prominent among these are vasomotor symptoms (manifesting as hot flashes, also known as hot flashes and night sweats), sleep distur-

bances, urogenital atrophy (manifesting as vaginal dryness, itching, and burning), bone loss (manifesting as osteoporosis and increased fracture risk), and altered lipid metabolism (manifesting as increased levels of LDL cholesterol and reduced levels of HDL cholesterol). Hormone therapy can prevent or attenuate these consequences.

There are two basic regimens for HT: (1) estrogen alone and (2) estrogen plus a progestin. The purpose of estrogen in both regimens is to control menopausal symptoms by replacing estrogen that was lost owing to menopause. The progestin is present for one reason only: to counterbalance estrogen-mediated stimulation of the endometrium, which can lead to endometrial hyperplasia and cancer. Accordingly, in women who have undergone hysterectomy (ie, who no longer have a uterus), the progestin is unnecessary, and hence is omitted. It should be noted that, although progestins can protect against estrogen-induced cancer of the *uterus*, progestins appear to *increase* the risk of estrogen-induced cancer of the *breast*. In addition, progestins appear to increase the risk of adverse cardiac events.

Use of HT has declined by 80% over the last decade. Why? Because evidence from two major studies demonstrated that the benefits of HT are more limited than previously believed, and the risks are greater than previously appreciated. Accordingly, authorities now agree that, for most women, the benefits of *long-term* HT to *prevent chronic disorders* do not justify the risks. However, use of *short-term* HT to *manage menopausal symptoms* is still deemed appropriate, provided women use the smallest effective dosage for the shortest time needed.

A note on nomenclature: In the discussion below, HT that consists of *estrogen plus a progestin* is abbreviated EPT (for estrogen/progestin therapy), and HT that consists of *estrogen alone* is abbreviated ET (for estrogen therapy). These distinctions are needed because, as we shall see, the benefits and risks of EPT and ET are not identical.

Landmark Studies: WHI and HERS

The results of two trials—the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study and its follow-up (HERS and HERS II)—caused major changes in recommendations regarding menopausal HT. Both trials were large, prospective, randomized, double-blind, placebo-controlled studies of the effects of HT in menopausal women. Although these trials have limitations—for example, the results may not apply to perimenopausal women—they are nonetheless the most informative studies on HT to date.

The WHI was designed to assess the benefits of HT as *primary prevention* against heart disease and other disorders in *healthy* postmenopausal women. More than 27,000 women were enrolled. The study had two arms. In one arm, women with an intact uterus were given either a daily placebo or daily EPT. The specific preparation used was Prempro, a combination of conjugated estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg). In the other arm of the trial, women who had undergone a hysterectomy received either a daily placebo or daily ET. The preparation used was Premarin, containing 0.625 mg of conjugated estrogens.

The WHI was originally scheduled to end in 2005, but both arms were terminated early. The EPT arm was stopped in July 2002, when the data showed that the risks of treatment—cardiovascular events and invasive breast cancer—exceeded

any benefits. The ET arm was stopped in February 2004, when the data showed that ET conferred no protection against coronary heart disease but did increase the risk of stroke. Table 61-1 summarizes the impact of EPT and ET on the incidence of major clinical events, both beneficial and adverse. Of note, neither regimen increased the incidence of death.

In contrast to the WHI, which was a *primary prevention* trial, HERS was designed to assess the benefits of HT as *secondary prevention* in women with *established* coronary heart disease (CHD). The study enrolled 2763 postmenopausal women with an intact uterus. Participants received either placebo or daily Prempro (the same EPT regimen used in the WHI). The outcome? EPT failed to protect against myocardial infarction (MI). Worse yet, during the first few years of treatment, the risk of MI actually increased.

Benefits and Risks of Hormone Therapy

Our understanding of the benefits and risks of HT continues to evolve. The principal benefits of postmenopausal EPT and ET are suppression of menopausal symptoms and prevention of osteoporosis. Known risks of EPT include CHD, stroke, thromboembolic events, breast cancer, and dementia. ET appears safer than EPT, but still can cause stroke, deep vein thrombosis (DVT), and other undesired effects. The benefits and risks of postmenopausal EPT and ET are summarized in Table 61-2.

Benefits of Hormone Therapy

Treatment with estrogen plus progestin confers four primary benefits: suppression of vasomotor symptoms, prevention of urogenital atrophy, prevention of osteoporosis and related fractures, and prevention of colorectal cancer. Treatment with estrogen alone confers the first three benefits, but not the fourth. To prevent urogenital atrophy, osteoporosis, and colorectal cancer, HT must continue lifelong. Despite long-held hopes, there is no proof that HT improves cardiovascular health.

Relief of Vasomotor Symptoms. Vasomotor symptoms (hot flashes) develop in about 70% of postmenopausal women. Episodes are characterized by sudden skin flushing, sweating, and a sensation of uncomfortable warmth. These episodes can occur at night, resulting in drenching sweats. Severe episodes can cause sleep disturbances, fatigue, and irritability. In most women, hot flashes abate within a few months to a few years; in others, they may persist for a decade or more. Hormone therapy is the most effective way to suppress symptoms.

Management of Urogenital Atrophy. In the absence of estrogen, urogenital degeneration is inevitable. Of all structures in the body, the urethra and vagina have the highest concentrations of estrogen receptors. Activation of these receptors maintains the functional integrity of the urethra and vaginal epithelium. Hence, when estrogen levels decline during menopause, these structures undergo degenerative change. Atrophy of the urethra causes urge incontinence and urinary frequency. Urethritis and urinary tract infections can also occur. Atrophy of the vaginal epithelium can lead to dryness and pain with intercourse. In addition, vaginal changes can encourage the growth of pathogenic bacteria, resulting in vaginal infections. Hormone therapy, either oral or topical, can reduce some of these undesirable outcomes.

Prevention of Osteoporosis and Related Fractures. Osteoporosis is characterized by bone demineralization, al-

TABLE 61-1 ■ Results of the Women's Health Initiative: Impact of Hormone Therapy on the Incidence of Major Adverse Clinical Events

Benefits/Harms	Events Prevented or Caused ^a	
	Estrogen Plus Progestin ^b	Estrogen Alone ^b
Adverse Events Prevented		
Hip fractures	5	6
Colorectal cancer	No effect? ^c	No effect
Adverse Events Caused		
Myocardial infarction (MI)	7	No/Yes ^d
Stroke	8	12
Pulmonary embolism	8	No effect
Deep vein thrombosis	10	6
Breast cancer	8	No effect? ^e
Dementia	23	No effect? ^f
Death	No effect	No effect

^aThe data represent the number of events prevented or caused each year for every 10,000 women using hormone therapy, compared with women taking placebo.

^bEstrogen plus progestin therapy is used for women who have a uterus; estrogen alone is used for women who have undergone a hysterectomy.

^cInitial results from the WHI indicated a reduction in colorectal cancer with estrogen alone, but not with estrogen plus progestin. However, a subsequent analysis of the data found no strong evidence for protection with either regimen.

^dIn women ages 50 to 59, estrogen alone appears to *protect* against MI, but in women over the age of 60, estrogen alone *increases* the risk of MI.

^eEstrogen alone did not increase the incidence of breast cancer, and may have caused a slight decrease. However, the decrease was not statistically significant, and was probably due to chance.

^fEstrogen alone increases the *combined* risk of mild cognitive impairment and dementia, but the increase in dementia by itself is not statistically significant.

tered bone architecture, and reduced bone strength. Compression fractures of the vertebrae are common, and can decrease height and produce a "dowager's hump." In osteoporotic women, fractures of the hip and wrist can result from minimal trauma. Osteoporosis occurs in a majority (about 70%) of elderly white females; the incidence in males and black females is much lower. The condition develops following surgical removal of the ovaries as well as after natural menopause. Estrogen deficiency is the principal cause: In the absence of estrogen, bone resorption accelerates, leading to a 12% loss of bone density shortly after menopause.

In menopausal women, HT can reduce bone resorption and slow the development of osteoporosis. More importantly, HT can decrease the risk of osteoporotic fractures, an effect demonstrated for the first time in the WHI. It should be noted that, although HT can indeed reduce fracture risk, the *absolute* reduction is relatively small: for every 10,000 women using HT, there would be only 5 or 6 fewer hip fractures per year. Like the WHI, HERS showed a reduction in fracture risk. However, in the HERS study the reduction was not statistically significant. It must be stressed that HT is primarily prophylactic:

TABLE 61-2 ■ Benefits and Risks of Menopausal Hormone Therapy

Benefits and Risks	Estrogen Plus Progestin	Estrogen Alone
Benefits		
Suppression of vasomotor symptoms	Yes	Yes
Preservation of urogenital integrity	Yes	Yes
Preservation of bone mineral density and prevention of osteoporotic fractures	Yes	Yes
Decreased risk of colorectal cancer	No? ^a	No
Risks		
Coronary heart disease (CHD)	Yes	Yes ^b
Myocardial infarction (MI)	Yes	Yes ^b
Stroke	Yes	Yes
Deep vein thrombosis	Yes	Yes
Pulmonary embolism	Yes	No
Breast cancer	Yes	No? ^c
Ovarian cancer	Yes? ^d	Yes
Uterine cancer	No	Yes ^e
Lung cancer	Yes	No
Gallbladder disease	Yes	Yes
Urinary incontinence	Yes	Yes
Dementia	Yes	No? ^f

^aInitial results from the Women's Health Initiative (WHI) indicated a reduction in colorectal cancer with estrogen alone, but not with estrogen plus progestin. However, a subsequent analysis of the WHI data found no strong evidence for protection with either regimen.

^bHormone therapy with estrogen alone increases the risk of CHD and MI in women over the age of 60. By contrast, in women ages 50 to 59, ET appears to protect against CHD and MI.

^cIn the Million Women Study (MWS), treatment with estrogen alone was associated with an *increased* risk of breast cancer, but only when HT was started shortly after menopause. By contrast, in the WHI, there were fewer cases of breast cancer among women using estrogen alone, compared with women taking placebo.

^dIn a large Danish study reported in 2009, estrogen plus progestin therapy increased the risk of ovarian cancer. However, an earlier study sponsored by the National Cancer Institute found no increased risk.

^eUterine cancer is a risk only for a woman with a uterus (obviously), and only if she uses estrogen in the absence of progestin, which should not be done.

^fIn the Women's Health Initiative Memory Study (WHIMS), estrogen alone increased the *combined* risk of mild cognitive impairment and dementia, but the increase in dementia by itself was not statistically significant.

Estrogen does little to reverse bone loss that has already occurred. Furthermore, beneficial effects on bone are not permanent: Following cessation of HT, 12% of bone mass is quickly lost.

The physiology of bone, as well as the management of osteoporosis, are discussed at length in Chapter 75.

Cardioprotection. As noted below, HT with estrogen alone appears to protect against CHD and MI—but only in *younger* women using *estrogen alone*. In older women using ET, and in all women using EPT, hormone use increases cardiac risk.

Improved Quality of Life? There is a widely held belief that HT can improve mood and make women feel more youthful and vibrant. However, data from HERS and the WHI indicate that quality-of-life (QOL) benefits are minimal. In the WHI, estrogen therapy failed to improve general health, physical function, vitality, mood, cognition, sexual satisfaction, or any other health-related QOL parameter. In HERS, QOL benefits were seen only in women with significant vasomotor symptoms. For these women, HT was associated with improved mental health, including a reduction in depressive symptoms—with no significant change in energy level or physical function.

Prevention of Colorectal Cancer? Does HT protect against colorectal cancer? Probably not. But the data are conflicting. A meta-analysis of the results of 18 observational studies indicated that, compared with women who have never used HT, current users have a 34% decreased risk of colon cancer. Furthermore, initial results from the WHI indicated a reduction in colorectal cancer with estrogen alone, but not with estrogen plus progestin. However, a subsequent analysis of the WHI data found no strong evidence for protection with either regimen.

Other Benefits. Postmenopausal HT appears to have a positive effect on wound healing, tooth retention, and glycemic control. After menopause, a woman's skin becomes thinner and wounds heal more slowly. However, among women taking HT, the rate of wound healing is close to that of premenopausal women. There is a direct correlation between duration of HT and prevention of tooth loss: for every 4.2 years of HT use, one additional tooth is retained. Hormone therapy greatly decreases the risk of developing type 2 diabetes and, among women who already have type 2 diabetes, HT can improve glycemic control.

Adverse Effects of Hormone Therapy

Cardiovascular Events. The results of HERS and the WHI dramatically changed our understanding of the cardiovascular effects of HT. In the past, we believed that HT conferred significant cardiovascular protection. Why? First, estrogen has beneficial effects: It reduces levels of LDL cholesterol, raises levels of HDL cholesterol, decreases oxidation of LDL, and improves vascular endothelial function. Second, in observational studies, HT was associated with a decreased incidence of CHD. Unfortunately, HERS and the WHI failed to demonstrate any cardiovascular benefit for HT—but did reveal significant cardiovascular risk.

Early results of HERS, published in 1998, raised serious doubts about the cardioprotective effects of HT. During the first year, women taking HT experienced 50% *more* coronary events than those taking placebo. However, over the next 3 years, women taking HT experienced 40% *fewer* coronary events. As in other studies, HT lowered LDL cholesterol (by 11%) and raised HDL cholesterol (by 10%). The increase in coronary events during the first year of HT was both unexpected and disturbing. After all, HT was supposed to protect against heart disease. The authors speculated that the initial increase in events was due to thrombogenic effects of HT, whereas the subsequent decrease was due to antiatherogenic effects. If their theory was correct, then longer use of HT should have revealed a net benefit. Unfortunately, in HERS II, a 2.7-year follow-up to the original HERS trial, the hoped-for net benefit did not materialize: The incidence of coronary events in women using HT for the longer time was no lower than in those taking placebo. In support of this observation, the Estrogen Replacement and Atherosclerosis Trial showed

that neither ET nor EPT reduces the progression of atherosclerosis, as measured by angiography. Similarly, the Women's Estrogen for Stroke Trial demonstrated that, among women with a prior ischemic stroke, ET does not reduce the incidence of stroke recurrence.

Data from the WHI indicate that, rather than protecting against cardiovascular events, both ET and EPT increase risk—although ET is somewhat safer than EPT. After 5.2 years of follow-up, women using EPT experienced a higher incidence of MI, stroke, pulmonary embolism, and DVT compared with women taking placebo. Fortunately, the *absolute* increase was relatively small: For every 10,000 women using EPT, there would be 7 more heart attacks each year, 8 more strokes, 8 more pulmonary emboli, and 10 more cases of DVT.

The cardiovascular risks and benefits of ET depend on the age of the user, as revealed in a 2011 analysis of data from the Women's Health Initiative Estrogen-Alone Trial. For all postmenopausal women, regardless of age, ET increases the risk of DVT and stroke. In addition, for women over the age of 60, ET increases the risk of MI and CHD. By contrast, for women ages 50 to 59, ET appears to *protect* against MI and CHD.

Endometrial Cancer. Estrogens increase the risk of endometrial hyperplasia and endometrial cancer, *but only when used alone*. When estrogens are combined with a progestin, the risk of endometrial cancer is reduced to the background level. Accordingly, in women with an intact uterus, it is standard practice to use EPT, rather than ET.

Breast Cancer. We have strong data showing that HT using EPT increases both the incidence of breast cancer and breast cancer mortality. Whether HT with estrogen alone poses a risk is less clear.

Two large studies—the Million Women Study (MWS), conducted in the United Kingdom, and the WHI, conducted in the United States—have shown that EPT increases the risk of breast cancer. In the WHI, the risk of invasive breast cancer was 26% higher for women who used EPT for 5 or more years compared with women who took a placebo. In absolute terms, this means that, for every 10,000 women using EPT, there would be 8 more cases of breast cancer per year. Furthermore, as shown in both the WHI and MWS, the risk of breast cancer is greater when EPT is started *early* (shortly after menopause) rather than 5 or more years later. How long is the risk of breast cancer elevated? Among women in the MWS, risk declined to that of never users within a few years after EPT was stopped. Of note, following the publication of WHI results in 2002, use of EPT dropped dramatically, as did the incidence of breast cancer.

Does HT with estrogen alone increase risk? Maybe. Maybe not. Trial results have been mixed. In the MWS, risk of breast cancer *was* increased by ET, but only when ET was started soon after menopause. Risk was not increased when ET was started 5 or more years after menopause onset. These data contrast with the results of the WHI, which found *no* increase in risk, regardless of whether ET was started early or late. In fact, among *younger* women (ages 50 to 59), ET was associated with a *decrease* in breast cancer risk. The seeming failure of estrogen to promote breast cancer in the WHI is a surprise. Why? Because (1) data from the MWS and other observational studies suggest that estrogen *supports* growth of breast cancer and (2) antiestrogens have been shown to *reduce* breast cancer risk in healthy women. The bottom line? Menopausal therapy with estrogen alone *might* increase breast cancer risk.

If so, the risk for most women appears to be small, especially with short-term use.

Ovarian Cancer. Menopausal HT appears to pose a small risk of ovarian cancer. However, data on this risk are conflicting. For example, in a large study sponsored by the National Cancer Institute, researchers concluded that HT does indeed increase the risk of ovarian cancer, but only when estrogen is used alone—not when estrogen is combined with a progestin. By contrast, in a large Danish study, reported in 2009, risk was increased by both HT regimens. Furthermore, risk was essentially the same regardless of treatment duration, estrogen dose, progestin type, or route of administration. Fortunately, risk declined to baseline within 2 years of stopping HT. How big is the risk? In the Danish study, there was one additional case of ovarian cancer for every 8300 HT users.

Lung Cancer. An analysis of data from the WHI, reported in 2009, indicated that postmenopausal EPT is associated with an increased risk of dying from non-small cell lung cancer (NSCLC), especially in current smokers. Of note, although EPT increased the risk of lung cancer death, it did not increase the incidence of lung cancer overall, suggesting that EPT promotes the aggressive growth of existing NSCLC, but does not initiate new cancers. How might EPT promote NSCLC growth? By activating receptors for estrogen and progestin on cancer cells. This possibility is supported by the observation that, among women with established lung cancer, treatment with tamoxifen (a drug that blocks estrogen receptors) is associated with a significant reduction in the risk of lung cancer death.

Gallbladder Disease. Several studies, including the WHI, HERS, and the Nurses' Health Study (NHS), have shown that use of postmenopausal ET and EPT increases the risk of cholecystitis, an inflammatory condition of the gallbladder caused by chronic gallstones. Cholecystectomy (removal of the gallbladder) is the usual remedy. In the NHS, the risk of cholecystitis depended on duration of HT use, being highest among women using HT for 5 or more years. In the HERS trial, the incidence of cholecystectomy among HT users was 48% higher than among nonusers. In the WHI, both ET and EPT increased the risk of gallbladder disease.

Dementia. Data from the estrogen-plus-progestin arm of the Women's Health Initiative Memory Study (WHIMS), released in 2003, indicate that EPT *increases* the risk of dementia, primarily Alzheimer's disease. The WHIMS evaluated 4532 subjects from the WHI, 2229 of whom were receiving EPT and 2303 of whom were receiving placebo. After a mean follow-up of 4 years, the incidence of dementia in the EPT group was twice that in the placebo group. Fortunately, although the relative risk was high (a twofold increase over placebo), the absolute risk was still relatively low: For every 10,000 women using EPT for 1 year, there would be 23 additional cases of dementia.

What about estrogen alone? According to the WHIMS data released in 2004, ET does not protect against dementia, and probably increases the risk. Among women using ET, there were more cases of mild cognitive impairment (MCI) and outright dementia than among women taking placebo—but neither increase was statistically significant. However, although ET did not increase the risk of MCI or dementia *individually*, pooling the data for MCI and dementia showed that ET *did* increase the risk for MCI plus dementia combined. Hence, like EPT, ET increases the risk of cognitive decline, although ET may not increase the risk of dementia *per se*.

Urinary Incontinence. Oral estrogen is often prescribed to treat urinary incontinence in postmenopausal women. However, data from the WHI indicate that estrogen confers no benefit, whether taken alone or combined with progestin. In fact, the WHI showed that HT *increases* the risk of incontinence in women who are not incontinent, and makes incontinence worse in women who already are. These results are unexpected, given there are biologically plausible mechanisms by which estrogen might be expected to improve urinary tract health. It may be that *intravaginal* estrogen could succeed where oral therapy has failed. However, there is a paucity of research on this topic.

Minor Adverse Effects. Minor adverse effects are common. Nausea occurs in up to 20% of women during the first 2 to 3 months of HT. Fluid retention may result in weight gain and breast tenderness. With cyclic regimens, menstrual bleeding occurs.

Warnings

After reviewing the WHI results, the Food and Drug Administration (FDA) ruled that *all* products intended for HT, whether they contain estrogen alone or estrogen combined with a progestin, must carry strengthened warnings. Although only one estrogen/progestin product [Prempro] was studied in the WHI, until data on other products become available, all estrogen-containing products are assumed to carry similar risks. Accordingly, product labels must now have a *black box warning* (the highest level of warning in drug labeling) that contains statements similar to these:

- Estrogens and progestin should not be used to prevent cardiovascular disease.
- The use of unopposed estrogens in women with an intact uterus increases the risk of endometrial cancer.
- If undiagnosed persistent or recurrent abnormal vaginal bleeding occurs, rule out malignancy with endometrial sampling or other tests.
- The Women's Health Initiative (WHI) reported that postmenopausal women treated for 5 years with conjugated estrogens combined with medroxyprogesterone acetate experienced increased risks of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, and invasive breast cancer.
- The Women's Health Initiative Memory Study (WHIMS) reported that postmenopausal women more than 65 years old treated for 4 to 5 years with conjugated estrogens combined with medroxyprogesterone acetate experienced an increased risk of developing probable dementia.
- In the absence of comparable data, products that contain other doses of other estrogens and other progestins should be assumed to have similar risks.
- There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
- Prescribers should order estrogens and progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

A warning is also included not to use estrogens during pregnancy. However, this warning is present because there is no therapeutic reason to use estrogens during pregnancy. This warning does not apply to the use of estrogens during IVF cycles.

To further minimize risks, the new labeling advises women who use HT to perform monthly breast self-examinations, have yearly breast exams by a healthcare provider, and undergo periodic mammograms (scheduled on the basis of the patient's age and risk factors). In addition, healthcare providers should advise women on ways to reduce the risk of osteoporosis (eg, taking calcium and vitamin D supplements, performing weight-bearing exercise) and heart disease (eg, treating hypertension, maintaining a healthy weight, reducing dietary fat, avoiding smoking).

Women at high risk of complications should not use HT. Among these are women with undiagnosed postmenopausal vaginal bleeding and women who have experienced blood clots, breast cancer, stroke, or MI.

Recommendations on Hormone Therapy Use

Given our current understanding of the risks and benefits of HT, the question arises: Should *any* woman use HT? The answer is "Yes"—provided the benefits for the individual outweigh the risks. To make this assessment, risk factors for the individual must be inventoried, and the hoped-for benefits should be clearly defined. For women with significant baseline risks (eg, personal or family history of breast cancer, cardiovascular disease), the risk of harm from HT goes up.

Over the last few years, several expert sources issued revised recommendations on HT. The recommendations below represent a composite of those offered by four groups: the North American Menopause Society, the Endocrine Society, the FDA, and the U.S. Preventive Services Task Force (USPSTF). These recommendations are based in large part on data from the WHI and HERS.

The recommendations below are based on studies using Premarin and Prempro. In the absence of data proving otherwise, we must assume that all other estrogen and estrogen/progestin products carry similar risks. Likewise, until more proof is available, we cannot assume that ET is significantly safer than EPT, except in younger postmenopausal women.

General Recommendations

In order to balance benefits and risks, an individual risk profile should be compiled for every woman considering HT. All candidates for HT should be informed of known risks. Women with multiple risk factors should consider alternative therapies. For most women, the benefits of *long-term* HT for disease prevention do not outweigh the risks, and hence long-term HT should generally be avoided. Conversely, the benefits of short-term therapy (less than 4 to 6 years) to treat menopausal symptoms often *do* justify the risks. To keep risk as low as possible, HT should be used in the lowest dosage and for the shortest time needed to accomplish treatment goals.

Use for Approved Indications

Hormone therapy has only three approved indications:

- Treatment of moderate to severe vasomotor symptoms associated with menopause
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause
- Prevention of postmenopausal osteoporosis

TABLE 61-3 • Intravaginal Estrogens for Menopausal Hormone Therapy*

Generic Name	Trade Name	Usual Maintenance Dosage
Vaginal Creams		
Conjugated estrogens	Premarin	Apply 0.5–2 gm/day (625 mcg conjugated estrogens/gm) [†]
Estropipate	Ogen	Apply 2–4 gm/day (1.5 mg estropipate/gm) [†]
Estradiol	Estrace	Apply 1–2 gm 1–3 times/wk (100 mcg estradiol/gm)
Vaginal Rings		
Estradiol	Estring	This 2-mg ring releases 7.5 mcg/day for 90 days
Estradiol acetate	Femring	This 12.4-mg ring releases 50 mcg/day for 90 days*
		This 24.8-mg ring releases 100 mcg/day for 90 days*
Vaginal Tablets		
Estradiol hemihydrate	Vagifem	Insert 1 tablet (10 or 25 mcg) every day for 2 wk, then 1 tablet twice a week thereafter

*All intravaginal estrogens are used to treat urogenital atrophy. With one product—Femring—estradiol is absorbed in amounts sufficient to cause systemic effects, both beneficial (eg, suppression of vasomotor symptoms) and adverse (eg, increased risk of thrombosis).

[†]Administer cyclically (3 weeks on and 1 week off). For short-term use only.

Hormone therapy should be restricted to achieving one or more of these goals. With the first two indications, duration of treatment is relatively short (typically 3 to 4 years), and hence the risk of harm is relatively low—except for women with established heart disease. In contrast, prevention of osteoporosis requires lifelong HT, and hence the risk of harm is higher.

The only indication for long-term *progestin* therapy is protection against endometrial cancer, which could be caused by unopposed estrogen. Accordingly, use of EPT should be limited to women with an intact uterus. For women who have had a hysterectomy, estrogen alone should be used.

Treatment of Vasomotor Symptoms. Hormone therapy is the most effective treatment for vasomotor symptoms (hot flashes, night sweats), and the only treatment approved by the FDA. Do the benefits of short-term therapy justify the risks? Probably, especially for younger women with severe symptoms and a favorable risk profile. To increase safety, the lowest effective dosage should be employed. Furthermore, because vasomotor symptoms subside over time, the need for continued HT should be reassessed at regular intervals.

Are there any alternatives to HT for controlling vasomotor symptoms? Yes—but they are less effective than estrogen. Trials have shown that two antidepressants—*escitalopram* [Lexapro] and *desvenlafaxine* [Pristiq]—can produce a modest but meaningful reduction in both the frequency and severity of hot flashes. Escitalopram is a selective serotonin reuptake inhibitor (SSRI); desvenlafaxine is a serotonin/norepinephrine reuptake inhibitor (SNRI). Other SSRIs and SNRIs are likely to be effective as well. By contrast, controlled trials have shown that soy isoflavones do *not* reduce hot flashes. In fact, these preparations may make symptoms worse.

Treatment of Symptoms of Vulvar and Vaginal Atrophy. Estrogen is the most effective treatment for reducing symptoms of menopause-related vulvar and vaginal atrophy, characterized by dryness, irritation, itching, and uncomfortable intercourse. Because systemic estrogen carries significant risks, the FDA recommends that, if HT is being used solely to manage vulvar and vaginal symptoms, a topical estrogen formulation should be considered. Options include vaginal creams, vaginal tablets, and vaginal rings (Table 61-3). Although long-term data are lacking, it seems likely that

topical estrogen is safer than oral estrogen. Why? Because, with nearly all topical formulations, blood levels of estrogen remain low. The only exception is the Femring, which releases enough estrogen to cause significant systemic effects.

Prevention of Osteoporosis. Hormone therapy reduces postmenopausal bone loss, and thereby decreases the risk of osteoporosis and related fractures. Unfortunately, when HT is stopped, bone mass rapidly decreases by about 12%. Hence, to maintain bone health, HT must continue lifelong. As a result, the risk of harm is high. Accordingly, alternative treatments are preferred. In fact, labeling of HT products now must carry the following advice: *When this product is prescribed solely to prevent postmenopausal osteoporosis, approved nonestrogen treatments should be carefully considered. Furthermore, HT should be considered only for women with significant risk of osteoporosis, and only when that risk outweighs the risks of HT.* As discussed in Chapter 75, effective alternatives to HT include raloxifene [Evista], bisphosphonates (eg, alendronate [Fosamax]), calcitonin [Miacalcin], and teriparatide [Forteo]. Of course, all women (not to mention men) should practice primary prevention of bone loss. How? By ensuring adequate intake of calcium and vitamin D, performing regular weight-bearing exercise, and avoiding smoking and excessive alcohol use.

Inappropriate Uses: Attempted Prevention of Heart Disease and Dementia

Heart Disease. As noted above under *Warnings*, HT should *not* be prescribed for the express purpose of preventing CHD. For most women, HT confers no protection. Rather, it increases the risk of CHD and MI. However, for one group of women—those ages 50 to 59 who have had a hysterectomy—HT with estrogen alone really does reduce the risk of CHD and MI. Nonetheless, use of ET specifically for this protection is not recommended.

To reduce risk of cardiovascular events, postmenopausal women should be counseled about alternative ways to promote cardiovascular health. Among these are avoiding smoking, performing regular aerobic exercise, decreasing intake of saturated fats, and taking prescribed drugs to treat hypertension, diabetes, and high cholesterol.

Alzheimer's Disease. Hormone therapy should not be used to prevent Alzheimer's disease. There is no evidence that either EPT or ET can protect against dementia, whereas there is evidence that EPT can *cause* dementia, and that ET can increase the combined risk of dementia and mild cognitive impairment.

Safety in Younger Women Who Don't Have a Uterus

For women under the age of 60 who have undergone hysterectomy, HT may be safer than for any other group. There are two reasons why. First, because these women no longer have a uterus, they are treated with estrogen alone, which is somewhat safer than estrogen combined with a progestin. Second, for younger women, the risks of estrogen therapy are lower than for older women. Specifically, compared with older women, younger women are at lower risk for estrogen-induced CHD, MI, and breast cancer. In fact, among younger

women, ET appears to protect against CHD and MI, and possibly against breast cancer too.

Discontinuing Hormone Therapy

Because the risks of HT are greater than previously appreciated, many women are discontinuing treatment. Unfortunately, discontinuation may cause vasomotor symptoms to return, typically within 4 days of the last HT dose. Women who had severe symptoms before initiating HT are at highest risk of developing intolerable symptoms when they stop.

What's the best way to quit? No one knows. There are two basic methods: immediate cessation and tapering slowly. However, there are no controlled studies to indicate which option might result in fewer symptoms. For women who choose to taper slowly, again there are two basic options, referred to as "dose tapering" and "day tapering." With dose tapering, dosing is done every day, but the size of the daily dose is gradually

TABLE 61-4 ■ Oral Drugs for Menopausal Hormone Therapy

Generic Name	Trade Name	Usual Dosage
Estrogens		
Conjugated estrogens, equine	Premarin	0.3–1.25 mg/day
Conjugated estrogens A, synthetic	Cenestin	0.3–1.25 mg/day
Conjugated estrogens B, synthetic	Enjuvia	0.3–1.25 mg/day
Esterified estrogens	Menest	0.3–2.5 mg/day
Estradiol, micronized	Estrace	0.5–2 mg/day
Estradiol acetate	Femtrace	0.45–1.8 mg/day
Estropipate	Ogen	0.75–6 mg/day
Estropipate	Ortho-Est	0.75–1.5 mg/day
Ethinyl estradiol	Estinyl	0.02 mg/day
Progestins*		
Medroxyprogesterone acetate	Provera	2.5–10 mg*
Megestrol acetate	Megace	20–40 mg*
Norethindrone	Micronor, Nor-QD	0.5 mg*
Norethindrone acetate	Aygestin	5 mg*
Norgestrel	Ovrette	0.075 mg*
Progesterone (micronized)	Prometrium	100–200 mg*
Estrogen/Progestin Combinations		
Conjugated estrogens/ medroxyprogesterone acetate	Prempro	0.3/1.5, 0.625/2.5, or 0.625/5 mg daily
Conjugated estrogens/ medroxyprogesterone acetate	Premphase	Days 1–14: 0.625 mg estrogen (alone) daily Days 15–28: 0.625/5 mg estrogen/progesterone daily
Estradiol/drospirenone	Angeliq	1/0.5 mg daily
Estradiol/norethindrone	Activella	0.5/0.1 or 1/0.5 mg daily
Estradiol/norgestimate	Prefest	1 mg estradiol every day; 0.09 mg norgestimate in a repeating cycle of 3 days on and 3 days off
Ethinyl estradiol/norethindrone	Femhrt	2.5 mcg/0.5 mg or 5 mcg/1 mg daily
Estrogen/Testosterone Combinations		
Esterified estrogens/ methyltestosterone	Covaryx	1.25 mg/2.5 mg daily
Esterified estrogens/ methyltestosterone	Covaryx HS	0.625/1.25 mg daily

*Progestins are used to counteract the effects of estrogen on the uterus. The progestin listed can be used when the regimen calls for taking estrogen and progestin separately, rather than using a combination product. In estrogen/progestin regimens, the estrogen is taken daily, and the progestin is taken daily or intermittently (eg, 14 days on, 14 days off).

TABLE 61-5 ■ Transdermal Drugs for Menopausal Hormone Therapy

Generic Name	Trade Name	Strength (mcg absorbed/day)	Application
Estrogens			
Transdermal Patches			
Estradiol	Menostar	14	Once weekly
	Climara	25, 37.5, 50, 60, 75, 100	Once weekly
	Alora	25, 50, 75, 100	Twice weekly
	Estradot	25, 37.5, 50, 75, 100	Twice weekly
	Oesclim*	25, 37.5, 50, 75, 100	Twice weekly
	Vivelle	25, 37.5, 50, 75, 100	Twice weekly
	Vivelle-Dot	25, 37.5, 50, 75, 100	Twice weekly
	Estraderm	50, 100	Twice weekly
Topical Emulsion			
Estradiol hemihydrate	Estrasorb	50	Once daily
Transdermal Spray			
Estradiol	Evamist	1.53–4.6 mg is applied*	Once daily
Topical Gel			
Estradiol	EstroGel	0.75 mg is applied*	Once daily
	Elestrin	0.52 or 1.04 mg is applied*	Once daily
	Divigel	0.25, 0.5, or 1 mg is applied*	Once daily
Estrogen/Progestin Combinations			
Transdermal Patches			
Estradiol/norethindrone	CombiPatch	50/140, 50/250	Twice weekly
Estradiol/ levonorgestrel	ClimaraPro	45/15	Once weekly

*Application of this dose produces blood levels of estrogen and estrone similar to those seen in the follicular phase of the ovulatory cycle.

reduced. If intense symptoms return following a dosage reduction, further reductions should be delayed until symptoms improve. With day tapering, the daily dose remains unchanged, but the number of days between doses is gradually increased—starting with dosing every other day, then every third day, and so on. Regardless of which method is used—dose tapering or day tapering—only the dosage of *estrogen* should be lowered; for women on EPT, the *progestin dosage should remain unchanged*. Why? Because lowering the progestin dosage might permit estrogen to stimulate endometrial growth, thereby posing a risk of endometrial hyperplasia.

Open Questions

Despite the valuable information provided by HERS and the WHI, women considering HT could use even more information to guide their choice. Important questions that remain unanswered include the following:

- Are Prempro and Premarin (the preparations employed in the WHI and HERS) safer in lower doses? If so, are they effective in lower doses?
- Are other estrogens and progestins safer than the hormones in Prempro and Premarin? If so, are they also effective? Information would be especially welcome for recently approved estrogens.
- What are the risks of intravaginal estrogen compared with oral estrogens (when the objective is preventing vaginal atrophy)?

- When the HT regimen contains a progestin, which dosing schedule is safer: continuous daily progestin or sequential progestin?
- How long should a woman remain on HT?
- Are there genetic factors that significantly alter the risk/benefit ratio of HT?
- Do the results of the WHI and HERS apply to perimenopausal women (in addition to postmenopausal women)?

When these questions have been answered, the risks and benefits of treatment options will be more clear, and hence women will be able to choose (or reject) HT with greater confidence than is possible today.

Drug Products for Hormone Therapy Preparations

Preparations for HT are listed in Tables 61-3, 61-4, and 61-5. Dosing may be oral, transdermal, or intravaginal. The oral estrogens employed most often are conjugated equine estrogens [Premarin] (prepared by extraction from *pregnant mares' urine*), estradiol [Estrace], estradiol acetate [Femtrace], and estropipate [Ogen]. For transdermal therapy, estradiol is the only estrogen employed, formulated in patches, gels, a spray, and an emulsion. Oral estrogen/progestin combinations include conjugated equine estrogens/medroxyprogesterone acetate [Prempro, Premphase], estradiol/norethindrone acetate [Activella], and ethinyl estradiol/norethindrone [Femhrt]. Combination estrogen/progestin patches are estradiol/norethindrone

[Combipatch] and estradiol/levonorgestrel [ClimaraPro]. Intra-vaginal products—formulated as tablets, creams, and rings—are used primarily to manage symptoms of urogenital atrophy.

Dosing Schedules

Every woman undergoing systemic HT receives an estrogen, and every woman with a uterus also receives a progestin to counteract the stimulant effects of estrogen on the endometrium. Several dosing schedules may be employed. In the WHI and HERS, estrogen and progestin were both administered *continuously*, thereby eliminating monthly bleeding. An

alternative is to give estrogen continuously but give the progestin cyclically (eg, on calendar days 15 through 28). However, cyclic progestin has the disadvantage of promoting monthly bleeding, which may explain why most women prefer continuous dosing.

Vaginal estrogens can be given continuously for 1 to 2 weeks, followed by dosing 1 to 3 times per week, titrating the dosing schedule based on symptoms. Estring remains in the vagina for 3 months, after which it is removed and replaced with a new ring.

KEY POINTS

- Estradiol is the principal endogenous estrogen.
- Progesterone is the principal endogenous progestational hormone.
- The first half of the 28-day menstrual cycle is called the follicular phase. The second half is called the luteal phase.
- During the follicular phase, estrogens produced by maturing ovarian follicles cause proliferation of the endometrium.
- During the luteal phase, progesterone produced by the corpus luteum causes the endometrium to become more vascular and the endometrial glands to secrete glycogen.
- Toward the end of the menstrual cycle, progesterone levels decline, causing breakdown of the endometrium, which results in menstrual bleeding.
- In addition to their role in the menstrual cycle, estrogens are required for the growth and maturation of the uterus, vagina, fallopian tubes, and breasts. Estrogens also control pigmentation of the nipples and genitalia.
- Estrogens suppress bone mineral resorption, and thereby have a positive effect on bone mass.
- Estrogens raise levels of HDL cholesterol and reduce levels of LDL cholesterol. These actions partially explain the low incidence of coronary heart disease in premenopausal women.
- Nausea is the most common adverse effect of exogenous oral estrogens.
- Prolonged use of estrogens alone is associated with an increased risk of endometrial hyperplasia and endometrial carcinoma. However, when estrogens are used in combination with a progestin, there is little or no risk of this cancer.
- Estrogens are classified in FDA Pregnancy Risk Category X—not because they are especially harmful to the fetus, but because they have no legitimate use in pregnancy.
- Symptoms of menopause result from a decline in ovarian production of estrogen.
- Menopausal hormone therapy (HT), formerly known as *hormone replacement therapy* (HRT), has three approved indications: suppression of vasomotor symptoms, prevention of urogenital atrophy, and prevention of bone loss and osteoporosis.
- Hormone therapy is not approved for cardiovascular protection, and should not be used for this purpose.
- The Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS)—two large, randomized, placebo-controlled trials—have given us the most statistically valid data to date on the benefits and risks of HT.
- We have two basic regimens for HT: estrogen alone (ET) and estrogen combined with a progestin (EPT). The purpose of the estrogen is to manage symptoms caused by estrogen loss. The progestin is present to counteract the adverse effects that unopposed estrogen has on the endometrium. In women who no longer have a uterus, the progestin is omitted.
- The major risks of HT are CHD, MI, DVT, pulmonary embolism, stroke, breast cancer, gallbladder disease, and dementia. Ovarian cancer and lung cancer are also a concern.
- Cardiovascular risks of HT depend on the regimen (EPT or ET) and the age of the user. For all women, regardless of age, EPT increases the risk of CHD, MI, DVT, pulmonary embolism, and stroke. For women over the age of 60, ET carries the same risks. For women ages 50 to 59, ET increases the risk of DVT, pulmonary embolism, and stroke, but appears to *protect* against CHD and MI. To reduce cardiovascular risk, postmenopausal women should avoid smoking, perform regular exercise, decrease intake of saturated fats, and take drugs as indicated to treat hypertension, diabetes, and high cholesterol.
- The risk of breast cancer depends on the regimen and how soon after menopause HT is started. Treatment with EPT clearly increases the risk of breast cancer and breast cancer mortality, especially when EPT is started soon after menopause. Whether ET increases risk is unclear. In the WHI, ET was *not* associated with increased risk, even when started soon after menopause. In fact, among younger women in the WHI, ET was associated with a *reduced* incidence of breast cancer.
- The benefits of using HT short term to reduce vasomotor symptoms generally outweigh the risks, especially in younger women using ET, rather than EPT. To keep risk low, women should use the smallest effective dose for the shortest time needed.
- The benefits of using HT short term to manage urogenital symptoms probably outweigh the risks. If this is the only reason for HT, a topical estrogen should be considered.

- For protection against osteoporosis, HT must be taken long term. When HT is discontinued, 12% of bone mass is lost. Because of the risks associated with prolonged HT, alternative therapies are preferred. Among these are raloxifene, bisphosphonates, calcitonin, and teriparatide. To promote bone health, all women should perform regular weight-bearing exercise, ensure adequate intake of calcium and vitamin D, and avoid smoking and excessive intake of alcohol.
- Premenstrual syndrome (PMS) consists of a constellation of psychologic and physical symptoms that develop in the luteal phase of the menstrual cycle and resolve with menses.
- The psychologic symptoms of PMS—including irritability, depression, mood lability, crying spells, and so-

cial withdrawal—are more disabling than the physical symptoms.

- To make a diagnosis of PMS, symptoms must be sufficiently intense, and must be absent between days 4 and 12 of the menstrual cycle.
- Fluoxetine [Prozac] and other SSRIs are the most effective drugs known for PMS. Reduction of psychologic symptoms is greater than reduction of physical symptoms (eg, breast tenderness, bloating, headache).

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Summary of Major Nursing Implications*

ESTROGENS

Conjugated estrogens
 Conjugated estrogens, synthetic
 Estradiol
 Estradiol acetate
 Estropipate
 Ethinyl estradiol

Preadministration Assessment

Therapeutic Goal

Estrogens are used primarily for contraception (see Chapter 62) and for menopausal HT, but only to prevent osteoporosis, suppress vasomotor symptoms, and manage symptoms related to vulvar and vaginal atrophy. Indications unrelated to HT are female hypogonadism, prostate cancer, and dysfunctional uterine bleeding.

Baseline Data

Assessment should include a breast examination, pelvic examination, lipid profile, mammography, and blood pressure measurement. If the indication for HT is vasomotor symptoms, menopause should be verified by a serum FSH level.

Identifying High-Risk Patients

Estrogens are *contraindicated* for patients with estrogen-dependent cancers, undiagnosed abnormal vaginal bleeding, active thrombophlebitis or thromboembolic disorders, or a history of estrogen-associated thrombophlebitis, thrombosis, or thromboembolic disorders. In addition, estrogens are *contraindicated* during pregnancy—not because they are especially harmful, but because they offer no proven benefit.

Implementation: Administration

Routes

Oral, IM, IV, transdermal, and intravaginal.

Administration

Transdermal Patch. Give the patient the following instructions for using estradiol transdermal patches:

- Apply to an area of clean, dry, intact skin on the abdomen or some other region of the trunk (but not the breasts or waistline) by pressing the patch firmly in place for 10 seconds.
- If the patch falls off, re-apply the same patch or, if necessary, apply a new patch.
- Remove the old patch and apply a new patch once or twice weekly according to the product specifications.
- Rotate the application site such that the same site is not used more than once each week.

Transdermal Emulsion. Instruct the patient to apply the emulsion each morning to the top of both thighs and the back of both calves.

Transdermal Gel. Instruct the patient to apply the gel once daily after showering to one arm, from the shoulder to the wrist.

Transdermal Spray. Instruct the patient to apply 1, 2, or 3 sprays once daily to the inner forearm, and then let it dry at least 2 minutes before dressing and at least 30 minutes before washing.

Intravaginal Cream. Instruct the patient to apply estrogen cream high into the vagina, usually at bedtime, using the applicator provided.

Intravaginal Ring. Instruct the patient to insert the ring as deeply as possible, and to leave it in place for 3 months, after which it should be removed, and then replaced with a new ring if indicated.

Intravaginal Tablet. Inform patients that dosing consists of 1 tablet daily for 2 weeks, followed by 1 tablet twice a week thereafter. Instruct patients to insert each tablet as far as comfortably possible using the applicator supplied.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Dosing Schedules for Hormone Therapy

Women with an intact uterus should receive estrogen plus progestin, whereas women who have had a hysterectomy should use estrogen alone. In both cases, dosing with oral estrogen is done *daily*. With estrogen plus progestin, the progestin component may be given *daily* or cyclically on 10 days per month.

Ongoing Evaluation and Interventions

Monitoring Summary

The patient should receive a yearly follow-up breast and pelvic exam.

Minimizing Adverse Effects

Nausea. Nausea is common early in treatment but diminishes with time. **Inform the patient that nausea can be reduced by taking estrogens with food and by dosing at night.**

Endometrial Hyperplasia and Cancer. Menopausal HT with estrogen alone increases the risk of endometrial carcinoma. Adding a progestin lowers this risk to the pre-treatment level. **Instruct the patient to notify the prescriber if persistent or recurrent vaginal bleeding develops, so that the possibility of endometrial carcinoma can be evaluated.**

Breast Cancer. Estrogen, combined with a progestin, produces a small increase in the risk of breast cancer in postmenopausal women. **To minimize risk, advise patients to perform monthly breast self-exams, have yearly breast exams by a healthcare professional, and receive periodic mammograms.** Estrogen alone *may* increase breast cancer risk, but only when HT is started soon after menopause onset. Among younger women, estrogen alone may actually *protect* against breast cancer.

Ovarian Cancer. In postmenopausal women, giving ET or EPT may pose a small risk of ovarian cancer. **Advise women using ET or EPT to undergo periodic evaluation for ovarian cancer.**

Lung Cancer. Menopausal EPT, but not ET, may increase the risk of lung cancer. **Advise women using EPT to undergo periodic evaluation for lung cancer.**

Cardiovascular Events. For all women, regardless of age, therapy with estrogen plus a progestin increases the risk of CHD, MI, DVT, pulmonary embolism, and stroke. For women over the age of 60, therapy with estrogen alone carries the same risks. For women ages 50 to 59, therapy with estrogen alone increases the risk of DVT, pulmonary embolism, and stroke, but may *protect* against CHD and MI. **To reduce cardiovascular risk, advise women to avoid smoking, perform regular exercise, decrease intake of saturated fats, and take appropriate drugs to treat hypertension, diabetes, and high cholesterol.**

Effects Resembling Those Caused by Oral Contraceptives. Use of estrogens for noncontraceptive purposes can produce adverse effects similar to those caused by oral contraceptives (eg, abnormal vaginal bleeding, hypertension, benign hepatic adenoma, reduced glucose tolerance). Nursing implications regarding these effects are summarized in Chapter 62.

Minimizing Adverse Interactions

The interactions of estrogens are probably similar to those seen with oral contraceptives. Implications regarding these interactions are summarized in Chapter 62.

PROGESTINS

Hydroxyprogesterone caproate
Levonorgestrel
Medroxyprogesterone acetate
Megestrol acetate
Norethindrone
Norethindrone acetate
Norgestimate
Norgestrel
Progesterone

Preadministration Assessment

Therapeutic Goal

Progestins are used for contraception (see Chapter 62) and to counteract endometrial hyperplasia that could be caused by unopposed estrogen during HT. Other uses include dysfunctional uterine bleeding, amenorrhea, endometriosis, and support of pregnancy in women with corpus luteum deficiency. Progestins are also used in IVF cycles and to prevent prematurity in women at high risk for preterm birth.

Baseline Data

The physical examination should include breast and pelvic examinations.

Identifying High-Risk Patients

Progestins are *contraindicated* in the presence of undiagnosed abnormal vaginal bleeding. *Relative contraindications* include active thrombophlebitis or a history of thromboembolic disorders, active liver disease, and carcinoma of the breast.

Implementation: Administration

Routes

Oral, IM, transdermal, intravaginal.

Administration

Advise patients to take oral progestins with food if GI upset occurs.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Gynecologic Effects. Inform patients about potential side effects (eg, breakthrough bleeding, spotting, and amenorrhea). Instruct patients to notify the prescriber if abnormal vaginal bleeding occurs.

Teratogenic Effects. High-dose therapy during the first 4 months of pregnancy has been associated with an increased incidence of birth defects (limb reductions, heart defects, masculinization of the female fetus). Accordingly, use of progestins during early pregnancy is not recommended.

*Patient education information is highlighted as blue text.

Effectiveness of Birth Control Methods

Selecting a Birth Control Method

Oral Contraceptives

Combination Oral Contraceptives

Progestin-Only Oral Contraceptives

Combination Contraceptives with Novel Delivery Systems

Transdermal Contraceptive Patch

Vaginal Contraceptive Ring

Long-Acting Contraceptives

Subdermal Etonogestrel Implants

Depot Medroxyprogesterone Acetate

Intrauterine Devices

Spermicides

Barrier Devices

Drugs for Medical Abortion

Mifepristone (RU 486) with Misoprostol

Methotrexate with Misoprostol

Prostaglandins: Misoprostol, Carboprost, and Dinoprostone

 Box 62-1. Emergency Contraception

Birth control can be accomplished by interfering with the reproductive process at any step from gametogenesis to nidation (implantation of a fertilized ovum). Pharmacologic methods of contraception include oral contraceptives, etonogestrel implants, injectable medroxyprogesterone acetate, intrauterine devices, vaginal rings, and transdermal patches. Nonpharmacologic methods include surgical sterilization (tubal ligation, vasectomy), mechanical devices (condom, diaphragm, cervical cap), and avoiding intercourse during periods of fertility (calendar method, temperature method, cervical mucus method).

Although we have birth control methods that are safe and effective, statistics show that unwanted pregnancy is common—suggesting that available methods are not used as widely or as effectively as they could be, and that alternatives to current methods are needed. In the United States, 49% of pregnancies are unplanned—which is no surprise given that 50% of those who are not planning a pregnancy fail to use contraception. Teenagers have the highest rate of unplanned pregnancies: Of all pregnancies that occur in this group, 82% are unplanned. Among women ages 20 to 24, the rate is somewhat lower: 58%. Of the unplanned pregnancies that occur every year, about 52% are carried to term, while 48% end in abortion.

Most of this chapter focuses on combination oral contraceptive pills—the most widely used *reversible* form of contra-

ception. Sterilization is used more often, but is not reversible. In preparing to study these agents and other forms of contraception, you should review Chapter 61, paying special attention to information on the menstrual cycle and the physiologic and pharmacologic effects of estrogens and progestins.

EFFECTIVENESS OF BIRTH CONTROL METHODS

The effectiveness of a birth control method can be expressed as the percentage of unplanned pregnancies that occur while using the method. Employing this criterion, Table 62-1 compares the effectiveness of the major birth control methods. As you can see, the most effective methods are Nexplanon, intrauterine devices (IUDs), and sterilization. Oral contraceptives (OCs), Depo-Provera, the contraceptive ring, and the contraceptive patch are close behind. The least reliable methods include barrier methods, periodic abstinence, spermicides, and withdrawal.

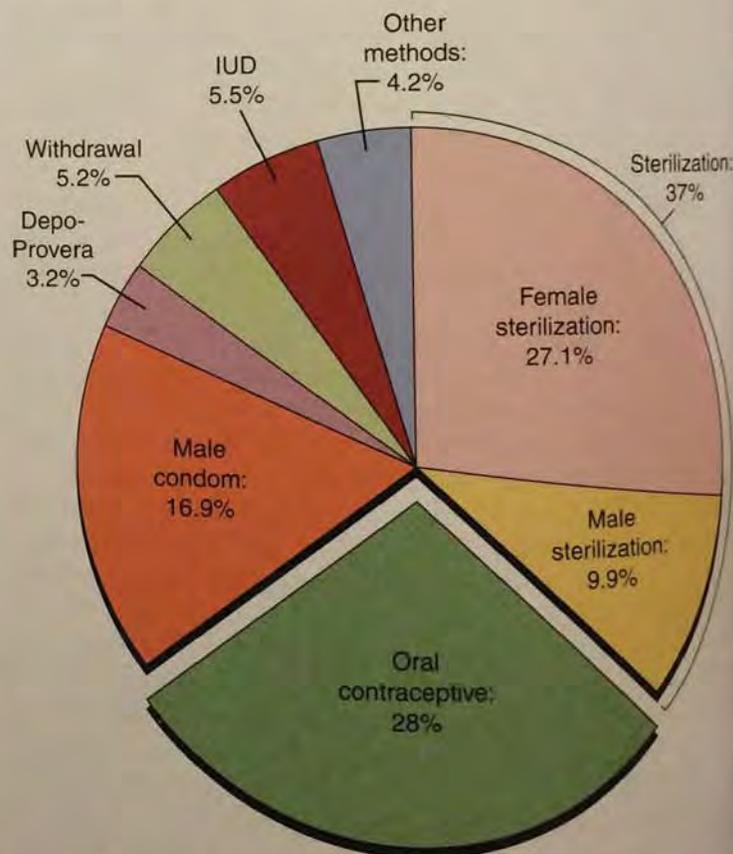


Figure 62-1 ■ Percentage use for birth control methods, United States, 2006-2008.

Note: The segment labeled "other methods" refers to Nexplanon, contraceptive patches, contraceptive ring, spermicides, cervical caps, female condoms, and other techniques. (Data from the Centers for Disease Control and Prevention.)

TABLE 62-1 ■ Effectiveness of Birth Control Methods

Birth Control Method	Failure Rate* (%)	
	Typical Use [†]	Perfect Use [‡]
No method	85	85
Extremely Effective		
Etonogestrel subdermal implant [Nexplanon]	0.05	0.05
Surgical sterilization		
<i>Female: tubal ligation</i>	0.5	0.5
<i>Male: vasectomy</i>	0.15	0.1
Intrauterine devices		
Copper T 380A [ParaGard]	0.8	0.6
Levonorgestrel T [Mirena]	0.2	0.2
Very Effective		
Oral contraceptives		
Combination pills	8	0.3
Progestin-only pills	8	0.3
Intramuscular medroxyprogesterone acetate [Depo-Provera]	3	0.3
Vaginal contraceptive ring [NuvaRing]	8	0.3
Contraceptive patch [Ortho Evra]	8	0.3
Effective		
Condoms		
<i>Male</i>	15	2
<i>Female [FC2 Female Condom]</i>	21	5
Diaphragm with spermicide	16	6
Least Effective		
Cervical cap		
<i>Parous</i>	29	—
<i>Nulliparous</i>	14	—
Contraceptive sponge [Today Sponge]		
<i>Parous</i>	32	20
<i>Nulliparous</i>	16	9
Spermicide alone	29	18
Periodic abstinence	25	3-5
Withdrawal	27	4

*Failure rate: percentage of women who have an unplanned pregnancy during first year of use.

[†]Typical use: failure rate usually observed in actual practice.

[‡]Perfect use: failure rate that would be expected if the birth control method were practiced exactly as it should be.

Note that Table 62-1 contains two columns of figures, one labeled *perfect use* and the other *typical use*. The *perfect use* figures represent pregnancy rates when a method of birth control is employed exactly as it should be (ie, consistently and with proper technique). The *typical use* figures represent pregnancy rates observed in actual practice. The higher pregnancy rates reported in the *typical use* column are largely an indication that methods of birth control are not always used when and as they should be.

SELECTING A BIRTH CONTROL METHOD

Figure 62-1 indicates the percentage of users who select a particular form of birth control. Perhaps surprisingly, the method chosen most frequently is sterilization: female sterilization (tubal ligation) plus male sterilization (vasectomy) are selected by 37% of birth control users. OCs or male condoms are chosen by most of the remaining birth control users.

Diaphragms, periodic abstinence, IUDs, and other techniques account for a small fraction of birth control use.

Several factors should be considered when choosing a method of birth control. Chief among these are *effectiveness*, *safety*, and *personal preference*. As indicated in Table 62-1, the most effective methods are etonogestrel subdermal implants [Nexplanon], intramuscular medroxyprogesterone acetate [Depo-Provera], sterilization, and IUDs. Three other methods—OCs, the contraceptive ring [NuvaRing], and the contraceptive patch [Ortho Evra]—are close behind. The remaining methods—condoms, the sponge, diaphragm, cervical cap, spermicides, and periodic abstinence—must be used in a near-perfect fashion to afford any reasonable level of protection.

When factoring safety into the selection equation, several guidelines apply. Combination OCs should be avoided by women with certain cardiovascular disorders (see below), as well as by women over 35 years old who smoke. For women in these categories, an alternative method (eg, diaphragm,

progestin-only pill, or IUD) is preferable. Although OCs are effective and relatively convenient, they can also cause significant side effects. Accordingly, women who consider the benefit/risk ratio unfavorable should be advised about alternative contraceptive techniques. Women who are not in a mutually monogamous relationship, and hence are at risk for a sexually transmitted disease (STD), should not use an IUD.

Personal preference is a major factor in providing the motivation needed for consistent implementation of a birth control method. Because even the best form of contraception will be less effective if improperly practiced, the importance of personal preference cannot be overemphasized. Practitioners should take pains to educate patients about the contraceptive methods available so that selection and use can be based on understanding.

Additional factors that bear on selecting a birth control method include family planning goals, age, frequency of sexual intercourse, and the individual's capacity for adherence. If family planning goals have already been met, sterilization of either the male or female partner may be desirable. For women who engage in coitus frequently, OCs or a long-term method (eg, Nexplanon, Depo-Provera, IUD) are reasonable choices. Conversely, when sexual activity is limited, use of a spermicide, condom, or diaphragm may be more appropriate. Since barrier methods combined with spermicides can offer some protection against venereal disease (as well as providing contraception), these combinations may be of special benefit to individuals who have multiple partners. If adherence is a problem (as it can be with OCs, condoms, and diaphragms), use of a long-term method (eg, vaginal contraceptive ring, IUD, Nexplanon, Depo-Provera) can confer more reliable protection.

To help women select the birth control method that suits them best, Planned Parenthood has created a step-by-step computerized selection tool, accessible online at www.plannedparenthood.org/all-access/my-method-26542.htm. This tool accounts for all of the factors noted above.

ORAL CONTRACEPTIVES

There are two main categories of OCs: (1) those that contain an estrogen *plus* a progestin, known as *combination OCs*, and (2) those that contain just a progestin, known as "minipills" or *progestin-only OCs*. Of the two groups, combination OCs are by far the more widely used.

Combination Oral Contraceptives

Since their introduction in the late 1950s, combination OCs have become one of our most widely prescribed families of drugs. These drugs are both safe and effective, although minor side effects are common.

Mechanism of Action

Combination OCs reduce fertility primarily by *inhibiting ovulation*. How? The estrogen in combination OCs suppresses release of FSH from the pituitary (and thereby inhibits follicular maturation), and progestin in combination OCs acts in the hypothalamus and pituitary to suppress the midcycle LH surge, which normally triggers ovulation. Secondary mechanisms include thickening of the cervical mucus (creating a barrier to the penetration of sperm), and alteration of the endometrium making it less hospitable for implantation.

TABLE 62-2 ■ Progestins Used in Combination Oral Contraceptives

Progestins	Comments
First Generation	
Ethinodiol diacetate Norethindrone	<ul style="list-style-type: none"> • Lower risk of thrombosis than with other progestins • Mildly androgenic
Second Generation	
Levonorgestrel Norgestrel	<ul style="list-style-type: none"> • Greater risk of thrombosis than with FGPs • More androgenic than FGPs • Prolonged half-life
Third Generation	
Desogestrel Norgestimate	<ul style="list-style-type: none"> • Greater risk of thrombosis than with FGPs (especially desogestrel) • Less androgenic than FGPs
Fourth Generation	
Dienogest Drospirenone	<p>For drospirenone <i>and</i> dienogest:</p> <ul style="list-style-type: none"> • Greater risk of thrombosis than with other progestins (especially drospirenone) • Less androgenic than FGPs • Low risk of acne and hirsutism <p>For <i>drospirenone only</i>:</p> <ul style="list-style-type: none"> • Risk of hyperkalemia

FGPs = first-generation progestins.

Components

Estrogens. Only three estrogens are employed: *ethinyl estradiol*, *mestranol*, and *estradiol valerate*. Most combination OCs use ethinyl estradiol. A few older products use mestranol, which undergoes conversion to ethinyl estradiol in the body. And one new product—*Natazia*—uses estradiol valerate, which undergoes conversion to estradiol in the body.

Progestins. Combination OCs employ eight different progestins, which can be grouped into four generations (Table 62-2). Progestins in all four generations are equally effective. Differences relate to side effects, especially thrombotic events, androgenic effects (acne, hirsutism, dyslipidemia), and hyperkalemia.

Drospirenone, a fourth-generation progestin, deserves comment. This unique compound has progestational, antiandrogen, and antialdosterone actions. The drug is a structural analog of spironolactone, a potassium-sparing diuretic that blocks receptors for aldosterone. Drospirenone was developed in an effort to reduce fluid retention caused by the estrogen component in combination OCs. (Estrogens promote fluid retention by activating the renin-angiotensin-aldosterone system. Drospirenone reduces fluid retention by blocking aldosterone receptors, thereby preventing retention of sodium and water. As a result, OCs made with drospirenone may cause less bloating, weight gain, and hypertension than other combination OCs.) The principal concern with drospirenone is *venous thromboembolism*, which occurs more often than with other progestins. Also, drospirenone can cause *hyperkalemia* (secondary to renal retention of potassium).

Effectiveness

As indicated in Table 62-1, OCs can be very effective. With perfect use, the failure rate is only 0.3%. However, with typical use, the failure rate is significantly higher: about 8%. Among women who are *overweight*, efficacy is somewhat reduced. Possible reasons include decreased blood levels of the hormones, sequestration in adipose tissue, and altered metabolism. However, even though efficacy of OCs is slightly

reduced in overweight women, these drugs are still more reliable than most of the alternatives.

Overall Safety

Determining the relative safety of combination OCs is complex. Part of the difficulty lies with the fact that much of our information on the adverse effects of OCs was gathered when these agents were employed in higher doses than those employed today. Newer data show that today's OCs, as currently prescribed, are considerably safer than indicated by older studies. An additional complication stems from the fact that the risk of mortality associated with OCs is much smaller than the risk associated with pregnancy and delivery. Keeping the above provisos in mind, we can make the following observations on OC safety. Of the contraceptive methods available, OCs produce the broadest spectrum of adverse effects, ranging from nausea to menstrual irregularity to rare thromboembolic disorders. However, despite their wide variety of undesired actions, when used by healthy women, OCs produce no greater mortality than any other form of birth control.

Adverse Effects

Combination OCs can cause a variety of adverse effects. However, although many types of effects may occur, severe effects are rare. Hence, when compared with the serious risks associated with pregnancy and childbirth, the risks of OCs are low. Nonetheless, because OCs are usually taken by women who are healthy, and because OCs represent a potential health hazard (albeit small), we must take steps to minimize risk. To this end, a full medical history should be obtained. If the history reveals an *absolute* contraindication to OC use (Table 62-3), OCs should not be prescribed. In women with *relative* contraindications, OCs should be used with caution. Should candidates for OCs undergo a thorough physical examination? Possibly, but the need is questionable.

Thromboembolic Disorders. Combination OCs have been associated with an increased risk of venous thromboembolism (VTE), arterial thromboembolism, pulmonary embolism, myocardial infarction (MI), and thrombotic stroke. Among OC users, the *relative* risk of a thrombotic event is 2 to 3 times the risk in nonusers. However, the *absolute* risk is still very small: about 8 to 10 events per 10,000 woman-years of OC use. Furthermore, the risk of thrombosis associated with OCs is considerably lower than the risk associated with pregnancy and delivery. How do OCs promote thrombosis? At least in part by raising levels of clotting factors. Thrombosis is not due to atherosclerosis.

Until the mid-1990s, we believed that thrombotic events were caused solely by the estrogen in combination OCs. However, it is now clear that the progestin can contribute too. Two newer progestins—*drospirenone* and *desogestrel*—appear to carry the greatest risk.

Fortunately, the risk of thrombotic events with OCs used today is much lower than with the OCs used in the past. Why? Because the amount of estrogen in OCs has been reduced. When combination OCs first became available, they contained high doses of estrogens (eg, 100 mcg ethinyl estradiol). Today's OCs contain no more than 50 mcg ethinyl estradiol (and usually less), and hence the risk of thromboembolism is quite low.

Major factors that increase the risk of thromboembolism are *heavy smoking*, *a history of thromboembolism*, and *thrombophilias* (genetic disorders that predispose to thrombosis).

TABLE 62-3 • Absolute and Relative Contraindications to the Use of Combination OCs

Absolute Contraindications

Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, coronary occlusion, or a past history of these conditions, or a condition that predisposes to these disorders
Abnormal liver function
Known or suspected breast cancer
Undiagnosed abnormal vaginal bleeding
Known or suspected pregnancy
Smokers over the age of 35

Relative Contraindications

Hypertension
Cardiac disease
Diabetes
History of cholestatic jaundice of pregnancy
Gallbladder disease
Uterine leiomyoma
Epilepsy
Migraine

Additional risk factors include diabetes, hypertension, cerebral vascular disease, coronary artery disease, and surgery in which immobilization increases the risk of postoperative thrombosis.

In the past, OCs were not recommended for women over the age of 35. Why? Because earlier studies indicated an increase in the risk of myocardial infarction for this group. However, re-analysis showed that the risk was limited to older women who smoked. With today's low-estrogen OCs, non-smokers may continue usage until menopause, with no greater risk of MI than among younger women.

Several measures can help minimize thromboembolic phenomena. Specifically:

- The estrogen dose in OCs should be no greater than required for contraceptive efficacy.
- OCs containing drospirenone or desogestrel should generally be avoided.
- OCs should not be prescribed for heavy smokers, women with a history of thromboembolism, or women with other risk factors for thrombosis.
- OCs should be discontinued at least 4 weeks prior to surgery in which postoperative thrombosis might be expected.
- Women should be informed about the symptoms of thrombosis and thromboembolism (eg, leg tenderness or pain, sudden chest pain, shortness of breath, severe headache, sudden visual disturbance) and instructed to consult the prescriber if these occur.

What about the cardiovascular risk for *former* OC users? Data from the Women's Health Initiative suggest that use of OCs in the past may *protect* against cardiovascular disease. Among women with a history of OC use, there was an 8% decrease in the overall incidence of cardiovascular disease, including a reduced risk of angina, myocardial infarction, peripheral vascular disease, transient ischemic attacks, and elevation of cholesterol.

Can women with a history of thrombosis use drugs for birth control? Yes. Although these women should avoid estro-

gen/progestin products, they can still use a progestin-only method. Options include the levonorgestrel intrauterine system [Mirena], medroxyprogesterone acetate injection [Depo-Provera], the etonogestrel subdermal implant [Nexplanon], and the "minipill"—all of which are discussed below.

Cancer. Oral contraceptives present no known risk of cancer—with the important exception of promoting (not causing) breast cancer growth. The effects of OCs on cancers of the ovaries, endometrium, cervix, and breast have been studied extensively. Effects on three of these cancers are clear: OCs protect against ovarian and endometrial cancer, and have no impact (positive or negative) on cervical cancer, which is caused by human papillomaviruses.

What about breast cancer? Until a decade ago, the question was unresolved: some studies found a link between OC use and breast cancer; others did not. Now we seem to have a definitive answer: OCs do *not* increase the risk of breast cancer for *most* women. This conclusion is based on data from the Women's Contraceptive and Reproductive Experience (Women's CARE) study, published in 2002. This major study, involving over 9000 women, found no association between present or past use of OCs and the development of breast cancer. This conclusion applied not only to study participants as a whole, but also to women in the following subgroups:

- Those who used OCs with high estrogen content
- Those who used OCs for a prolonged time
- Those who began OC use during adolescence
- Those with a first-degree relative with breast cancer

These results should reassure women who are OC users.

However, although this study shows that OCs do not increase risk for *most* women, the results of another large recent study show that OCs *do* increase risk for *some* women, specifically, women who have the *BRCA1* gene mutation. Even without taking OCs, these women have a very high—50% to 80%—lifetime risk of breast cancer. OCs increase this risk by one-third. The same study found that OCs do *not* increase risk in women with the *BRCA2* mutation.

It is important to note that, although OCs do not *cause* breast cancer, estrogens can promote the growth of *existing* breast carcinoma. Accordingly, women with this disease should not take OCs.

Hypertension. Combination OCs can cause hypertension, but the risk with today's low-estrogen preparations is very low. How do OCs raise blood pressure? By increasing blood levels of two compounds: angiotensin (a potent vasoconstrictor) and aldosterone (a hormone that promotes salt and water retention). If hypertension develops, and if OCs are determined to be the cause, two options are open: (1) discontinue the OC or (2) continue the OC and manage the hypertension with drugs.

Abnormal Uterine Bleeding. By altering the endometrium, OCs may decrease or eliminate menstrual flow. In addition, breakthrough bleeding and spotting may occur, especially with the use of extended-cycle OCs (eg, Seasonique, Seasonale). Spotting and bleeding can also occur with monthly-cycle OCs, most often during the first 3 months when low-estrogen OCs are used. If a period is missed while taking monthly-cycle OCs, the possibility of pregnancy should be assessed. Following discontinuation of OCs, normal menstruation usually resumes, although the first period

may be delayed. Women with a pretreatment history of irregular menses will return to their previous pattern when OCs are discontinued.

Use in Pregnancy and Lactation. OCs have no therapeutic role during pregnancy, and hence are *contraindicated for use by pregnant women*. Pregnancy should be ruled out prior to starting OC use, and, if pregnancy should occur despite OC use, dosing should stop immediately. Women should be assured, however, that inadvertent use of OCs during early pregnancy poses no risk of fetal harm. Because OCs have no role in pregnancy—and *not* because they are harmful—these drugs are classified in FDA Pregnancy Risk Category X.

Combination OCs enter breast milk and reduce milk production, especially in the early stages of lactation. In contrast, progestin-only OCs have little or no effect on milk production, and hence are preferred for contraception during lactation, at least early on. (Later, when the milk supply is well established, and especially with the addition of solids to the infant's diet, use of combination OCs may resume.)

Stroke in Women with Migraine. When used by women who experience migraine headaches, OCs may increase the risk of thrombotic stroke. However, the absolute increase is low: only 8 cases per 100,000 women at age 20, and rising to 80 cases per 100,000 women at age 40. Because the risk is low, OCs are generally considered safe for women with migraine, provided they are under age 35, don't smoke, and are healthy, and provided their headaches are not preceded by visual changes known as an aura (migraine with aura has a greater risk of stroke than migraine without aura). Migraine and its management are discussed at length in Chapter 30.

Benign Hepatic Adenoma. Hepatic adenoma is a rare complication seen in women who use OCs that contain *mes- tranol*. These highly vascular, nonmalignant tumors are usually picked up as incidental findings on a computed tomography scan or magnetic resonance imaging. If hepatic adenoma is diagnosed, discontinuing OCs usually results in spontaneous tumor regression.

Effects Related to Estrogen or Progestin Imbalance. Many of the mild side effects of combination OCs result from an excess or deficiency of estrogen or progestin. Effects that can result from an excess of estrogen include nausea, breast tenderness, and edema. Progestin excess can increase appetite and cause fatigue and depression. A deficiency in either hormone can cause menstrual irregularities. Side effects related to hormonal imbalance are summarized in Table 62-4.

Quite often, these effects can be reduced by adjusting the estrogen/progestin balance of an OC regimen. With most women, therapy is initiated with an OC containing 30 to 35 mcg of ethinyl estradiol. If significant nausea occurs, it can be managed by dosing at bedtime or, if needed, switching to an OC with less estrogen. Using less estrogen can also reduce breast discomfort. During the first 3 months of use, spotting and breakthrough bleeding are common, and usually resolve on their own. If they don't, they can be managed by increasing the estrogen dosage, or by using a product that contains a different progestin. For women who experience androgenic effects (eg, acne, hirsutism), switching to an OC that has drospirenone or dienogest can help. Other side effects can be reduced by making similar adjustments. When substituting one combination OC for another, the change is best made at the beginning of a new cycle.

TABLE 62-4 ■ Side Effects Caused by an Excess or Deficiency in the Estrogen or Progestin Content of an Oral Contraceptive Regimen

Estrogen		Progestin	
Excess	Deficiency	Excess	Deficiency
Nausea	Early or midcycle breakthrough	Increased appetite	Late breakthrough bleeding
Breast tenderness	bleeding	Weight gain	Amenorrhea
Edema	Increased spotting	Depression	Hypermenorrhea
Bloating	Hypomenorrhea	Tiredness	
Hypertension		Fatigue	
Migraine		Hypomenorrhea	
Cervical mucorrhea		Breast regression	
Polyposis		Monilial vaginitis	
		Acne, oily scalp*	
		Hair loss*	
		Hirsutism*	

*Caused by progestins that have strong androgenic activity.

Hyperkalemia. *Drospirenone*, a fourth-generation progestin, promotes renal retention of potassium, and can thereby cause hyperkalemia. Accordingly, the drug is inappropriate for women with conditions that predispose to hyperkalemia (eg, renal insufficiency, adrenal insufficiency, liver disease). Furthermore, drospirenone should be used with caution in women taking other drugs that can elevate serum potassium. Important among these are angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, potassium-sparing diuretics, potassium supplements, and nonsteroidal anti-inflammatory drugs (when taken daily). If women taking these drugs are using a drospirenone-containing OC, potassium levels should be checked during the first cycle of use.

Glucose Intolerance. Oral contraceptives can elevate blood glucose levels. This diabetogenic effect is caused by the *progestin* in OCs. Glucose intolerance is most likely in patients who are already diabetic or have experienced gestational diabetes. Because hypoglycemic agents (eg, insulin) can control glucose elevations induced by OCs, the presence of diabetes does not preclude OC use. Prediabetic women should be monitored for development of hyperglycemia. Glucose intolerance may occur less with OCs that contain *desogestrel* or *norgestimate*.

Other Adverse Effects. Rarely, OCs may precipitate *gallbladder disease* in women who already have gallstones or a history of gallbladder disease. OCs can occasionally cause *ocular injury* (eg, retinal vascular occlusion, retinal edema, optic neuropathy). Accordingly, if visual changes occur, OCs should be discontinued until the underlying cause is diagnosed. Combination OCs have been associated with an increased risk of *systemic lupus erythematosus*, primarily in women who recently began OC use. Rarely, OCs cause *melasma*, characterized by dark brown patches on the face.

Noncontraceptive Benefits of OCs

OCs decrease the risk of several disorders, including ovarian cancer, endometrial cancer, ovarian cysts, pelvic inflammatory disease (PID), benign breast disease, iron deficiency anemia, and acne. In addition, OCs favorably affect menstrual symptoms: cramps are reduced, menstrual flow is reduced in volume and duration, and menses are more predictable. In women with premenstrual syndrome or premenstrual dysphoric disorder, OCs can reduce symptom intensity. In some women with menstrually associated migraine, OCs can reduce migraine frequency. Surprisingly, OCs may even benefit women with rheumatoid arthritis.

Drug Interactions

Drugs and Herbs That Reduce the Effects of OCs. Products that induce hepatic cytochrome P450 can accelerate OC metabolism, and can thereby reduce OC effects. Products that induce P450 include *rifampin* (used for tuberculosis),

ritonavir (used for HIV infection), several *antiepileptic agents* (carbamazepine, phenobarbital, phenytoin, and primidone), and *St. John's wort* (an herb used widely for depression). Women taking OCs in combination with any of these agents should be alert for indications of reduced OC blood levels, such as breakthrough bleeding or spotting. If these signs appear, it may be necessary to either (1) increase the estrogen dosage of the OC, (2) combine the OC with a second form of birth control (eg, condom), or (3) switch to an alternative form of birth control.

Drugs Whose Effects Are Reduced by OCs. OCs can decrease the benefits of warfarin and hypoglycemic agents. By increasing levels of clotting factors, OCs can decrease the effectiveness of *warfarin*, an anticoagulant. By increasing levels of glucose, OCs can counteract the benefits of insulin and other hypoglycemic agents used in diabetes. Accordingly, when combined with OCs, warfarin and hypoglycemic agents may require increased dosage.

Drugs Whose Effects Are Increased by OCs. OCs can impair the hepatic metabolism of several agents, including *theophylline*, *tricyclic antidepressants*, *diazepam*, and *chlor-diazepoxide*. Because of reduced clearance, these drugs may accumulate to dangerous levels. If signs of toxicity appear, dosage of these drugs should be reduced.

Preparations

The combination OCs in current use are listed in Table 62-5. As you can see, nearly all of these products contain the same estrogen: ethinyl estradiol. In contrast, eight different progestins are employed. Products in the table are listed in order of increasing estrogen content. The OCs with low estrogen are safer. As a rule, high-estrogen OCs are reserved for women taking drugs that induce P450. Products with unique properties are discussed immediately below.

Bayaz and Safyral. In addition to an estrogen and a progestin, these combination OCs contain *levomefolate*, a metabolite of folic acid. The purpose is to reduce the risk of fetal neural tube defects—*anencephaly* and *spina bifida*—if pregnancy should occur despite contraceptive use. As discussed in Chapter 81 (Vitamins), neural tube defects can result if folic acid is low early in pregnancy.

Natazia. *Natazia*, introduced in 2010, has two unique components: *estradiol valerate* and *dienogest*, a fourth-generation progestin. *Estradiol valerate* is a prodrug that undergoes rapid conversion to estradiol, the predominant endog-

TABLE 62-5 ■ Composition of Combination Oral Contraceptives

Trade Name	mcg	Estrogen	mg	Progestin
28-DAY-CYCLE OCs				
Monophasic				
Loestrin Fe ^a	10	Ethinyl estradiol	1	Norethindrone
Junel 1/20	20	Ethinyl estradiol	1	Norethindrone
Junel Fe 1/20				
Loestrin 21 1/20				
Loestrin Fe 1/20				
Loestrin 24 Fe ^b				
Microgestin 1/20				
Microgestin Fe 1/20				
Aviane-28	20	Ethinyl estradiol	0.1	Levonorgestrel
Lessina				
Lutera				
Sronyx				
Gianvi ^c	20	Ethinyl estradiol	3	Drospirenone
YAZ ^c				
Beyaz ^{c,d}				
Generess Fe ^e	25	Ethinyl estradiol	0.8	Norethindrone
Levora	30	Ethinyl estradiol	0.15	Levonorgestrel
Nordette-28				
Portia-28				
Cryselle	30	Ethinyl estradiol	0.3	Norgestrel
Low-Ogestrel-21				
Low-Ogestrel-28				
Lo/Ovral-28				
Junel 1.5/30	30	Ethinyl estradiol	1.5	Norethindrone
Junel Fe 1.5/30				
Loestrin 21 1.5/30				
Loestrin Fe 1.5/30				
Microgestin 1.5/30				
Microgestin Fe 1.5/30				
Apri	30	Ethinyl estradiol	0.15	Desogestrel
Desogen				
Ortho-Cept				
Reclipsen				
Solia				
Ocella	30	Ethinyl estradiol	3	Drospirenone
Safyral ^d				
Yasmin				
Kelnor 1/35	35	Ethinyl estradiol	1	Ethinodiol diacetate
Zovia 1/35				
Balziva	35	Ethinyl estradiol	0.4	Norethindrone
Femcon Fe ^e				
Ovcon-35 ^e				
Zenchant				
Brevicon-28	35	Ethinyl estradiol	0.5	Norethindrone
Modicon-28				
Necon 0.5/35				
Nortrel 0.5/35				
Necon 1/35	35	Ethinyl estradiol	1	Norethindrone
Norinyl 1 + 35				
Nortrel 1/35				
Ortho-Novum 1/35				
MonoNessa	35	Ethinyl estradiol	0.25	Norgestimate
Ortho-Cyclen-28				

^aThe cycle for Loestrin Fe is 26 active tablets followed by 2 ferrous fumarate tablets.

^bThe cycle for Loestrin 24 Fe is 24 active tablets followed by 4 ferrous fumarate tablets.

^cThe cycle for Gianvi, YAZ, and Beyaz is 24 active tablets followed by 4 inert tablets.

^dEach tablet of Beyaz and Safyral contains 0.451 mg levomefolate (a metabolite of folic acid) to help prevent fetal neural tube defects if pregnancy should occur despite contraceptive use.

^eGeneress Fe, Ovcon-35, and Femcon Fe are the only chewable OCs available (they may also be swallowed whole).

TABLE 62-5 ■ Composition of Combination Oral Contraceptives—cont'd

Trade Name	mcg	Estrogen	mg	Progestin
28-DAY-CYCLE OCs—cont'd				
Monophasic—cont'd				
Previfem				
Sprintec				
Ovcon-50	50	Ethinyl estradiol	1	Norethindrone
Ogestrel 0.5/50	50	Ethinyl estradiol	0.5	Norgestrel
Zovia 1/50	50	Ethinyl estradiol	1	Ethinodiol diacetate
Necon 1/50	50	Mestranol	1	Norethindrone
Norinyl 1 + 50				
Biphasic				
Necon 10/11	35	Ethinyl estradiol	0.5	Norethindrone (phase 1)
	35	Ethinyl estradiol	1	Norethindrone (phase 2)
Azurette	20	Ethinyl estradiol	0.15	Desogestrel (phase 1)
Kariva	10	Ethinyl estradiol	0	Desogestrel (phase 2)
Mircette				
Triphasic				
Caziant	25	Ethinyl estradiol	0.1	Desogestrel (phase 1)
Cesia	25	Ethinyl estradiol	0.125	Desogestrel (phase 2)
Cyclessa				
Velivet	25	Ethinyl estradiol	0.15	Desogestrel (phase 3)
Aranelle	35	Ethinyl estradiol	0.5	Norethindrone (phase 1)
Leena	35	Ethinyl estradiol	1	Norethindrone (phase 2)
Tri-Norinyl	35	Ethinyl estradiol	0.5	Norethindrone (phase 3)
Ortho-Novum 7/7/7	35	Ethinyl estradiol	0.5	Norethindrone (phase 1)
Necon 7/7/7	35	Ethinyl estradiol	0.75	Norethindrone (phase 2)
Nortrel 7/7/7	35	Ethinyl estradiol	1	Norethindrone (phase 3)
Enpresse	30	Ethinyl estradiol	0.05	Levonorgestrel (phase 1)
Trivora	40	Ethinyl estradiol	0.075	Levonorgestrel (phase 2)
	30	Ethinyl estradiol	0.125	Levonorgestrel (phase 3)
Ortho Tri-Cyclen Lo	25	Ethinyl estradiol	0.18	Norgestimate (phase 1)
Tri LoSprintec	25	Ethinyl estradiol	0.215	Norgestimate (phase 2)
	25	Ethinyl estradiol	0.25	Norgestimate (phase 3)
Ortho Tri-Cyclen	35	Ethinyl estradiol	0.18	Norgestimate (phase 1)
TriNessa	35	Ethinyl estradiol	0.215	Norgestimate (phase 2)
Tri-Previfem				
Tri-Sprintec	35	Ethinyl estradiol	0.25	Norgestimate (phase 3)
Estrostep Fe	20	Ethinyl estradiol	1	Norethindrone (phase 1)
Tilia	30	Ethinyl estradiol	1	Norethindrone (phase 2)
Tilia Fe	35	Ethinyl estradiol	1	Norethindrone (phase 3)
Tri-Legest Fe				
Quadriphasic				
Natazia	3	Estradiol valerate	0	Dienogest (phase 1)
	2	Estradiol valerate	2	Dienogest (phase 2)
	2	Estradiol valerate	3	Dienogest (phase 3)
	1	Estradiol valerate	0	Dienogest (phase 4)
EXTENDED-CYCLE OCs				
Introvale ^f	30	Ethinyl estradiol	0.15	Levonorgestrel
Jolessa ^f				
Quasense ^f				
Seasonale ^f				
Seasonique ^g				
LoSeasonique ^g	20	Ethinyl estradiol	0.1	Levonorgestrel
CONTINUOUS OC				
Lybrel ^h	20	Ethinyl estradiol	0.09	Levonorgestrel

^fThe cycle for Introvale, Jolessa, Quasense, and Seasonale is 84 active tablets followed by 7 inert tablets.

^gThe cycle for Seasonique and LoSeasonique is 84 active tablets followed by 7 low-estrogen tablets (10 mcg ethinyl estradiol).

^hLybrel is taken continuously, without interruption.

enous estrogen. Dienogest, which is much like drospirenone (see discussion of *Components* above), has strong progestational activity and antiandrogenic activity. However, in contrast to drospirenone, dienogest does not cause potassium retention, and hence there is no need to monitor potassium levels. Unlike all other combination OCs, Natazia employs a *four-phase dosing schedule*, in which the amount of estradiol decreases over the monthly cycle, and the amount of progestin (dienogest) increases. Because of this schedule, duration of withdrawal bleeding is shorter than with other combination OCs, and the intensity of bleeding is lighter. In women who normally experience heavy or prolonged menstrual bleeding, Natazia can reduce blood loss.

Dosing Schedules

With only one exception, combination OCs are dosed in a *cyclic pattern*. For most products, each cycle is *28 days long* (see Table 62-5). However, with a few newer products, the cycle is either *extended* (to 91 days) or *continuous* [Lybrel].

28-Day-Cycle Schedules. The 28-day regimens are subdivided into four groups: *monophasic*, *biphasic*, *triphasic*, and *quadriphasic* (*four-phasic*). In a monophasic regimen, the daily doses of estrogen and progestin remain constant throughout the cycle of use. In the other regimens, either the estrogen, the progestin, or both change as the cycle progresses. The biphasic, triphasic, and quadriphasic schedules reflect efforts to more closely simulate ovarian production of estrogens and progestins. However, these preparations appear to offer little or no advantage over monophasic OCs.

Most 28-day cycle products are taken in a repeating sequence consisting of 21 days of an active pill followed by 7 days on which either (1) no pill is taken, (2) an inert pill is taken, or (3) an iron-containing pill is taken. The sequence is begun on either (1) the first day of the menstrual cycle or (2) the first Sunday after the onset of menses. With the first option, protection is conferred immediately, and hence no backup contraception is needed. With a Sunday start, which is done to have menses occur on weekdays rather than the weekend, protection may not be immediate, and hence a condom should be used during the first cycle. With both options, each dose should be taken at the same time every day (eg, with a meal or at bedtime). Successive dosing cycles should commence every 28 days, even if there is breakthrough bleeding or spotting.

Extended-Cycle and Continuous Schedules. Many specialists recommend taking combination OCs for an extended time, rather than following the traditional 28-day cycle. Why? Because doing so decreases episodes of withdrawal bleeding with its associated menstrual pain, premenstrual symptoms, headaches, and other problems. Prolonged use of OCs is possible because these drugs suppress endometrial thickening, and hence monthly bleeding is not required to slough off hypertrophied tissue. At this time, only seven products—*Introvale*, *Jolessa*, *Quasense*, *Seasonale*, *Seasonique*, *LoSeasonique*, and *Lybrel*—are packaged and marketed for prolonged use. The following regimens are employed:

- *Introvale*, *Jolessa*, *Quasense*, and *Seasonale*—active pills for 84 days, then no pills for 7 days
- *Seasonique* and *LoSeasonique*—active pills for 84 days, then low-dose estrogen pills for 7 days
- *Lybrel*—active pills are taken continuously, with no scheduled interruption

Hence, with *Introvale*, *Jolessa*, *Quasense*, *Seasonale*, *Seasonique*, and *LoSeasonique*, withdrawal bleeding occurs just 4 times a year, instead of 13 as with conventional cycles. With

Lybrel, withdrawal bleeding occurs only when dosing is finally stopped. However, although these products decrease episodes of *scheduled* bleeding, *breakthrough bleeding* can be more common.

It is important to note that there is nothing special about the estrogen/progestin combinations used in these extended-cycle products. Put another way, we could get the same results with other combination OCs, provided they are *monophasic*. To achieve an extended schedule, the user would simply purchase four packets of a 28-day product (each of which contains 21 active pills), and then take the active pills for 84 days straight.

What to Do in the Event of Missed Doses

The chances of ovulation (and hence pregnancy) from missing one OC dose are small. However, the risk of pregnancy becomes progressively larger with each successive omission.

For products that use a *28-day cycle*, the following recommendations apply:

- If *1 or more pills* are missed in the *first week*, take one pill as soon as possible and then continue with the pack. Use an additional form of contraception for 7 days.
- If *1 or 2 pills* are missed during the *second or third week*, take one pill as soon as possible and then continue with the *active* pills in the pack—but skip the placebo pills and go straight to a new pack once all the active pills have been taken.
- If *3 or more pills* are missed during the *second or third week*, follow the same instructions given for missing 1 or 2 pills, but use an additional form of contraception for 7 days.

Important note: The response to a missed dose of *Natazia*, as described in the package insert, is more complex than with other combination OCs.

For combination OCs that use an *extended or continuous cycle*, up to 7 days can be missed with little or no increased risk of pregnancy, provided the pills had been taken *continuously for the prior 3 weeks*.

Progestin-Only Oral Contraceptives

Progestin-only OCs, also known as “minipills,” contain a progestin but no estrogen. Because they lack estrogen, minipills do not cause thromboembolic disorders, headaches, nausea, or most of the other adverse effects associated with combination OCs. Unfortunately, although slightly safer than combination OCs, the progestin-only preparations are less effective, and are more likely to cause irregular bleeding (breakthrough bleeding, spotting, amenorrhea, inconsistent cycle length, variations in the volume and duration of monthly flow). Irregular bleeding is the major drawback of these products and the principal reason that women discontinue them. Seven products are available: *Camila*, *Errin*, *Heather*, *Jolivette*, *Micronor*, *Nor-QD*, and *Nora-BE*. All contain 0.35 mg *norethindrone*.

Contraceptive effects of the minipill result largely from altering cervical secretions. Under the influence of progestins, cervical glands produce a thick, sticky mucus that acts as a barrier to penetration by sperm. Progestins also modify the endometrium, making it less favorable for nidation. Compared with combination OCs, minipills are weak inhibitors of ovulation, and hence this mechanism contributes little to their effects. Unlike combination OCs, whose administration is cyclic, progestin-only OCs are taken continuously. Use is initiated on day 1 of the menstrual cycle and one pill is taken

daily thereafter. A backup contraceptive method should be used for the first 7 days. Dosing should be done at the same time each day.

If one or more doses is missed, the following guidelines apply. If 1 pill is missed, it should be taken as soon as remembered, and backup contraception should be used for at least 2 days. If two pills are missed, the regimen should be restarted, and backup contraception should be used for at least 2 days. In addition, if two or more pills are missed and no menstrual bleeding occurs, a pregnancy test should be done.

COMBINATION CONTRACEPTIVES WITH NOVEL DELIVERY SYSTEMS

Two combination contraceptives—a *transdermal patch* and a *vaginal ring*—have the same mechanism as combination OCs, but they deliver hormones in novel ways. Like combination OCs, both of these contraceptives contain two hormones—an estrogen and a progestin—that undergo absorption into the systemic circulation, and then prevent pregnancy primarily by suppressing ovulation. What's different is how the hormones are delivered: With the patch, the hormones are absorbed through the skin, and with the vaginal ring, the hormones are absorbed through the vaginal mucosa. Otherwise, the pharmacology of these contraceptives is essentially identical to that of combination OCs.

Transdermal Contraceptive Patch

The *Ortho Evra* transdermal contraceptive patch, approved in 2001, has the same mechanism as combination OCs. Furthermore, these products have the same contraceptive efficacy and the same incidence of breakthrough bleeding and spotting. The principal difference between them lies with their dosing schedules: Whereas combination OCs must be taken every day, the patch is applied just once a week. As a result, the patch is more convenient than OCs, and hence adherence is better.

The *Ortho Evra* patch contains 750 mcg of *ethinyl estradiol* (the estrogen found in most combination OCs) and 6 mg of *norelgestromin* (the active metabolite of norgestimate, a progestin found in some OCs). Each day, the patch releases 20 mcg of ethinyl estradiol and 150 mcg of norelgestromin. Following release, these hormones penetrate the skin, enter capillaries, and undergo distribution throughout the body. Plasma levels plateau 2 days after the first patch is applied.

Application of the patch, which is 1.75 inches square (about the size of a matchbook), is done once a week for 3 weeks, followed by 1 week off (to permit normal menstruation). Patches are applied to the lower abdomen, buttocks, upper outer arm, or upper torso (front or back)—but not to the breasts, or skin that is red, cut, or irritated. To enhance adhesion, the skin should be clean and dry, and free of lotions, creams, or oils.

How effective is the patch? In clinical trials, the pregnancy rate was about 1 for every 100 woman-years of patch use. However, among women who weighed 90 kg (198 lbs) or more, the pregnancy rate was significantly higher, suggesting the patch may be inappropriate for women in this weight group.

When should patch use begin? For women not currently using OCs, the first patch should be applied during the first 24 hours of the menstrual period. For women switching from OCs, the first patch should be applied on the first day of withdrawal bleeding.

In clinical trials, 4.6% of patches became partially or completely detached. When this occurs, the patch should be reattached or replaced. If the patch has been off less than 24 hours, backup contraception is unnecessary. However, if the patch has been off more than 24 hours, a new cycle should be started, accompanied by backup contraception during the first 7 days.

The most common adverse effects are breast discomfort, headache, local irritation, nausea, and menstrual cramps. Compared with *Triphasil* (a combination OC), the patch produces a higher incidence of breast discomfort (11.7% vs. 5.8%) and dysmenorrhea (13.3% vs. 9.6%). Contraindications and drug interactions are the same as for combination OCs.

Does the patch cause more venous thromboembolism (VTE) than do OCs? Possibly. Three epidemiologic studies have examined the question. In

two of the studies, the risk of VTE in women using the patch was double the risk in women using combination OCs. However, in the third study, there was no difference in risk. Of note, women who use the patch are exposed to 60% more estrogen than women who use an OC containing 35 mcg of estrogen. The higher estrogen exposure could increase the risk of VTE.

Vaginal Contraceptive Ring

In 2001, the FDA also approved *NuvaRing*, a hormonal contraceptive device designed for vaginal insertion. Like combination OCs, the ring contains an estrogen/progestin combination that prevents pregnancy largely by suppressing ovulation. Adverse effects, drug interactions, warnings, and contraindications for the ring are the same as for combination OCs. The ring is made of transparent, flexible material and looks like a very skinny doughnut, with an overall diameter of 2.1 inches and a cross-sectional diameter of one-eighth inch. Insertion is done by the user.

The *NuvaRing* contains 2.7 mg of *ethinyl estradiol* and 11.7 mg of *etonogestrel* (the active metabolite of desogestrel, a progestin found in some OCs). Each day, the ring releases 15 mcg of ethinyl estradiol and 120 mcg of etonogestrel. Following release, the hormones penetrate the vaginal mucosa, undergo absorption into the blood, and then distribute throughout the body. Contraception results from systemic effects—not from local effects in the vagina.

One ring is inserted once each month, left in place for 3 weeks, and then removed; a new ring is inserted 1 week later. During the ring-free week, withdrawal bleeding occurs. The new ring should be inserted on schedule, even if bleeding is still ongoing. If a ring is expelled before 3 weeks have passed, it can be washed off in warm water (not hot water) and reinserted. If the expelled ring cannot be reused, a new one should be inserted. If more than 3 hours elapse between ring expulsion and reinsertion, contraceptive effects may be diminished, and hence backup contraception should be used for 7 days.

Initiating ring use is done as follows:

- For women not currently using contraception, ring use should start anytime during days 1 through 5 of the menstrual cycle, even if bleeding is ongoing; backup contraception should be used during the first 7 days.
- For women switching from combination OCs, ring use should start within 7 days of taking the last active OC; no backup contraception is needed.
- For women switching from progestin-only OCs, ring use should start on the same day the last pill is taken, which can be any day of the month; backup contraception should be used during the first 7 days.
- For women switching from Nexplanon, ring use should start on the same day that the implant is removed; backup contraception should be used during the first 7 days.
- For women switching from a levonorgestrel-containing IUD, ring use should start on the same day the IUD is removed; backup contraception should be used during the first 7 days.
- For women switching from IM progestin injections, ring use should start on the day of the next scheduled injection; backup contraception should be used during the first 7 days.

The most common adverse effects are vaginitis, headaches, upper respiratory infection, leukorrhea, sinusitis, weight gain, and nausea. Common reasons for discontinuing the ring include foreign body sensations, coital problems, ring expulsion, vaginal symptoms, headache, and emotional lability. The risk of serious adverse effects—thrombosis, embolism, and hypertension—is the same as with combination OCs.

LONG-ACTING CONTRACEPTIVES

Subdermal Etonogestrel Implant

A subdermal system [*Nexplanon*, formerly sold as *Implanon*] for delivery of etonogestrel is available for long-term, reversible contraception. As indicated in Table 62-1, *Nexplanon* is among the most effective contraceptives available. An older subdermal system, known as *Norplant*, has been withdrawn.

Description. *Nexplanon* consists of a single 4-cm rod that contains 68 mg of etonogestrel, a synthetic progestin. The rod is implanted subdermally in the groove between the biceps and triceps in the nondominant arm. Etonogestrel then diffuses

slowly and continuously, providing blood levels sufficient for contraception for 3 years, after which the rod is removed. If continued contraception is desired, a new rod is implanted.

Mechanism of Action. Etonogestrel suppresses ovulation and thickens cervical mucus. In addition, it causes the endometrium to become involuted and hence hostile to implantation.

Pharmacokinetics. Daily release of etonogestrel is 60 to 70 mcg initially and gradually declines to 25 to 30 mcg over 3 years. Absorbed drug is slowly metabolized by the liver. When the rod is removed, etonogestrel becomes undetectable within 5 to 7 days.

Drug Interactions. Agents that induce hepatic enzymes—such as barbiturates, phenytoin, rifampin, carbamazepine, topiramate, HIV protease inhibitors, and St. John's wort—may reduce the efficacy of Nexplanon. Accordingly, Nexplanon should not be used by women taking these drugs.

Adverse Effect: Irregular Bleeding. In women using Implanon, bleeding episodes are irregular and unpredictable. In clinical trials, amenorrhea occurred in 22% of women; infrequent bleeding (less than 3 bleeding or spotting episodes in 90 days) occurred in 34% of women; frequent bleeding (more than 5 bleeding or spotting episodes in 90 days) occurred in 7% of women, and prolonged bleeding (more than 14 days of bleeding in 90 days) occurred in 18% of women. Despite effects on bleeding, levels of hemoglobin were unaffected over 3 years. The general pattern of irregular and unpredictable bleeding does not change while using Nexplanon. Bleeding irregularities are the leading reason for discontinuing the device.

Use During Breast-feeding. Nexplanon is safe to use during breast-feeding. Very little etonogestrel is excreted in breast milk. In a controlled clinical trial, there were no significant effects on the physical or psychomotor development of infants. Also, Nexplanon had no effect on the production or quality of milk, even when implanted just a few days postpartum.

Depot Medroxyprogesterone Acetate

Depot medroxyprogesterone acetate (DMPA), injected IM or subQ, protects against pregnancy for 3 months or longer. How? The drug inhibits secretion of gonadotropins, and thereby (1) inhibits follicular maturation and ovulation, (2) thickens the cervical mucus, and (3) causes thinning of the endometrium, making implantation unlikely. When injections are discontinued, return of fertility is delayed (by an average of 9 months).

DMPA is available in two formulations for contraception. One is injected IM [Depo-Provera] and the other is injected subQ [Depo-subQ Provera 104]. Dosages are 150 mg and 104 mg, respectively, injected once every 3 months. To ensure that the recipient is not pregnant, the first dose should be given either (1) during the first 5 days of a normal menstrual period, (2) within the first 5 days postpartum (if not breast-feeding), or (3) at the sixth week postpartum (if exclusively breast-feeding).

Most adverse effects are like those seen with other progestin-only contraceptives. Menstrual disturbances are common; menstruation may be irregular at first and then, after 6 to 12 months, may cease entirely. Mild weight gain (about 3.5 pounds) is likely during the first year. Women may also experience abdominal bloating, headache, depression, and decreased libido. However, it is unclear that DMPA is the cause. Although DMPA has produced uterine and mammary

cancers in animals, a large-scale study has shown no increase in the risk of cervical, ovarian, or breast cancer in women—and the risk of endometrial cancer is actually reduced.

DMPA poses a risk of reversible bone loss, but this risk does not outweigh the benefits of treatment. During the first 1 to 2 years of DMPA use, bone mineral density (BMD) declines rapidly, at a rate of 1% to 2% per year. However, after this time, the rate of bone loss slows down. Importantly, when DMPA is discontinued, BMD returns to pretreatment levels, typically within 30 months. Whether DMPA-induced bone loss increases the risk of fractures is unclear. While this story was still evolving, the FDA, in 2004, revised the label for DMPA to include a black box warning that recommends against using the drug for more than 2 years. However, in the light of data gathered since 2004, this warning appears unwarranted. Accordingly, in 2008, an American College of Obstetricians and Gynecologists (ACOG) committee counseled that practitioners should not let concerns about bone loss deter them from prescribing DMPA or cause them to limit prescriptions to 2 years. In addition, the committee recommended against routine testing of BMD in women on DMPA. When counseling patients about this issue, practitioners should point out that any risk of fracture with DMPA is theoretical, whereas the risks associated with pregnancy are very real.

Intrauterine Devices

IUDs are among the most reliable forms of reversible birth control (see Table 62-1). In addition, the IUDs available today are very safe when used by appropriate clients (see below). Worldwide, over 85 million women use these devices. However, despite their safety and efficacy, IUDs are not popular in the United States: Among women who use birth control, only 5.5% choose an IUD. Nonuse of IUDs is largely the legacy of the Dalkon Shield, a poorly designed IUD associated with a high rate of pelvic infection.

Two IUDs are currently available: (1) the *copper T 380A* [ParaGard] and (2) the *levonorgestrel-releasing intrauterine system* [Mirena]. As indicated in Table 62-1, both are extremely effective. IUDs are placed within 7 days of the onset of menses, and a replacement can be inserted during any phase of the menstrual cycle. ParaGard can remain in place for 10 years and Mirena for 5 years. How do these devices prevent conception? Both IUDs, which are T shaped, produce a harmless local inflammatory response that is spermicidal. ParaGard, whose active ingredient is copper, may also inhibit implantation. Mirena, whose active ingredient is levonorgestrel, also causes endometrial involution and thickening of the cervical mucus. Neither device prevents ovulation.

With proper counseling and client selection, both IUDs are very safe. The principal risk is pelvic inflammatory disease (PID) secondary to a sexually transmitted disease (STD). Accordingly, IUDs should be used only by women with a low risk for STDs—that is, by women who are monogamous, and are confident that their partners are too. The risk for PID is highest during the first 20 days after insertion, with a rate of 9.7 cases per 1000 woman-years of use. One month after insertion, the risk declines to only 1.4 cases per 1000 woman-years of use.

Both IUDs can cause cramping and alteration of menses. Cramping is most intense upon IUD insertion, and can be minimized by applying a topical anesthetic (2% lignocaine intracervical gel) or by premedicating with ibuprofen. With ParaGard, monthly bleeding is increased. With Mirena, light spotting and amenorrhea are common.

In addition to providing long-term contraception, Mirena and ParaGard have other uses. Owing to its ability to greatly reduce menstrual bleeding, Mirena is approved for treating *menorrhagia* (heavy menstrual bleeding) in women who want to use an IUD for contraception. As discussed in Box 62-1, ParaGard can be used for *emergency contraception*. In one study, the pregnancy rate with postcoital placement was reduced to 0.2%.

SPERMICIDES

Spermicides are chemical surfactants that kill sperm by destroying their cell membrane. These drugs are available in the form of a foam, gel, jelly, suppository, vaginal film, and contraceptive sponge. All formulations can be purchased without a prescription. When used alone, spermicides are only

BOX 62-1 ■ SPECIAL INTEREST TOPIC

EMERGENCY CONTRACEPTION

Emergency contraception (EC) is defined as contraception that is implemented *after* intercourse. Women can use EC to prevent pregnancy following unprotected intercourse, which can result from sexual assault, contraceptive failure (eg, broken condom), or occasional lack of forethought. Safe and effective methods of EC have been available for decades. However, products marketed specifically for EC are relatively new.

The data on unintended pregnancy are staggering. In the United States, nearly 50% of women ages 15 to 44 report having had at least one unintended pregnancy. Among teenagers, 88% of pregnancies are unintended. Of the 6 million pregnancies that occur each year, about 3.5 million are accidental. Every year, unintended pregnancies lead to 1.4 million abortions and 1.1 million births that women did not want—at least not yet. Clearly, if EC were used widely, most abortions and unwanted births could be avoided.

EC can be accomplished in two basic ways: Taking an *emergency contraceptive pill* (ECP), also known as a *morning-after pill*, or inserting a copper-T intrauterine device (IUD). Taking an ECP is most common. Furthermore, of the three basic types of ECPs—progestin-only pills, ulipristal-containing pills, and estrogen/progestin pills—the progestin-only pills are used most widely.

Progestin-Only ECPs

Three progestin-only products are available: Plan B One-Step, Plan B, and Next Choice. All three contain *levonorgestrel*. These products are packaged and marketed specifically for emergency contraception. This contrasts with the estrogen/progestin products, which are marketed as oral contraceptives (OCs), but can be used off-label for EC.

Plan B One-Step

In the United States, Plan B One-Step is the most widely used ECP. The product consists of a single, high-dose (1.5-mg) tablet of *levonorgestrel*, a progestin found in many combination OCs. The package insert calls for taking the tablet within 72 hours of unprotected intercourse. However, although early implementation is best, Plan B One-Step and other ECPs can still be effective when started up to 5 days after intercourse. Success is indicated by onset of menstrual bleeding in about 21 days.

Plan B One-Step reduces the odds of pregnancy by 89%, which is better than it may seem. In the absence of Plan B One-Step, the pregnancy rate from a single act of unprotected intercourse is about 8% (ie, 8 women in 100 would become pregnant). However, among women using Plan B One-Step, only 1 in 100 is likely to become pregnant—a reduction of 89%.

How does Plan B One-Step work? Primarily by delaying or stopping ovulation. Inhibition of fertilization may also contribute. Of note, *levonorgestrel* is *not* effective after fertilization has occurred.

The major side effects of Plan B One-Step are heavier menstrual bleeding (30.9%), nausea (13.7%), abdominal pain (13.3%), headache (10.3%), dizziness (9.6%), and vomiting (6%). Nausea and vomiting can be reduced by taking an antiemetic (eg, prochlorperazine) 1 hour before dosing. If vomiting occurs within 2 hours of dosing, a repeat dose may be needed. Importantly, if

pregnancy does occur, having used *levonorgestrel* will not increase the risk of major congenital malformations, pregnancy complications, or any other adverse pregnancy outcomes.

Does Plan B One-Step cause abortion? NO! Plan B One-Step will not terminate an existing pregnancy, and will not harm a fetus if present. Recall that pregnancy is defined as implantation of a fertilized egg. Since Plan B acts prior to fertilization and implantation, it cannot be considered an abortifacient.

How can you get Plan B One-Step? For woman age 17 and older, Plan B One-Step is now available over the counter. No prescription is required. However, you do need a government-issued ID to prove your age, and a licensed pharmacist must dispense the drug. For women who are not yet 17, Plan B One-Step is still available, but a prescription is required. Prescriptions can be obtained from private physicians, clinics run by Planned Parenthood, and student health departments at colleges and universities.

It's a good idea to keep Plan B One-Step on hand "just in case." Remember, the drug works best when taken right after intercourse. By purchasing Plan B One-Step in advance, you can avoid delay.

Plan B and Next Choice

Plan B and Next Choice consist of two 0.75-mg tablets of *levonorgestrel* (one-half the amount in a single Plan B One-Step tablet). According to the package inserts, women should take 1 tablet within 72 hours of intercourse, and a second tablet 12 hours later. However, taking both tablets at the same time is just as effective. (This is equivalent to taking one tablet of Plan B One-Step.) As with Plan B One-Step, these ECPs can still be effective when started up to 5 days after intercourse, but are most effective when taken earlier. Adverse effects are similar to those of Plan B One-Step. If vomiting occurs within 2 hours of dosing, a repeat dose may be required. Like Plan B One-Step, Plan B and Next Choice can be obtained without a prescription (by woman age 17 and older) or with a prescription (by woman under age 17).

Ulipristal Acetate ECP

In 2010, the FDA approved a new emergency contraceptive: *ulipristal acetate* [ella], a drug that acts as an agonist/antagonist at receptors for progestin. Like *levonorgestrel*, *ulipristal acetate* prevents conception primarily by suppressing ovulation. Despite this similarity, *ulipristal acetate* and *levonorgestrel* differ in two important ways. First, *ulipristal acetate* remains highly effective when taken up to *five* days (120 hours) after intercourse, whereas *levonorgestrel* is most effective when taken within *three* days (72 hours) of intercourse. Second, whereas *levonorgestrel* [Plan B, Plan B One-Step, Next Choice] is available without a prescription for women age 17 and older, *ulipristal acetate* [ella] requires a prescription for all women, regardless of age. The dosage for *ulipristal acetate* is 1 tablet (30 mg), taken up to 5 days after unprotected intercourse. Principal adverse effects are headache (19%), nausea (13%), dysmenorrhea (13%), and abdominal pain (8%). If vomiting occurs within 3 hours of dosing, an additional dose may be required.

Continued

Estrogen/Progestin ECPs (Yuzpe Regimen)

The *Yuzpe regimen*, first described in 1974 by Professor A. Alfred Yuzpe, consists of two doses of an OC that contains an estrogen (ethinyl estradiol) plus a progestin (levonorgestrel or norgestrel). The first dose should be taken within 72 hours of unprotected intercourse, and the second dose 12 hours later. Pregnancy is prevented by interfering with ovulation, fertilization, and implantation. Like other ECPs, this regimen will not cause abortion. Compared with Plan B One-Step, this regimen is less effective (75% vs. 89%) and causes more nausea (50% vs. 13.3%) and vomiting (19% vs. 6%). Combination OCs that can be used for EC are shown in the table below. However, because other ECPs are more effective, better tolerated, and readily available, these alternatives are used infrequently.

Mifepristone as an ECP

One drug—*mifepristone* (RU 486)—can prevent pregnancy or cause abortion, depending on when it is taken. If mifepristone

is taken within 5 days of unprotected intercourse, it will prevent pregnancy from occurring, and hence can be considered an ECP. However, if mifepristone is taken after this time, it may terminate pregnancy that has already begun, and hence can be considered an abortifacient. When used as an ECP, mifepristone is 100% effective. The drug is available in the United States, but is not approved for EC.

The Copper IUD

Insertion of a *copper IUD* within 5 days of unprotected intercourse can prevent pregnancy in most women. The method is more than 99.9% effective, allowing less than 1 pregnancy for every 1000 IUD recipients. IUD insertion has the additional benefit of providing ongoing contraception for up to 10 years. Although using an IUD for EC is highly effective, the technique does have drawbacks: the IUD is expensive, not all women are candidates, and obtaining one quickly may be difficult.

EMERGENCY CONTRACEPTIVE PILLS*

Trade Name*	Number of Doses [†]	Pills/Dose	Ethinyl Estradiol/Dose (mcg)	Levonorgestrel/Dose (mg)	Ulipristal Acetate/Dose (mg)
Ulipristal Acetate ECP					
ella	1	1 white	—	—	30
Progestin-Only ECPs					
Plan B One-Step	1	1 white	—	1.5	—
Plan B	2 [‡]	1 white	—	0.75	—
Next Choice	2 [‡]	1 peach	—	0.75	—
Estrogen/Progestin ECPs (Yuzpe Regimen)					
Cryselle	2	4 white	120	0.6 [§]	—
Lo/Ovral	2	4 orange	120	0.6 [§]	—
Low-Ogestrel	2	4 white	120	0.6 [§]	—
Nordette	2	4 orange	120	0.6	—
Levora	2	4 white	120	0.6	—
Portia	2	4 pink	120	0.6	—
Seasonale	2	4 pink	120	0.6	—
Seasonique	2	4 blue-green	120	0.6	—
Jolessa	2	4 pink	120	0.6	—
Quasense	2	4 white	120	0.6	—
Lybrel	2	6 yellow	120	0.54	—
Enpresse	2	4 orange	120	0.5	—
Trivora	2	4 pink	120	0.5	—
Aviane	2	5 orange	100	0.5	—
LoSeasonique	2	5 orange	100	0.5	—
Sronyx	2	5 white	100	0.5	—
Lessina	2	5 pink	100	0.5	—
Lutera	2	5 white	100	0.5	—
Ogestrel	2	2 white	100	0.5 [§]	—

*Only four products—Plan B, Plan B One-Step, Next Choice, and ella—are packaged and marketed specifically for EC. All the rest are ordinary OCs that can be used for EC if needed (color indicates which pills in a multipill pack are to be taken.)

[†]For all ECPs—except ella and Plan B One Step—formal protocols call for two doses, the first taken within 72 hours of intercourse, and the second 12 hours later. However, starting within 120 hours of intercourse can still be effective.

[‡]Package labeling calls for taking 2 doses 12 hours apart. However, taking both doses at once is just as effective.

[§]The progestin in these OCs is norgestrel, a 50:50 mixture of levonorgestrel:dextronorgestrel. Only the levonorgestrel is active.

moderately effective (see Table 62-1). Combined use with a diaphragm or condom increases efficacy. As indicated in Table 62-6, spermicidal preparations contain either *nonoxynol 9* or *octoxynol 9*.

Spermicides are generally devoid of serious side effects. Studies show no relationship between spermicides and birth defects. However, there is some evidence that *nonoxynol 9* may increase the risk of HIV transmission. The apparent mechanism is promotion of vaginal, cervical, anal, and rectal lesions that facilitate HIV penetration to cells. Allergic reactions (to the drug or vehicle) occur in some women.

Correct use is required for contraceptive efficacy. The spermicide must be applied prior to coitus, but no more than 1 hour in advance (when used alone). Containers for foam preparations must be shaken thoroughly before each use to ensure dispersal of the spermicide. Suppositories should be inserted at least 10 to 15 minutes before intercourse to allow time for dissolution. Spermicides should be re-applied each time intercourse is anticipated. Douching should be postponed for at least 6 hours following coitus.

The contraceptive sponge [Today Sponge] is a soft, porous, polyurethane disk impregnated with 1000 mg of *nonoxynol 9*. When inserted to cover the cervix, it protects against conception by (1) releasing spermicide, (2) absorbing seminal fluid, and (3) blocking penetration of sperm. Unlike other spermicide products, which must be re-applied before each act of intercourse, a single sponge is effective for 24 hours, regardless of how often coitus takes place. After 24 hours, the sponge should be removed. The rate of unintended pregnancy with the sponge is high: 16% among typical *nulliparous* users, and 32% among *parous* users. The most common adverse effects are vaginal irritation and dryness. The Today Sponge was voluntarily withdrawn in 1995 and then re-introduced in 2005.

BARRIER DEVICES

Barrier devices—male condoms, female condoms, diaphragms, and the cervical cap—are nonpharmacologic options for birth control. Of the barrier devices available, condoms for men are by far the most commonly employed.

Condoms for Men. The condom is a thin sheath, made of latex, polyurethane, or lamb's intestine, that fits snugly over the penis, and hence traps ejaculate released during intercourse. As indicated in Figure 62-1, condoms are the fourth most common form of birth control. The typical-use failure rate is 15%.

In the United States, most condoms are made of latex, which is impermeable to bacteria and viruses. Hence, in addition to protecting against pregnancy, latex condoms offer protection against STDs. There is good evidence that condom use protects against HIV, chlamydia, trichomonas, and gonorrhea, and probably against infection with human papillomaviruses (HPVs). Protection against syphilis, chancroid, and genital herpes is less certain. Lubricants that contain mineral oil can rapidly decrease the barrier strength of latex—by as much as 90%—and therefore should be avoided. Allergy to latex can develop in men and women, especially with repeated exposure.

Like latex condoms, polyurethane condoms offer some protection against STDs. In addition, they are thinner than latex condoms, possibly stronger, and don't cause allergies. However, the failure rate with polyurethane is higher than with latex.

In contrast to latex and polyurethane condoms, condoms made from lamb's intestine are permeable to viruses, and hence do not protect against viral STDs.

Condom for Women. The *FC2 Female Condom*, made of synthetic rubber, is a loose-fitting, tubular pouch that has flexible rings at both ends. The ring at the closed end anchors the pouch over the cervix. The ring at the open end, which is larger than the ring at the closed end, is placed over the labia and serves as an external anchor. The *FC2* condom is pre-lubricated, available without prescription, and should be used just once and then discarded. Because it is made of synthetic rubber, the *FC2* condom is safe for people with latex allergy. Like male condoms, the female condom provides some protection against STDs. At this time, the female condom is the only safe and effective woman-initiated method for protecting against HIV infection. The pregnancy failure rate with typical use is 21%. The *FC2 Female Condom*, approved in 2009, has replaced the older version, formerly available as the *Reality* female condom.

Diaphragm. The diaphragm is a soft rubber cap with a metal spring to reinforce its rim. The device must be fitted by a healthcare provider, and the user must be taught how to insert and remove the device. When in place over the cervical os, the diaphragm holds spermicidal jelly or cream against the cervix and blocks access of sperm to the cervix. Spermicide must be re-applied externally with repeated intercourse. The diaphragm can be inserted as long as 6 hours prior to intercourse, and must remain in place for at least 6 hours after. Owing to the risk of toxic shock syndrome, the diaphragm should not remain in place more than 24 hours. With typical use, the failure rate is about 16%.

Cervical Cap. The cervical cap is a small, pliant, cup-shaped device that fits snugly over the cervix. Suction holds it in place. The device must be fitted by a healthcare provider, and the user must be taught how to insert it. Like the diaphragm, the cap is filled with spermicidal cream or jelly prior to use, and can be inserted up to 6 hours before intercourse. There is no need to apply additional spermicide with repeated intercourse. The cap should remain in place for at least 8 hours after intercourse, and probably no longer than 48 hours (although the manufacturer says it can stay in place 48 hours). The typical-use failure rate is about 18%. At this time, the cervical cap is unavailable in the United States. The one product that had been available—*Prentif Cavity-Rim Cervical Cap*—has been discontinued.

DRUGS FOR MEDICAL ABORTION

Mifepristone (RU 486) with Misoprostol

Mifepristone (RU 486) [Mifeprex] is a synthetic steroid that blocks receptors for progesterone and glucocorticoids. In the United States, the drug has one approved indication: termination of early intrauterine pregnancy; cotreatment with misoprostol is usually required. Investigational uses include breast cancer, ovarian cancer, meningiomas, Cushing's syndrome, uterine fibroids, and endometriosis. In addition, mifepristone is the most effective drug known for emergency contraception, although it is not used routinely for this purpose (Box 62-1). Mifepristone was approved for use in the United States on September 20, 2000.

Mifepristone, followed by misoprostol, is a safe and effective alternative to surgery for termination of early pregnancy. Together, these drugs terminate

TABLE 62-6 • Spermicides

Formulation	Active Ingredient	Trade Name
Foam	Nonoxynol 9 (12.5%)	Delfen Contraceptive
Jelly	Nonoxynol 9 (3%)	Gynol II Extra Strength Contraceptive*
Gel	Nonoxynol 9 (4%)	Conceptrol Disposable Contraceptive
	Nonoxynol 9 (3.5%)	Advantage 24*
	Nonoxynol 9 (2.2%)	K-Y Plus*
	Nonoxynol 9 (2%)	Shur Seal*
	Octoxynol 9 (1%)	Ortho-Gynol Contraceptive*
Suppository	Nonoxynol 9 (2.27%)	Encare
	Nonoxynol 9 (100 mg)	Semceid
Sponge	Nonoxynol 9 (1000 mg)	Today Sponge
Vaginal Film	Nonoxynol 9 (28%)	VCF

*Intended for use only in combination with a vaginal diaphragm.

pregnancy in about 95% of women. Principal adverse effects are abdominal pain and vaginal bleeding, which are unavoidable aspects of abortion. There is also a small risk of infection. In contrast to surgical abortion, which is generally unavailable before 8 weeks of gestation, abortion with mifepristone is performed early—within 7 weeks of conception.

Mechanism of Action. Mifepristone promotes abortion through blockade of progesterone receptors. Although mifepristone also blocks receptors for glucocorticoids, this action does not contribute to abortion. In the pregnant uterus, the drug has three effects. First, blockade of progesterone receptors leads to decidual breakdown and detachment of the conceptus. Second, mifepristone promotes cervical softening and dilation. Third, mifepristone increases uterine production of prostaglandins and renders the myometrium more responsive to the contractile effects of these prostaglandins. All three effects lead to expulsion of the conceptus. If mifepristone alone fails to induce abortion, the patient is given 400 mcg of oral misoprostol, a synthetic prostaglandin that reinforces uterine contractions induced by mifepristone. The pharmacology of misoprostol is discussed separately below.

Clinical Trials. In a study conducted in France, the abortion success rate with mifepristone/misoprostol was nearly 99%. Success was defined as termination of pregnancy with complete expulsion of the conceptus. All women in the study had amenorrhea for less than 50 days prior to receiving mifepristone. Dosing was done as follows: Each patient received a 600-mg oral dose of mifepristone and, if abortion had not occurred within 48 hours, each was given a 400-mcg dose of oral misoprostol; a second dose of misoprostol (200 mcg) was offered if abortion had not occurred by 4 hours after the first dose. Only 5.5% of the pregnancies terminated prior to dosing with misoprostol; with the addition of misoprostol, either one or two doses, the cumulative success rate was 98.7%. In the majority of patients (69%), abortion occurred within 4 hours of the first misoprostol dose.

In the United States, success with mifepristone/misoprostol has also been good—although not quite as good as in France. In 1999, American researchers reported that the abortion rate with mifepristone/misoprostol declined with increasing duration of gestation. Success was greatest (92%) when gestation was 49 days or less, falling to 83% during days 50 to 56 of gestation, and to 77% during days 57 to 63. The dosages employed were the same as in the French study. Why the success rate was lower than in the French study is unknown.

There is good evidence that *intravaginal* misoprostol is more effective and better tolerated than oral misoprostol. In one study, women received 600 mg of oral mifepristone, followed by 800 mcg of misoprostol, either PO or intravaginally. Following intravaginal misoprostol, 95% of conceptuses were expelled without the need for surgery, compared with only 87% following oral misoprostol. With intravaginal dosing, abortion occurred within 4 hours in 93% of patients, compared with 78% of patients receiving oral misoprostol. The incidence of nausea and vomiting with intravaginal dosing was significantly lower than with oral dosing. Intravaginal misoprostol—but not oral misoprostol—has been associated with very rare cases of severe sepsis, one heart attack, and one death (from hemorrhage) following a ruptured ectopic pregnancy. However, a causal relationship between these events and mifepristone/misoprostol has not been established.

Adverse Effects. The most common side effects are bleeding (100%), cramping (80%), nausea (60%), vomiting (26%), diarrhea (20%), and headache (31%). The most serious adverse effects are severe bleeding and sepsis.

Successful abortion necessarily causes abdominal pain (cramping) and bleeding. Nearly all women experience these events. About 80% of patients experience transient cramping, beginning 1 hour after taking misoprostol; most women require an opioid analgesic for relief. Bleeding and spotting typically last 9 to 16 days. However, in some women, bleeding persists for 30 days or more. About 1% of women experience severe bleeding; treatment measures include curettage, uterotonic drugs (eg, methylergonovine, ergonovine), and infusion of fluids, blood, or both.

Mifepristone/misoprostol has been associated with a few cases of serious bacterial infection, including very rare cases of fatal septic shock. Accordingly, patients and providers should be alert for typical signs of sepsis (sustained fever of 100.4°F or higher, severe abdominal pain, pelvic tenderness). However, in two confirmed cases of sepsis caused by *Clostridium sordellii*, these signs were absent. Instead, the patients presented with nausea, vomiting, and diarrhea, without fever or abdominal pain. In patients with typical or atypical presentation, the possibility of infection should be evaluated immediately.

The bleeding caused by mifepristone/misoprostol could mask bleeding due to a ruptured ectopic pregnancy. Accordingly, before mifepristone/misoprostol is used, ectopic pregnancy must be ruled out. This is best done by a routine ultrasound examination.

Misoprostol (but not mifepristone), a proven teratogen, can cause Möbius' syndrome, a rare fetal anomaly. Hence if the mifepristone/misoprostol fails to induce abortion, performing surgical abortion should be considered.

Contraindications. Major contraindications to mifepristone/misoprostol are ectopic pregnancy, hemorrhagic disorders, or use of anticoagulant drugs. Because mifepristone blocks receptors for glucocorticoids, it should not be used in women with adrenal insufficiency and those on long-term glucocorticoid therapy.

Preparations, Dosage, and Administration. Mifepristone [Mifeprex] is supplied in single-dose packets containing three 200-mg tablets. The dosage is 600 mg taken all at once—followed in 2 days by 400 mcg of misoprostol (if mifepristone did not induce complete abortion by itself). Mifepristone is available only through qualified physicians; it is not sold in pharmacies.

FDA-Approved Protocol for Abortion. Under the FDA-approved protocol, induction of abortion with mifepristone/misoprostol requires *three visits to a qualified physician*. In order to dispense mifepristone, a physician must be qualified to determine pregnancy duration and to diagnose ectopic pregnancy. In addition, the physician must either (1) be able to perform surgical abortion (in the event mifepristone/misoprostol fails) as well as curettage (in the event of severe bleeding), or (2) have a commitment from a colleague to perform these procedures.

Day 1. Mifepristone (600 mg) is taken—but only after several conditions have been met. The physician must rule out ectopic pregnancy and must ensure that the pregnancy is indeed early (defined as pregnancy in which no more than 49 days have elapsed since the beginning of the last menstrual period). If necessary, ultrasound should be performed to confirm that pregnancy is intrauterine and not beyond the 49-day limit. Also, the patient must read a Medication Guide supplied by the manufacturer, and both the patient and physician must sign a Patient Agreement Form stating that the patient understands the benefits and risks of the procedure and has decided to end the pregnancy. Finally, the patient must be given clear instruction on whom to call and what to do in the event of an emergency.

Day 3. Two days after taking mifepristone, the patient returns to the physician, who performs a physical examination or ultrasound scan to determine if abortion has occurred. If abortion has not occurred, the patient takes misoprostol (400 mcg PO). *Note:* Although the FDA-approved protocol says that misoprostol dosing should be oral, intravaginal misoprostol is often used instead.

Day 14. About 14 days after taking mifepristone, the patient returns to the physician, who confirms by physical examination or ultrasound scan that pregnancy has been terminated. If the woman is still pregnant, surgical abortion should be considered.

Methotrexate with Misoprostol

Methotrexate, followed by misoprostol, is a safe and effective alternative to surgical termination of early pregnancy. Methotrexate induces abortion owing to its toxicity to trophoblastic tissue; misoprostol contributes by promoting uterine contraction. Abortion is accomplished by giving an intramuscular injection of methotrexate (50 mg/m²) followed in 4 to 8 days by 800 mcg of intravaginal misoprostol. If abortion does not occur in 24 hours, dosing with misoprostol is repeated. In one study, 14% of patients required the second dose of misoprostol, but 96% eventually aborted. The procedure is more effective at 49 days of gestation (or less) than between days 50 and 56. Side effects include nausea, vomiting, diarrhea, headache, dizziness, and hot flushes. Acetaminophen plus codeine is usually sufficient to relieve pain. The vast majority of women who have undergone the procedure said they would recommend it.

Prostaglandins: Misoprostol, Carboprost, and Dinoprostone

Prostaglandins are synthesized in all tissues of the body, where they act as local hormones. Unlike true hormones, which travel to distant sites to produce their effects, prostaglandins act on the very tissues in which they are made; degradation of prostaglandins is so rapid that they rarely escape their tissue of origin intact. Although the prostaglandins produce a broad spectrum of physiologic effects, their clinical use is limited. In obstetrics, prostaglandins are indicated for induction of abortion, cervical ripening prior to labor induction, and control of postpartum hemorrhage. Use of prostaglandins for abortion is discussed here. Use for cervical ripening and control of postpartum hemorrhage is discussed in Chapter 64.

Nomenclature

Nomenclature regarding the prostaglandins can be confusing, and hence deserves clarification. Each prostaglandin has three names: a traditional name, an official generic name, and a trade name. Misoprostol, carboprost, and dinoprostone are *generic names*. For carboprost, the traditional name

15-methyl-prostaglandin F_2 alpha and the trade name is *Hemabate*. For dinoprostone, the traditional name is *prostaglandin E₂*; trade names are *Cervidil*, *Prepidil*, and *Prostin E2*♣. For misoprostol, a synthetic analog of prostaglandin E_1 , the trade name is *Cytotec*.

Physiologic and Pharmacologic Effects

Uterine Stimulation. Prostaglandins increase the force, frequency, and duration of uterine contractions. In the early months of pregnancy, the fetus is more responsive to prostaglandins than to oxytocin. During the second and third trimesters, prostaglandins can induce contractions of sufficient strength to cause complete evacuation of the uterus.

Like oxytocin, prostaglandins appear to have a physiologic role as promoters of uterine contraction, spontaneous labor, and delivery. Observations supporting this statement include: (1) exogenous prostaglandins can induce uterine contractions that are very similar in frequency and duration to contractions that occur spontaneously; (2) the ability of the uterus to synthesize prostaglandins increases at term; (3) the prostaglandin content of amniotic fluid, umbilical blood, and maternal blood increases at term and during labor; and (4) labor is delayed and prolonged by agents that inhibit prostaglandin synthesis.

Cervical Softening. Local application of prostaglandins produces cervical softening. This softening results from breakdown of collagen, and hence mimics the process by which natural cervical ripening occurs. Softening of the cervix does not depend on uterine stimulation.

Therapeutic Uses

Abortion. All three prostaglandins—misoprostol, carboprost, and dinoprostone—can be used to induce abortion. Misoprostol (in combination with methotrexate or mifepristone [RU 486]) is used *early* in pregnancy as well as in the *second trimester*. Carboprost and dinoprostone are used in the *second trimester only*. With all three drugs, uterine contractions develop slowly. As a result, about 18 hours must pass between dosing and expulsion of the fetus. Unlike other abortifacients, prostaglandins are not fetocidal, and hence the aborted fetus may show transient signs of life. Following passage of the fetus and placenta, the patient should be examined for possible cervical or uterine laceration.

Control of Postpartum Hemorrhage. *Carboprost* is indicated for control of postpartum hemorrhage. The drug is reserved for bleeding that has been refractory to more conventional agents (oxytocin, ergot alkaloids). In these situations, carboprost may be lifesaving. Use of carboprost to control postpartum hemorrhage is discussed in Chapter 64.

Induction of Labor. *Misoprostol* has been used to induce labor. The regimen recommended by the American College of Obstetricians and Gynecologists consists of 25 mcg vaginally repeated every 3 to 6 hours as needed.

Cervical Ripening. *Dinoprostone* and *misoprostol* can be used to initiate ripening of the cervix prior to induction of labor. This application is discussed in Chapter 64.

Adverse Effects

Gastrointestinal reactions are extremely common with dinoprostone and result from the ability of prostaglandins to stimulate smooth muscle of the alimentary canal. Vomiting and diarrhea occur in up to 62% of those treated. Nausea also occurs often. These responses can be reduced by pretreatment with antiemetic and antidiarrheal medications.

Intense uterine contractions can result in *cervical or uterine laceration*. The patient should be examined thoroughly for trauma following expulsion of the fetus and placenta.

Fever is seen with dinoprostone. When hyperthermia develops, it is important to distinguish between drug-induced fever and pyrexia resulting from endometritis. With dinoprostone, there is a 10% incidence of headache, shivering, and chills.

Precautions and Contraindications

Prostaglandins are *contraindicated* for women with active disease of the heart, lungs, kidneys, or liver. Carboprost should be avoided in women with a history of asthma or hypertension.

Preparations, Dosage, and Administration

Dinoprostone. Dinoprostone [Prepidil, Cervidil, Prostin E2♣] is available in three formulations: (1) 20-mg vaginal suppositories, (2) 10-mg vaginal inserts, and (3) a 0.5-mg gel. Dinoprostone suppositories [Prostin E2♣] are used for abortion. The gel [Prepidil] and vaginal inserts [Cervidil] are used for cervical ripening.

For *induction of abortion* (weeks 12 to 20), one 20-mg vaginal suppository is inserted initially, followed by one suppository every 3 to 5 hours as needed.

Carboprost Tromethamine. Carboprost tromethamine [Hemabate] is available in solution (250 mcg/mL) for IM administration. For *induction of abortion* (weeks 13 to 20), the dosage is 250 mcg initially followed by 250 mcg every 1.5 to 3.5 hours as needed. For *control of postpartum bleeding*, a single 250-mcg dose is injected.

Misoprostol. Misoprostol [Cytotec] is available in 100- and 200-mcg tablets. For induction of abortion in the *first trimester*, misoprostol is used in combination with mifepristone or methotrexate (see above for dosages and routes of administration); dosing options for misoprostol include 400 mcg PO and 800 mcg vaginally. For induction of abortion in the *second trimester*, the dosage is 200 mcg administered vaginally every 6 to 12 hrs until abortion occurs.

KEY POINTS

- The most effective methods of birth control are etonogestrel subdermal implants [Nexplanon], intramuscular medroxyprogesterone acetate [Depo-Provera], IUDs, and sterilization. OCs and transdermal patches are a close second.
- Sterilization is the most common form of birth control. OCs and male condoms come next.
- A long-term method of birth control (eg, Nexplanon, Depo-Provera, IUD) is a good choice when adherence is a problem.
- There are two main categories of OCs: (1) combination OCs, which contain an estrogen plus a progestin, and (2) progestin-only OCs, aka minipills.
- Almost all combination OCs use the same estrogen: ethinyl estradiol. In contrast, eight different progestins are employed.
- Combination OCs act primarily by inhibiting ovulation.
- Although combination OCs can cause a variety of adverse effects, serious events are rare.
- Thrombotic events with combination OCs are caused by the progestin as well as the estrogen.
- The risk of thrombotic events is lowest with combination OCs that (1) have a low dose of estrogen and (2) contain a first-generation progestin. Conversely, risk is high with OCs that contain drospirenone or desogestrel.
- The risk of thrombotic events is increased in women who smoke and in those with thrombophilias.
- When used by nonsmoking women with normal cardiovascular function, OCs produce no greater mortality than other active forms of birth control.
- Combination OCs *protect* against ovarian and endometrial cancer, and do *not* increase the risk of breast cancer.
- OCs are contraindicated during pregnancy, not because they are dangerous, but because they have no legitimate use during pregnancy. If accidental pregnancy occurs, OCs should be discontinued.

- The efficacy of OCs can be reduced by agents that induce hepatic drug-metabolizing enzymes (eg, rifampin, phenobarbital, St. John's wort).
- Because they lack estrogen, progestin-only OCs are safer than combination OCs—but are less effective and cause more menstrual irregularity.
- Progestin-only OCs prevent pregnancy by causing production of thick, sticky mucus (which creates a barrier to migration of sperm) and by suppressing endometrial growth (which discourages nidation).
- Subdermal etonogestrel implants [Nexplanon] are active for 3 years, and are among the most effective contraceptives available.

- Nexplanon has the same mechanism as progestin-only pills: production of thick, sticky mucus and involution of the endometrium.
- Injectable medroxyprogesterone acetate [Depo-Provera] is active for 3 months, and is one of the most effective contraceptives available.
- Depo-Provera prevents pregnancy mainly by suppressing ovulation. In addition, it thickens cervical mucus and alters the endometrium such that nidation is discouraged.

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Summary of Major Nursing Implications*

COMBINATION ORAL CONTRACEPTIVES

Preadministration Assessment

Therapeutic Goal

Prevention of unwanted pregnancy.

Baseline Data

Assess for a history of hypertension, diabetes, thrombophlebitis, thromboembolic disorders, cerebrovascular disease, coronary artery disease, breast carcinoma, estrogen-dependent neoplasm, and benign or malignant liver tumors.

Identifying High-Risk Patients

Absolute contraindications to OC use are thromboembolic disorders, cerebrovascular disease, coronary occlusion, abnormal liver function, known or suspected breast carcinoma, undiagnosed abnormal genital bleeding, known or suspected pregnancy, and smokers older than 35. *Relative contraindications* are diabetes, hypertension, cardiac disease, history of cholestatic jaundice of pregnancy, gallbladder disease, uterine leiomyoma, epilepsy, and migraine.

Women anticipating elective surgery in which postoperative immobilization increases the risk of thrombosis should stop OCs prior to surgery.

Implementation: Administration

Dosing Schedule

Provide the client with the following dosing instructions:

- Initiate dosing on the first day of menses, or the first Sunday after the onset of menses.
- For most combination OCs, the approved dosing schedule consists of 21 days of active drug followed by 7 days off (for the 7 "off" days, the manufacturer may provide inert tablets, iron-containing tablets, or no tablets).
- For one combination OC—*Loestrin Fe*—the dosing schedule is 26 days of active drug followed by 2 days off.

- For four combination OCs—*Gianvi*, *Beyaz*, *YAZ*, and *Loestrin 24 Fe*—the dosing schedule is 24 days of active drug followed by 4 days off.
- For four extended-cycle OCs—*Introvale*, *Jolessa*, *Quasense*, and *Seasonale*—the dosing schedule is 84 days of active drug followed by 7 days off.
- For two other extended-cycle OCs—*Seasonique* and *LoSeasonique*—the dosing schedule is 84 days of active drug followed by 7 days of using a low-estrogen pill.
- For *Lybrel*, dosing is done continuously.
- For all OCs, take pills at the same time each day (eg, with a meal, at bedtime).

Responding to Missed Doses

For women using a 28-day-cycle combination OC—except *Natazia*—provide the following instructions regarding missed doses:

- If 1 or more pills are missed in the *first week*, take one pill as soon as possible and then continue with the pack. Use an additional form of contraception for 7 days.
- If 1 or 2 pills are missed during the *second or third week*, take one pill as soon as possible and then continue with the active pills in the pack—but skip the placebo pills and go straight to a new pack once all the active pills have been taken.
- If 3 or more pills are missed during the *second or third week*, follow the same instructions given for missing 1 or 2 pills, but use an additional form of contraception for 7 days.

Note: The response to a missed dose of *Natazia* is more complex than with other combination OCs. Consult the package insert for details.

Inform women using an *extended-cycle or continuous OC* that, once the pills have been taken daily for at least 3 weeks, up to 7 days can be missed with little or no increased risk of pregnancy.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Postpartum Use

Inform the client that OCs can be initiated 2 weeks after delivery if breast-feeding is not intended. (For breast-feeding mothers, the progestin-only minipill can be started immediately postpartum.)

Promoting Adherence

Counsel the client about the importance of taking OCs as prescribed. Encourage the client to read the package insert provided with combination OCs.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Thrombotic Disorders. Combination OCs slightly increase the risk of thrombosis and thromboembolism. To minimize the risk of a thrombotic event, (1) use OCs of low estrogen content, (2) avoid OCs that contain drospirenone or desogestrel, (3) avoid OCs in women with known risk factors for thrombotic disorders, and (4) discontinue OCs at least 4 weeks prior to elective surgery in which postoperative thrombosis might be expected. Inform the client about symptoms of thrombosis and thromboembolism (eg, leg tenderness or pain, sudden chest pain, shortness of breath, severe headache, sudden visual disturbance) and instruct her to notify the prescriber if these develop.

Hypertension. Perform periodic determinations of blood pressure. If hypertension is detected, discontinue OCs. Blood pressure usually normalizes. However, for women with chronic hypertension, OCs can be used as long as the blood pressure is normal.

Abnormal Uterine Bleeding. During initial use, combination OCs may cause breakthrough bleeding or spotting. This usually resolves with continued use. Bleeding is less likely with low-estrogen OCs.

Instruct the client to notify the prescriber if two consecutive periods are missed; the possibility of pregnancy must be evaluated.

Instruct the client to notify the prescriber if bleeding irregularities persist; an alternative OC may be tried.

Inform the client that, once OCs are discontinued, menses quickly return to normal.

Use in Pregnancy and Lactation OCs are contraindicated during pregnancy, not because they are dangerous, but because they have no therapeutic role. Pregnancy should be ruled out prior to OC use. Instruct the client to cease OC use if accidental pregnancy should occur.

Inform the client that OCs can reduce milk production early in lactation. Once the milk supply is established, OC use can be resumed.

Glucose Intolerance. OCs can elevate plasma glucose levels. Advise clients with diabetes to monitor blood glucose levels closely; dosage of insulin or oral hypoglycemic medication may need to be increased. Monitor the prediabetic client for hyperglycemia.

Stroke in Women with Migraine. When used by women with migraine, OCs may increase the risk of thrombotic stroke. To minimize risk, OCs should be reserved for

migraineurs who are under age 35, don't smoke, are generally healthy, and have migraine without aura.

Hyperkalemia. Combination OCs that contain *drospirenone* (eg, Yasmin, YAZ) pose a risk of hyperkalemia, and hence should not be used by (1) women with conditions that predispose to hyperkalemia (eg, renal insufficiency, adrenal insufficiency, liver disease) or by (2) women taking drugs that can increase potassium levels (see below).

Minimizing Adverse Interactions

Agents That Reduce OC Levels. Levels of OCs can be reduced by agents that induce hepatic drug-metabolizing enzymes (eg, phenobarbital, phenytoin, troglitazone, rifampin, ritonavir, St. John's wort). Advise women who are taking these agents to be alert for indications of reduced OC levels (eg, breakthrough bleeding, spotting), and to notify the prescriber if these occur. An increase in OC dosage or use of an alternative method of birth control may be required.

Drugs Whose Effects Are Reduced by OCs. OCs can reduce the effects of some drugs, including *warfarin*, *insulin*, and some *oral hypoglycemics*. When combined with OCs, these drugs may require a greater than normal dosage.

Drugs Whose Effects Are Increased by OCs. OCs can increase blood levels of several drugs, including *theophylline* and *imipramine*. Women using these drugs in combination with OCs should be alert for signs of toxicity; dosage reduction for theophylline or imipramine may be required.

Drugs That Elevate Potassium. Drugs that elevate serum potassium (eg, potassium supplements, potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) should be avoided by women using OCs that contain *drospirenone*, which promotes potassium retention.

PROGESTIN-ONLY ORAL CONTRACEPTIVES

Preadministration Assessment

Therapeutic Goal

Prevention of unwanted pregnancy.

Implementation: Administration

Dosing Schedule

Instruct the client to initiate the minipill on day 1 of the menstrual cycle and to take one pill every day thereafter. Pills should be taken at the same time each day (eg, with a meal, at bedtime).

Responding to Missed Doses

Provide the client with the following instructions regarding missed doses:

- If 1 pill is missed, take it as soon as the omission is remembered. Use a backup form of contraception for 2 days.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

- If 2 pills are missed, take 2 pills as soon as the omission is remembered, discard the second pill, and use a backup form of contraception for 2 days.
- If 3 pills are missed, the minipill should be stopped. Do not resume use until menstruation occurs or until pregnancy has been ruled out.

*Patient education information is highlighted as blue text.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Menstrual Irregularities. Breakthrough bleeding, spotting, amenorrhea, inconsistent cycle length, and variations in the amount and duration of monthly flow are common and unavoidable. Forewarn the client of these effects.

Drug Therapy of Infertility

Infertility: Causes and Treatment Strategies

Female Infertility

Male Infertility

Drugs Used to Treat Female Infertility

Drugs for Controlled Ovarian Stimulation

Dopamine Agonists for Hyperprolactinemia

Drugs for Endometriosis

Infertility (subfertility) is defined as a decrease in the ability to reproduce. This contrasts with sterility, which is the complete absence of reproductive ability. About 10% of couples attempting to have children experience infertility. Failure to conceive may be due to reproductive dysfunction of the male partner, the female partner, or both. When medical treatment is implemented, approximately one-half of infertile couples achieve pregnancy. To date, drug therapy of female infertility has been considerably more successful than drug therapy of male infertility.

In treating infertility, the chances of success are greatly enhanced by accurate diagnosis. A thorough history of both partners is essential, including information on frequency and timing of coitus and use of drugs that might lower fertility. Routine evaluation should include a semen analysis, determination of fallopian tube patency, and assessment of ovulation. If the patient reports regular menstrual cycles, ovulation is presumed, and hence there is no need to determine estrogen and progesterone levels.

In this chapter, we discuss infertility in two stages. First, we discuss the underlying causes of reproductive dysfunction. Second, we discuss the fertility-promoting drugs. As preparation to study these agents, you should review Chapter 61 for information on the menstrual cycle and information on the biosynthesis and physiologic and pharmacologic effects of estrogens and progestins. Pay special attention to the roles of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH).

INFERTILITY: CAUSES AND TREATMENT STRATEGIES

Female Infertility

Female infertility can result from dysfunction in all phases of the reproductive process. The most critical phases are follicular maturation, ovulation, transport of the ovum through the fallopian tubes, fertilization of the ovum, nidation (implantation), and growth and development of the conceptus. These events can take place only if the ovaries, uterus, hypothalamus, and pituitary are functioning properly. If the activity of

any of these structures is disturbed, fertility can be impaired. Causes of female infertility that respond to drug therapy are discussed below.

Anovulation and Failure of Follicular Maturation

In the absence of adequate hormonal stimulation, ovarian follicles will not ripen and ovulation will not take place. Frequently, these causes of infertility can be corrected with drugs. The agents used to promote follicular maturation and/or ovulation are *clomiphene*, *menotropins*, *follitropins* (eg, *urofollitropin*), and *human chorionic gonadotropin* (hCG). Clomiphene induces follicular maturation and ovulation by promoting release of FSH and LH from the pituitary; in some cases, induction of ovulation requires co-treatment with hCG. Menotropins and follitropins are used in conjunction with hCG: Menotropins and follitropins act directly on the ovary to promote follicular development; after follicles have matured, hCG is given to induce ovulation. Because hCG acts on mature follicles to cause ovulation, the drug is used only after follicular maturation has been induced with another agent (menotropins, a follitropin, or clomiphene). The pharmacology of clomiphene, menotropins, follitropins, and hCG is discussed below.

Unfavorable Cervical Mucus

In the periovulatory period, the cervical glands normally secrete large volumes of thin, watery mucus. These secretions, which are produced under the influence of estrogen, facilitate passage of sperm through the cervical canal. If the cervical mucus is scant or of inappropriate consistency (thick, sticky), sperm will be unable to pass through to the uterus. Production of unfavorable mucus may occur spontaneously or as a side effect of clomiphene (see below).

Cervical mucus can be restored to its proper volume and consistency by administering estrogen. Two regimens have been employed. In one, ethinyl estradiol is given beginning early in the menstrual cycle (on day 6, 7, or 8) and continued through day 12 or 13; dosages range from 20 to 80 mcg/day. In the other regimen, conjugated estrogens are administered from day 5 through day 15 of the cycle; dosages range from 2.5 to 5 mg/day. When used to counteract the effects of clomiphene on the cervical mucus, estrogens are administered for 10 days beginning 1 day after the last clomiphene dose.

Hyperprolactinemia

Elevation of prolactin levels may be caused by a pituitary adenoma or by disturbed regulation of the healthy pituitary. Amenorrhea, galactorrhea, and infertility may all occur in association with excessive prolactin. The mechanism by which hyperprolactinemia impairs fertility is unknown. Hyperprolactinemia can be treated with *cabergoline*, *bromocriptine*, and other dopamine agonists.

Endometriosis

Endometriosis is a condition in which endometrial tissue has become implanted outside the uterus, usually on the ovaries, pelvic peritoneum, or rectovaginal septum. These endometrial implants respond to hormonal stimulation in much the same way as the normally situated endometrium. Endometriosis affects about 5.5 million women in the United States and Canada, and is a common cause of infertility. When pregnancies do occur, the rate of spontaneous abortion is high (about 50%).

The mechanism by which endometriosis reduces fertility is not always clear. In some cases, infertility results from ovarian or tubal adhesions that impede transport of the ovum. However, when endometriosis is mild, a visible cause of infertility may be absent.

Endometriosis can be treated with surgery, drugs, or both. Surgery reduces symptoms of endometriosis and increases fertility. In contrast, although drugs can reduce discomfort, they do not enhance fertility. First-line agents for pain relief are *nonsteroidal anti-inflammatory drugs* (NSAIDs) and *combination oral contraceptives*. *Gonadotropin-releasing hormone agonists*—leuprolide and nafarelin—are also effective, but can't be used long term owing to side effects, especially osteoporosis and hot flashes.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a combined endocrine-metabolic disorder characterized by androgen excess and insulin resistance. Symptoms include irregular periods, anovulation, infertility, acne, and hirsutism. About 50% of patients are obese. PCOS increases the risk for diabetes, hyperlipidemia, hypertension, and cancer of the ovaries and endometrium. The syndrome was first described in a woman whose ovaries were enlarged and covered with multiple fluid-filled cysts. However, the presence of cysts is not required for a positive diagnosis. Hence the disease name can be misleading. PCOS is the most common endocrine disorder in young women, affecting 5% to 7% of women of reproductive age.

PCOS can be treated with lifestyle changes and drugs. The goal is to restore regular menstruation and ovulation, reverse hyperandrogenism (and thereby eliminate acne and hirsutism), and decrease the long-term risk of diabetes, cancer, and heart disease. Treatment options include the following:

- *Weight loss*, through exercise and diet, can reduce insulin and androgen levels, improve insulin sensitivity, restore menstruation and ovulation, and increase pregnancy rates.
- *Clomiphene* [Clomid, Milophene, Serophene] is considered a first-line drug for inducing ovulation. It may be used alone or in combination with metformin.
- *Metformin* [Glucophage, others], a drug for type 2 diabetes, increases insulin sensitivity and decreases insulin levels, which, through an indirect mechanism, lowers androgen levels. The net result is improved glucose tolerance, improved ovulation, and increased pregnancy rates.
- *Pioglitazone* [Actos], another drug for type 2 diabetes, acts like metformin, causing an increase in insulin sensitivity, and a decrease in insulin levels and androgen levels. However, pioglitazone can harm the fetus, and hence should not be used by women trying to become pregnant.
- *Oral contraceptives* can restore regular periods and reduce acne and hirsutism, but obviously won't improve fertility.

- *Spirolactone* has antiandrogenic actions, and can thereby decrease hirsutism and acne. The drug can harm the fetus, and hence must not be used during pregnancy.

Male Infertility

For about 50% of infertile couples, failure to conceive is due entirely to reproductive dysfunction in the male. The most common cause is decreased density or motility of sperm, or semen of abnormal volume or quality. The most obvious cause is erectile dysfunction (ED). In most cases, infertility in males is not associated with an identifiable endocrine disorder. Unfortunately, with the exception of ED, male infertility is generally unresponsive to drugs.

Hypogonadotropic Hypogonadism

A few males may be incapable of spermatogenesis owing to insufficient gonadotropin secretion. In these rare cases, drugs may help. If the gonadotropin deficiency is only partial, sperm counts can be increased using hCG (alone or in combination with menotropins). If the deficiency is severe, treatment with androgens is required (see Chapter 65). If therapy with hCG and menotropins is intended, the patient should be informed that treatment will be both prolonged (3 to 4 years) and expensive.

Erectile Dysfunction

Inability to achieve erection is the most conspicuous cause of male infertility. Sildenafil [Viagra] and other drugs for ED are discussed in Chapter 66.

Idiopathic Male Infertility

Idiopathic infertility is defined as infertility for which no cause can be identified. About 25% to 40% of male infertility is idiopathic. Since the cause is unknown, specific drug therapy is impossible. Accordingly, treatment is empiric (trial and error). Several drugs, including androgens, clomiphene, and hCG, have been administered in hopes of improving idiopathic infertility in males. However, success is rare.

DRUGS USED TO TREAT FEMALE INFERTILITY

Drugs for Controlled Ovarian Stimulation

The term *controlled ovarian stimulation* refers to the use of drugs to facilitate follicular maturation and ovulation. Following ovulation, fertilization can be accomplished either naturally (through sexual intercourse) or through assisted reproduction technology (eg, *in vitro* fertilization). Of the drugs discussed below, six are used to promote follicular maturation, two are used to stimulate ovulation, and two are used to prevent premature stimulation of ovulation by endogenous hormones (Table 63-1).

Clomiphene

Therapeutic Use. Clomiphene [Clomid, Milophene, Serophene] is used to promote follicular maturation and ovulation in selected infertile women.

Mechanism of Fertility Promotion. Clomiphene blocks receptors for estrogen. Receptor blockade in the hypothalamus and pituitary makes it appear to these structures that es-

TABLE 63-1 ■ Drugs for Controlled Ovarian Stimulation

Generic Name	Trade Name	Mechanism of Action
Drugs That Promote Follicular Maturation		
Clomiphene	Clomid, Milophene, Serophene	Clomiphene blocks estrogen receptors in the hypothalamus and pituitary, and thereby causes a compensatory increase in the release of LH and FSH, which then act on the ovary to promote follicular maturation (and possibly ovulation).
Menotropins	Repronex, Menopur	Menotropins is a 50:50 mixture of FSH and LH that acts on the ovary to promote follicular maturation. Treatment is followed by hCG to induce ovulation.
Follitropins		Follitropins are preparations of FSH that act on the ovary to promote follicular maturation. Treatment is followed by hCG to induce ovulation.
Follitropin alfa	Gonal-F	
Follitropin beta	Follistim AQ, Puregon*	
Urofollitropin	Bravelle	
Lutropin alfa	Luveris	Lutropin alfa is a recombinant form of LH used in combination with follitropin alfa [Gonal-F] to promote follicular maturation. Treatment is followed by hCG to induce ovulation.
Drugs That Stimulate Ovulation		
Human chorionic gonadotropin (hCG)	Choron 10, Gonic, Novarel, Pregnyl, Profasi	hCG is similar in structure and identical in action to LH. The drug acts on the ovary to induce ovulation.
Choriogonadotropin alfa	Ovidrel	Choriogonadotropin is a recombinant form of hCG that acts on the ovary to induce ovulation.
Drugs That Prevent Premature Ovulation		
Ganirelix	Generic only	These drugs are GnRH antagonists that block endogenous release of LH, and thereby prevent possible premature ovulation in women receiving drugs to promote follicular maturation.
Cetrorelix	Cetrotide	

trogen levels are low. In response, the pituitary increases secretion of gonadotropins (LH and FSH), and these hormones then stimulate the ovary, promoting follicular maturation and ovulation. In properly selected patients, the ovulation rate is about 90%. Because of its mechanism, clomiphene can induce ovulation only if the pituitary is capable of producing LH and FSH, and only if the ovaries are capable of responding. Success is impossible in women with primary pituitary or ovarian failure. Accordingly, pituitary and ovarian function should be verified prior to clomiphene therapy. If treatment produces follicular maturation but ovulation fails to occur, it may be possible to induce ovulation by adding hCG to the regimen (see below).

Monitoring. Effects on the ovary can be monitored with serial ultrasound exams. When treatment is successful, the scans will show progressive follicular enlargement, followed by conversion of the follicle to a corpus luteum after ovulation occurs.

Adverse Effects. Common side effects include hot flushes (similar to the vasomotor responses of menopause), nausea, abdominal discomfort, bloating, and breast engorgement. Some patients experience visual disturbances (blurred vision, visual flashes), which usually reverse following drug

withdrawal. Multiple births (usually twins) occur in 8% to 10% of clomiphene-facilitated pregnancies. Patients should be told of this possibility.

Very rarely, clomiphene can cause ovarian hyperstimulation. Symptoms include low abdominal pain, pressure, weight gain, and swelling. Hyperstimulation can be minimized by avoiding unnecessarily large doses. If undue ovarian enlargement occurs, clomiphene use should cease. The ovaries will then regress to normal size.

Some actions of clomiphene may *interfere* with conception. Luteal-phase defect may be induced, but can be corrected by giving progesterone. Because it has antiestrogenic actions, clomiphene may force the production of scant and viscous cervical mucus; estrogen therapy can render cervical secretions more hospitable to sperm.

Clomiphene should be avoided during pregnancy. Although no human fetal defects have been reported, clomiphene has produced developmental abnormalities in animals.

Preparations, Dosage, and Administration. Clomiphene [Clomid, Milophene, Serophene] is supplied in 50-mg oral tablets. The initial course of treatment consists of 50 mg once daily for 5 days. If cyclic menstrual bleeding has been occurring, therapy should begin on the fifth day after the onset of menses. If menstruation has been absent, dosing can start any

time (assuming pregnancy has been ruled out). If the first course of treatment fails to induce ovulation, a second 5-day course (using 100 mg/day) may be tried. The second course may begin as early as 30 days after the previous one. Doses may be increased in subsequent courses. However, doses above 100 mg/day are rarely needed. Once a dose that induces ovulation has been established, that dose should be used for a maximum of three cycles. If pregnancy has not occurred, further treatment is unlikely to succeed. When ovulation does occur, it is usually within 5 to 10 days after the last clomiphene dose; patients should be instructed to have coitus at least every other day during this interval.

Menotropins

Menotropins [Repronex, Menopur]—also known as human menopausal gonadotropin, or hMG—consists of equal amounts of LH and FSH activity. Commercial menotropins is prepared by extraction from the urine of postmenopausal women.

Therapeutic Actions and Uses. Anovulatory Women. Menotropins, in conjunction with hCG, is used to promote follicular maturation and ovulation in anovulatory patients. Menotropins acts directly on the ovaries to cause maturation of follicles. Once follicles have ripened, hCG is given to induce ovulation.

Menotropins is employed when gonadotropin secretion by the pituitary is insufficient to provide adequate ovarian stimulation. Candidates must have ovaries capable of responding to FSH and LH; menotropins is of no help in women with primary ovarian failure. Among properly selected patients, the rate of ovulation approaches 100%. It should be noted that menotropins is very expensive.

Ovulatory Women. Menotropins can be used to induce development of multiple follicles in ovulatory women participating in an *in vitro* fertilization program.

Men. Menotropins has been used off-label to promote spermatogenesis in males with primary or secondary hypogonadotropic hypogonadism.

Adverse Effects. The most serious adverse response is *ovarian hyperstimulation syndrome*, a condition characterized by sudden enlargement of the ovaries. Mild to moderate ovarian enlargement is common, occurring in about 20% of patients. This condition is benign and resolves spontaneously after discontinuing drug use. Of greater concern is ovarian enlargement that occurs rapidly and that may be accompanied by ascites, pleural effusion, and considerable pain. If this manifestation of ovarian stimulation occurs, menotropins should be withdrawn and the patient hospitalized. Treatment is usually supportive (bed rest, analgesics, fluid and electrolyte replacement). Paracentesis can be used to remove some excess ascitic fluid. If rupture of ovarian cysts occurs, surgery may be required to stop bleeding. Enlargement of the ovaries is most likely during the first 2 weeks of treatment. To ensure early detection, the patient should be examined at least every other day while taking menotropins, and for 2 weeks after stopping. Ovarian stimulation can be minimized by keeping the dosage as low as possible.

Pregnancies facilitated by menotropins often result in *multiple births*: 15% of pregnancies result in twins, and 5% of pregnancies result in three or more babies.

Monitoring Therapy. Ovarian responses to menotropins must be monitored to determine timing of hCG administration and to minimize the risk of ovarian enlargement. Responses can be monitored by ultrasonography of the developing follicles and by measuring serum estrogen. When ultrasonography

indicates that follicles have enlarged to 6 to 20 mm and when serum estrogen is 200 pg/mL per maturing follicle, then menotropins administration should cease and hCG should be injected.

Preparations, Dosage, and Administration. Menotropins [Repronex, Menopur] is supplied as a powder or pellet to be reconstituted immediately prior to use. Ampules of menotropins contain either (1) 75 international units (IU) of FSH activity plus 75 IU of LH activity or (2) 150 IU of FSH activity plus 150 IU of LH activity. Repronex is administered subQ or IM; Menopur is administered subQ.

Menotropins is used sequentially with hCG: After follicular maturation has been induced with menotropins, hCG is injected to promote ovulation. For the initial cycle, the contents of 1 menotropins ampule are injected daily for 9 to 12 days. When estrogen measurements indicate follicular maturation has occurred, menotropins is discontinued; hCG (5000 to 10,000 USP units) is injected 24 hours after the last menotropins dose. Ovulation occurs 2 to 3 days after injecting hCG. Accordingly, patients should be instructed to have intercourse on the evening before hCG injection and on the following 2 to 3 days. If there is evidence of ovulation but conception does not take place, treatment should be repeated for two more courses using the same menotropins dosage. If treatment remains ineffective, two additional courses may be tried, using twice as much menotropins as previously. If there is still no conception, further treatment is unlikely to help.

Follitropins

Description. Three follitropins are available: *urofollitropin* [Bravelle], *follitropin alfa* [Gonal-F], and *follitropin beta* [Follistim AQ, Puregon]. All three are preparations of FSH. Urofollitropin is a highly purified preparation of FSH extracted from the urine of postmenopausal women. Follitropin alfa and follitropin beta are produced by recombinant DNA technology. A long-acting preparation—*corifollitropin alfa* [Elonva]—is available in Europe, but not in the United States or Canada.

Use in Women. The actions, uses, and adverse effects of the follitropins are much like those of menotropins (a 50:50 mixture of FSH and LH). Like menotropins, the follitropins act directly on the ovary to stimulate follicle maturation. All three follitropins are employed to stimulate ovulation in anovulatory women, and to promote production of multiple follicles in ovulatory women participating in an *in vitro* fertilization program. For both indications, the follitropins are used sequentially with hCG: The follitropin is given first to promote follicle maturation; then hCG is given to stimulate ovulation. As with menotropins, multiple births are relatively common. The principal adverse effect of the follitropins is ovarian hyperstimulation syndrome. All of the follitropins are administered subQ; follitropin beta may also be given IM.

Use in Men. One agent—*follitropin alfa*—is approved for promoting spermatogenesis in males with primary or secondary hypogonadotropic hypogonadism.

Lutropin Alfa

Lutropin alfa [Luveris] is a recombinant form of LH. The drug is approved for combined use with follitropin alfa [Gonal-F] to promote follicular maturation in infertile, hypogonadotropic, hypogonadal women with profound LH deficiency. Following treatment with lutropin alfa/follitropin alfa, hCG is injected to induce ovulation. Adverse effects of the combination include headache, abdominal pain, nausea, breast pain, ovarian enlargement, and ovarian hyperstimulation syndrome.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a polypeptide hormone produced by the placenta. hCG is similar in structure and identical in action to luteinizing hormone.

Therapeutic Use. hCG is used to promote follicular maturation and ovulation in women who are infertile because of ovulatory failure. The drug causes ovulation by simulating the midcycle LH surge. When hCG is used to promote ovulation, follicular maturation must first be induced with another agent, usually menotropins. hCG can also be used in conjunction with clomiphene when treatment with clomiphene alone has failed to produce ovulation.

Adverse Effects. The most severe adverse response to hCG is *ovarian hyperstimulation syndrome*. If this occurs, hospitalization and discontinuation of hCG are indicated.

hCG may also provoke *rupture of ovarian cysts* with resultant bleeding into the peritoneal cavity. Additional adverse effects include edema, injection-site pain, and central nervous system disturbances (headache, irritability, restlessness, fatigue).

Preparations, Dosage, and Administration. Commercial hCG is prepared by extraction from the urine of pregnant women. hCG is supplied as a powder that must be reconstituted for use. Administration is by IM injection. The usual dose for induction of ovulation is 5000 to 10,000 USP units. Trade names are *Choron 10*, *Gonic*, *Novarel*, *Pregnyl*, and *Profasi*.

Prior to giving hCG, follicular maturation must be induced with another agent (clomiphene, menopins, or a follitropin). When used in conjunction with clomiphene, hCG is administered 7 to 9 days after the last clomiphene dose. When used in conjunction with menopins or a follitropin, hCG is injected 1 day after the last menopins or follitropin dose.

Choriogonadotropin Alfa

Choriogonadotropin alfa [Ovidrel] is a form of hCG produced by recombinant DNA technology. The drug's physicochemical, immunologic, and biologic activities are equivalent to those of naturally occurring hCG, produced by extraction from the urine of pregnant women. However, unlike urine-derived hCG, which must be injected IM, choriogonadotropin alfa is injected subQ. As a result, administration is more comfortable (IM injections can be painful). Choriogonadotropin alfa has two indications. First, like natural hCG, the drug is given to *trigger ovulation* in women who are infertile owing to anovulation. Second, the drug is used to *promote late follicular maturation and early luteinization* in women undergoing assisted reproductive technology (eg, *in vitro* fertilization). For both indications, follicular maturation must first be induced with a follicle-stimulating agent (eg, menopins). Choriogonadotropin alfa (250 mcg) is then given as a single subQ injection 1 day after the last dose of the follicle-stimulating agent. Major adverse effects are the same as those of natural hCG: ovarian hyperstimulation syndrome, rupture of ovarian cysts, and multiple births.

Gonadotropin-Releasing Hormone Antagonists

Gonadotropin-releasing hormone (GnRH) antagonists are used to prevent a premature surge of endogenous LH in women undergoing controlled ovarian stimulation (with menopins or follitropin [FSH]). As discussed above, after follicles have matured under the influence of exogenous menopins or FSH, the patient is given an injection of hCG (LH) to cause ovulation. However, in some women, the natural midcycle LH surge occurs early, causing ovulation before the eggs have fully matured. As a result, the chances of successful conception and implantation are reduced. The GnRH antagonists prevent LH release, and thereby eliminate the chance of premature ovulation.

Two GnRH antagonists are available: *ganirelix* (generic only) and *cetrorelix* [Cetrodite]. Both drugs block GnRH receptors, and thereby prevent GnRH from promoting the production and release of LH from the pituitary. Various dosing schedules are employed. One option for either drug is to give 250 mcg subQ daily, beginning in the early follicular phase and continuing until the day of hCG administration. Injections are made by the patient into the upper thigh or the region around the navel.

Dopamine Agonists for Hyperprolactinemia

Two dopamine agonists—cabergoline and bromocriptine—are approved for hyperprolactinemia. Both drugs are derivatives of ergot, an alkaloid found in plants. Cabergoline is better tolerated than bromocriptine, and dosing is more convenient. Accordingly, cabergoline is preferred.

Cabergoline

Therapeutic Use. Cabergoline, formerly available as Dostinex, is used to correct amenorrhea and infertility associated with excessive prolactin secretion. If galactorrhea is present, this consequence of hyperprolactinemia may also be corrected. When the source of excessive prolactin is a pituitary adenoma, cabergoline can induce tumor regression. Effects on prolactin begin within hours of dosing and persist about 14 days. To monitor treatment, prolactin should be measured monthly until the level is normal (below 20 pg/mL).

In addition to its use in hyperprolactinemia, cabergoline is used in Parkinson's disease, although the drug is not approved for this disorder.

Mechanism of Fertility Promotion. Cabergoline is a dopamine receptor agonist. By activating dopamine receptors in the anterior pituitary, cabergoline inhibits prolactin secretion. The result is normalization of the menstrual cycle and a return of fertility. The mechanism by which reducing prolactin levels leads to a return of ovulation is unknown.

Pharmacokinetics. Administration is oral, and absorption is not affected by food. Plasma levels peak 2 to 3 hours after dosing, but absolute bioavailability is unknown. Cabergoline undergoes extensive hepatic metabolism followed by excretion in the urine and feces. The elimination half-life is prolonged, about 65 hours. In patients with severe hepatic impairment, cabergoline levels may rise.

Adverse Effects. The most common adverse effects are nausea (29%), headache (26%), and dizziness (17%). Orthostatic hypotension may occur, but is rare at recommended doses. Adverse effects can be minimized by initiating treatment at low doses. Like other ergot derivatives, cabergoline may pose a risk of valvular heart damage.

Preparations, Dosage, and Administration. Cabergoline is supplied in 0.5-mg tablets. The initial dosage is 0.25 mg twice a week, administered with or without food. Dosage may be increased in 0.25-mg increments to a maximum of 1 mg twice a week. At least 4 weeks should separate each rise in dosage. After prolactin has been maintained at a normal level for at least 6 months, treatment can stop.

Bromocriptine

Actions and Therapeutic Uses. Like cabergoline, bromocriptine [Parlodel] activates dopamine receptors in the pituitary, and can thereby reduce prolactin secretion. As a result, it can correct amenorrhea, galactorrhea, and infertility. If hyperprolactinemia is caused by a pituitary adenoma, bromocriptine can induce regression of the tumor (in addition to reducing prolactin secretion). Continuous treatment can suppress tumor growth for years. Bromocriptine is also used in Parkinson's disease (see Chapter 21).

Adverse Effects. When bromocriptine is used for infertility, adverse effects are frequent but usually mild. Nausea occurs in 50% of patients. Headache, dizziness, fatigue, and abdominal cramps are also common. Orthostatic hypotension may occur, but is rare at the doses employed. Teratogenic effects have not been reported. Adverse effects can be minimized by taking bromocriptine with meals and initiating treatment at low doses. Like cabergoline and other ergot derivatives, bromocriptine may pose a risk of valvular heart injury.

Preparations, Dosage, and Administration. Bromocriptine mesylate is supplied in 2.5-mg tablets and 5-mg capsules. Dosing is begun at 2.5 mg once a day and then gradually increased to 2.5 mg 2 or 3 times a day. All doses should be administered with food. Normalization of the menstrual cycle may occur rapidly (within a few days) or may require up to 2 months of treatment. As soon as pregnancy is achieved, use of bromocriptine should cease. As a rule, administration should not resume until after delivery. If treatment is not reinstated, hypersecretion of prolactin is almost certain to recur within a year.

Drugs for Endometriosis

As noted above, the first-line drugs for pain of endometriosis are NSAIDs (eg, ibuprofen) and combination oral contraceptives, usually taken cyclically. The NSAIDs are discussed in Chapter 71. The oral contraceptives are discussed in Chapter 62. The drugs discussed below—GnRH agonists and danazol—cause regression of endometrial implants. Both are considered second- or third-line treatments.

GnRH Agonists

Leuprolide and nafarelin are synthetic analogs of GnRH. Both drugs are used to relieve pain of endometriosis. However, although they can reduce symptoms, they do not increase fertility. In the United States, leuprolide is used more widely than nafarelin.

Leuprolide. Therapeutic Uses. Leuprolide [Lupron Depot, Eligard] is a GnRH analog with several approved uses. In addition to endometriosis,

the drug is indicated for uterine fibroids, central precocious puberty, and advanced prostate cancer (see Chapter 103). Discussion here is limited to treatment of endometriosis.

Mechanism of Action. Like the normal endometrium, ectopic endometrial implants are dependent on ovarian hormones. Leuprolide suppresses endometriosis by indirectly suppressing ovarian hormone production. How? Initial doses actually increase hormone production. Why? Because leuprolide, like endogenous GnRH, acts on the pituitary to promote release of FSH and LH, which in turn act on the ovary to stimulate hormone production. However, in contrast to endogenous GnRH, which has a short half-life and is released in a *pulsatile* fashion, leuprolide has a long half-life and blood levels remain steady. As a result, leuprolide causes continuous activation of pituitary GnRH receptors, which has the paradoxical effect of *suppressing* FSH and LH release, thereby depriving the ovary of the stimulation needed for hormone production. By decreasing production of ovarian hormones, the drug reduces the area of endometriosis and improves symptoms. It must be stressed that leuprolide does not produce cure. Within 6 months after the drug is withdrawn, symptoms return in up to 50% of women who had previously been rendered symptom free.

Adverse Effects. Most undesired effects are secondary to estrogen deficiency. Common responses include hot flushes, vaginal dryness, decreased libido, mood changes, and headache. Nasal irritation also occurs (with administration by nasal spray). Leuprolide is teratogenic and must not be used during pregnancy.

The adverse effect of greatest concern is *bone loss*. After 3 to 6 months of treatment, bone mass and mineral content may decrease. To minimize the risk of osteoporosis, the manufacturer recommends that treatment last no more than 6 months.

Preparations, Dosage, and Administration. For treatment of endometriosis, a depot formulation is used. Dosing consists of either 3.75 mg IM once a month or 11.25 mg IM every 3 months. As noted, treatment should stop after 6 months.

Nafarelin. Like leuprolide, nafarelin [Synarel] is a GnRH analog that can reduce symptoms of endometriosis, but does not improve fertility. Nafarelin has the same mechanism as leuprolide (suppression of LH and FSH release) as well as the same adverse effects (hot flushes, vaginal dryness, amenorrhea, headache, depression, osteoporosis). Nafarelin is supplied as a nasal spray. (The drug cannot be given orally owing to rapid degradation by

GI enzymes.) The initial dosage is 200 mcg (1 spray) in the morning and evening. Doses should alternate between nostrils. Treatment should begin between days 2 and 4 of the menstrual cycle.

Danazol

Therapeutic Use. Danazol can improve symptoms of endometriosis, but does not increase fertility. Treatment leads to complete regression of endometrial implants in the majority of patients. However, implants will eventually recur after treatment stops. In addition to the therapy of endometriosis, danazol has been used to treat *angioneurotic edema* and *fibrocystic breast disease*. Since the introduction of nafarelin and leuprolide, use of danazol for endometriosis has sharply declined. Today, the drug is given only when nafarelin and leuprolide are contraindicated.

Mechanism of Action. Danazol acts by multiple mechanisms to induce regression of endometrial implants. First, the drug inhibits several of the enzymes needed to synthesize ovarian hormones, and thereby deprives the implant of the hormonal environment it needs for maintenance. Second, danazol suppresses secretion of pituitary gonadotropins (FSH and LH), and thereby further decreases the availability of ovarian hormones. Lastly, danazol may act directly on the implant to block ovarian hormone receptors. All of these actions result in atrophy of ectopic endometrial tissue. The normal endometrium atrophies as well.

Adverse Effects and Interactions. Danazol is weakly androgenic and may induce virilization. Potential manifestations include acne, deepening of the voice, and growth of facial hair. These effects usually reverse after treatment stops. Danazol may also cause edema, and therefore should be used with caution in patients with cardiac and renal disorders. Thrombotic events have been reported, including fatal strokes. Liver impairment may also occur, and hence liver function should be assessed at baseline and periodically thereafter. Danazol may intensify the anticoagulant effects of warfarin. Lastly, the drug can masculinize the female fetus, and hence is contraindicated during pregnancy.

Preparations, Dosage, and Administration. Danazol is supplied in capsules (50, 100, and 200 mg) for oral use. A dosage of 200 to 300 mg twice daily is usually effective. To ensure that danazol is not taken during pregnancy, therapy should be initiated at the time of menstruation. The usual course of treatment is 3 to 9 months.

KEY POINTS

- Infertility (subfertility) is defined as a decrease in reproductive ability, whereas sterility is a complete absence of reproductive ability.
- Infertility in a couple may result from infertility in the male partner, the female partner, or both.
- Clomiphene is used to promote follicular maturation and ovulation.
- Clomiphene acts by blocking estrogen receptors in the hypothalamus and pituitary, causing a compensatory increase in the release of LH and FSH, which then act on the ovary to promote follicular maturation and ovulation.
- Menotropins is a 50:50 mixture of LH and FSH.
- Menotropins is used sequentially with hCG: Menotropins is given to promote follicular maturation, then hCG is given to promote ovulation.
- The most serious adverse effect of menotropins is ovarian hyperstimulation syndrome, characterized by sudden enlargement of the ovaries.
- hCG is given to stimulate ovulation (after another agent, such as menotropins, has been given to promote follicular maturation).
- Like menotropins, hCG can cause ovarian hyperstimulation syndrome.
- Cabergoline is a dopamine agonist used to suppress excessive prolactin release.
- Two GnRH agonists—leuprolide and nafarelin—can promote regression of endometrial implants, but these drugs will not increase fertility.

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Summary of Major Nursing Implications*

CLOMIPHENE

The implications summarized here apply only to the use of clomiphene for promoting maturation of ovarian follicles and ovulation. (Clomiphene has also been used investigatively to increase fertility in males.)

Preadministration Assessment

Therapeutic Goal

Promotion of follicular maturation and ovulation in carefully selected patients.

Baseline Data

Take a complete health and gynecologic history, and assess for tubal patency. Ovarian and pituitary function must be confirmed. Pregnancy must be ruled out.

Identifying High-Risk Patients

Clomiphene is *contraindicated* during pregnancy and in women with liver disease or abnormal uterine bleeding of undetermined origin.

Implementation: Administration

Route

Oral.

Administration Schedule

If cyclic menstrual bleeding has been occurring, begin therapy 5 days after the onset of menses. If menstruation has been absent, begin any time.

The initial course consists of 50 mg once daily for 5 days. If ovulation fails to occur, additional courses may be tried, each beginning no sooner than 30 days after the previous course.

Implementation: Measures to Enhance Therapeutic Effects

Timing of Coitus

Advise the couple to have coitus at least every other day during the 5- to 10-day period that follows the last clomiphene dose.

Adjunctive Use of hCG

If ovulation fails to occur under the influence of clomiphene alone, injecting hCG 7 to 9 days after the last clomiphene dose may bring success.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor treatment with serial ultrasound exams of the ovary. Success is indicated by progressive follicular enlargement followed by conversion of the follicle to a corpus luteum.

Minimizing Adverse Effects

Ovarian Enlargement. Instruct the patient to notify the prescriber if pelvic pain occurs (an indication of ovarian enlargement). If ovarian enlargement is diagnosed, clomi-

phene should be withdrawn, after which ovarian size usually regresses spontaneously.

Reduced Fertility. Clomiphene may cause luteal-phase defect, which can be corrected with progesterone. Alteration of cervical mucus may occur; estrogens can be used to restore the volume and fluidity of cervical secretions.

Multiple Births. Inform the couple that multiple births (usually twins) are not uncommon in clomiphene-facilitated pregnancies.

Visual Disturbances. Forewarn the patient about possible visual disturbances (blurred vision, visual flashes), and instruct her to notify the prescriber if these occur. Visual aberrations usually cease following drug withdrawal.

Other Adverse Effects. Common side effects include hot flushes (similar to the vasomotor responses of menopause), nausea, abdominal discomfort, bloating, and breast engorgement. Inform the patient about these effects, and instruct her to notify the prescriber if they are especially disturbing.

MENOTROPINS

The implications summarized here refer only to the use of menotropins (together with hCG) for induction of follicular maturation and ovulation. (Menotropins is also used to treat infertility in males.)

Preadministration Assessment

Therapeutic Goal

Induction of follicular maturation and ovulation (in conjunction with hCG) in carefully selected patients.

Baseline Data

A thorough gynecologic and endocrinologic evaluation should precede treatment. Ovarian function must be verified. Obtain a baseline value for serum estrogen.

Identifying High-Risk Patients

Menotropins is *contraindicated* in the presence of pregnancy, primary ovarian failure, thyroid dysfunction, adrenal dysfunction, ovarian cysts, and ovarian enlargement (other than that caused by polycystic ovary syndrome).

Implementation: Administration

Route

Intramuscular.

Administration

Reconstitute powdered menotropins with sterile saline immediately prior to injection.

Menotropins is employed sequentially with hCG. Administer menotropins for 9 to 12 days (to promote follicular maturation). Twenty-four hours after the last dose, inject hCG. Ovulation follows in 2 to 3 days.

Ultrasonography and serum estrogen level are used to assess follicular maturation. Upon follicular maturation, menotropins is discontinued and hCG is injected.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Implementation: Measures to Enhance Therapeutic Effects

Timing of Coitus

Advise the couple to have intercourse on the evening before hCG injection and on the following 2 to 3 days (ie, during the probable period of ovulation).

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Ovarian Hyperstimulation Syndrome. Rapid ovarian enlargement can occur, sometimes associated with pain, ascites, pleural effusion, and shortness of breath. If ovarian enlargement is excessive, discontinue menotropins and hospitalize the patient. Treatment is supportive (bed rest, analgesics, fluid and electrolyte replacement). Paracentesis can be used to remove excess ascitic fluid. If ovarian cysts rupture, surgery may be required to stop bleeding. To ensure early detection of ovarian enlargement, the patient should be examined at least every other day during menotropins use, and for 2 weeks after dosing stops.

Other Adverse Effects. Inform the couple that multiple births are relatively common in menotropins-facilitated pregnancies.

HUMAN CHORIONIC GONADOTROPIN

The implications summarized here apply only to the use of hCG in the treatment of female infertility.

Preadministration Assessment

Therapeutic Goal

Induction of ovulation in women who are infertile because of anovulation. Pretreatment with menotropins, urofollitropin, or clomiphene is required.

Implementation: Administration

Route

Intramuscular.

Administration

hCG must be used in conjunction with menotropins, a follitropin, or clomiphene. When used with menotropins or a follitropin, hCG is injected 1 day after the last menotropins dose. When used with clomiphene, hCG is administered 7 to 9 days after the last clomiphene dose.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Ovarian Hyperstimulation Syndrome. See *Minimizing Adverse Effects* for menotropins.

CABERGOLINE

Preadministration Assessment

Therapeutic Goal

Treatment of female infertility occurring secondary to hyperprolactinemia.

Identifying High-Risk Patients

Cabergoline should be used with *caution* in patients with severe hepatic insufficiency.

Implementation: Administration

Route

Oral.

Administration

Instruct patients to take cabergoline twice a week, with or without food.

Treatment can stop after prolactin levels have been maintained in the normal range (below 20 pg/mL) for at least 6 months.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Nausea, Headache, and Dizziness. Initiating treatment at low doses may help minimize these effects.

*Patient education information is highlighted as blue text.

Drugs That Affect Uterine Function

DRUGS FOR PRETERM LABOR

Drugs Used to Suppress Preterm Labor

Control of Myometrial Contraction and Mechanisms of Tocolytic Drug Action

Specific Tocolytic Drugs

Drugs Used to Prevent Preterm Labor

Hydroxyprogesterone Caproate

Antibiotics

DRUGS FOR CERVICAL RIPENING AND INDUCTION OF LABOR

Prostaglandins: Dinoprostone and Misoprostol

Oxytocin

DRUGS FOR POSTPARTUM HEMORRHAGE

Oxytocin and Misoprostol

Carboprost Tromethamine

Ergot Alkaloids: Ergonovine and Methylergonovine

DRUGS FOR MENORRHAGIA

Tranexamic Acid

Other Drugs for Menorrhagia

Most of the drugs discussed in this chapter have applications related to labor and delivery. Some are used to delay or prevent preterm labor. Some are used to induce labor. And some are used to control postpartum hemorrhage. In addition to these drugs, we discuss one other group: drugs used to decrease menorrhagia (heavy menstrual bleeding).

Drugs that alter uterine function fall into two major groups: *oxytocic drugs* and *tocolytic drugs*. The oxytocic drugs, also known as *uterotonic drugs*, stimulate uterine contraction. In contrast, the tocolytic drugs cause uterine relaxation. Clinical applications of the oxytocic and tocolytic drugs are summarized in Table 64-1.

DRUGS FOR PRETERM LABOR

Preterm birth, defined as birth before 37 weeks' gestation, is the leading cause of newborn morbidity and mortality. Infants who survive preterm birth are at increased risk of infection, cerebral palsy, intracranial hemorrhage, and, most commonly, neonatal respiratory distress syndrome. In the United States, about 12.5% of all live births (540,000 annually) are premature. These preterm births account for 75% of neonatal mortality and 50% of congenital neurologic deficits. Risk factors for preterm delivery include a previous preterm delivery, multifetal pregnancy, cervical or uterine abnormalities, intrauter-

ine infection and inflammation, and social factors (poverty, limited education, unmarried status, inadequate prenatal care). The annual cost of preterm births is estimated at \$26 billion—about \$52,000 per infant. Drugs for preterm labor fall into two major groups: drugs used to *suppress* preterm labor that has already started, and drugs used to *prevent* preterm labor from ever occurring. The first group is larger and used more widely.

DRUGS USED TO SUPPRESS PRETERM LABOR

All of the drugs employed to suppress preterm labor are *tocolytics*. That is, they all promote uterine relaxation, and thereby delay delivery. Be aware, however, that benefits are limited: These drugs can only suppress labor *briefly*, not long term. On average, delivery is postponed by only 48 hours. Hence, birth still takes place prior to term. If tocolytics don't permit pregnancy to reach term, what are they good for? The answer: Almost nothing—if they are used *alone*. However, when tocolytics are combined with glucocorticoids, which accelerate fetal lung development (see Chapter 107), the outcome can be improved: Infants experience less respiratory distress syndrome, intraventricular hemorrhage, and mortality. Tocolytics also buy time to treat infection, if present. Unfortunately, tocolytic drugs can pose a risk to the fetus. Accordingly, the ultimate goal of treatment is to extend fetal time in the womb, but without causing significant fetal or neonatal harm.

Control of Myometrial Contraction and Mechanisms of Tocolytic Drug Action

Contraction of the myometrium (uterine smooth muscle) is regulated by multiple mediators, including beta-adrenergic agonists, oxytocin, and prostaglandins (Fig. 64-1). As a result, there are multiple ways in which drugs can suppress uterine activity. However, although these drugs work through different mechanisms, they all have one thing in common: Ultimately, they all *decrease the availability of phosphorylated light-chain (LC) myosin*, the form of myosin that interacts with actin to cause contraction. As indicated in Figure 64-1, four classes of tocolytic drugs—beta-adrenergic agonists, calcium channel blockers, cyclooxygenase (COX) inhibitors, and oxytocin receptor antagonists—work to reduce the activity of myosin LC kinase, the enzyme that converts myosin to its phosphorylated form. A fifth group—the nitric oxide donors—work to increase the activity of myosin LC phosphatase, the enzyme that removes phosphate from myosin, thereby converting it to its inactive form. Note also that three drug groups—COX inhibitors, oxytocin receptor antagonists, and calcium channel blockers—*decrease the re-*

TABLE 64-1 Applications of Selected Tocolytic and Oxytocic Drugs

Drug	Trade Name	Applications				
		Delay of Preterm Labor	Induction of Cervical Ripening	Induction of Labor	Control of Postpartum Hemorrhage	Induction of Abortion
Tocolytic Drugs						
Beta₂-adrenergic Agonist						
Terbutaline	Brethine	✓				
Calcium Channel Blocker						
Nifedipine	Adalat, Procardia, others	✓				
Cyclooxygenase Inhibitor						
Indomethacin	Indocin	✓				
Nitric Oxide Donor						
Nitroglycerin	Nitro-Dur, others	✓				
Oxytocin Antagonist						
Atosiban*	Antocin*	✓				
Oxytocic (Uterotonic) Drugs						
Prostaglandins						
Dinoprostone	Cervidil, Prepidil		✓†	✓		✓
Misoprostol	Cytotec		✓†	✓		✓
Carboprost	Hemabate				✓	✓
Oxytocin Receptor Agonist						
Oxytocin	Pitocin			✓	✓	
Ergot Alkaloids						
Ergonovine	Ergotrate				✓	
Methylergonovine	Methergine				✓	

*Not available in the United States.

†Cervical ripening is unrelated to uterotonic actions.

lease of calcium from the sarcoplasmic reticulum (SR). As indicated in the figure, calcium combines with calmodulin to form a complex that increases myosin light-chain kinase activity. Hence, in the absence of sufficient free calcium, myosin LC kinase activity declines, causing the phosphorylation of myosin to decline as well.

Specific Tocolytic Drugs

Multiple drugs can suppress preterm labor. Options include terbutaline (a beta₂-adrenergic agonist), nifedipine (a calcium channel blocker), and COX inhibitors (eg, indomethacin). All of these drugs appear equally good at suppressing labor, and hence there is no obvious "first-choice" agent among them. Accordingly, selection is based primarily on side effects, which are summarized in Table 64-2. Interestingly, none of the drugs currently employed to suppress preterm labor has been approved for this use by the Food and Drug Administration (FDA).

Terbutaline, a Beta₂-Adrenergic Agonist

Terbutaline, used primarily for asthma (see Chapter 76), is a selective beta₂ agonist that can effectively suppress preterm labor. By activating beta₂ receptors in the uterus, terbutaline increases production of cyclic AMP (cAMP), a mediator that leads to suppression of myosin light-chain kinase activity. The result is a decrease in both the intensity and frequency of contractions. Unfortunately, although terbutaline is effective,

it poses a significant risk to the mother. Adverse effects result from activating beta₁ receptors as well as beta₂ receptors. (Although terbutaline is classified as beta₂ selective, it can activate beta₁ receptors too, albeit less readily than beta₂ receptors.) Effects of greatest concern are pulmonary edema, hypotension, and hyperglycemia in the mother, and tachycardia in both the mother and fetus. For suppression of labor, terbutaline is administered subQ, not PO. The initial dosage is 250 mcg every 20 minutes for up to 3 hours. Dosing should stop after 48 hours, and should be interrupted if the maternal heart rate exceeds 120 beats per minute. Although terbutaline can be used to *suppress* preterm labor, it should not be given to *prevent* preterm labor.

Nifedipine, a Calcium Channel Blocker

Nifedipine [Adalat, Procardia, others] can suppress preterm labor for at least 48 hours. Efficacy equals that of terbutaline—and safety is superior. How does nifedipine work? It blocks calcium channels, and thereby inhibits entry of calcium into myometrial cells. As a result, release of calcium from the SR is reduced, and hence the activity of myosin light-chain kinase is reduced as well. Maternal side effects, which are rare, include transient tachycardia, facial flushing, headache, dizziness, and nausea. Hypotension may occur in hypovolemic patients. There is some concern that nifedipine may compromise uteroplacental blood flow. In animal studies, calcium channel blockers have caused acidosis, hypoxemia, and hypercapnia in the newborn. To suppress preterm labor, an initial loading dose (30 mg sub-

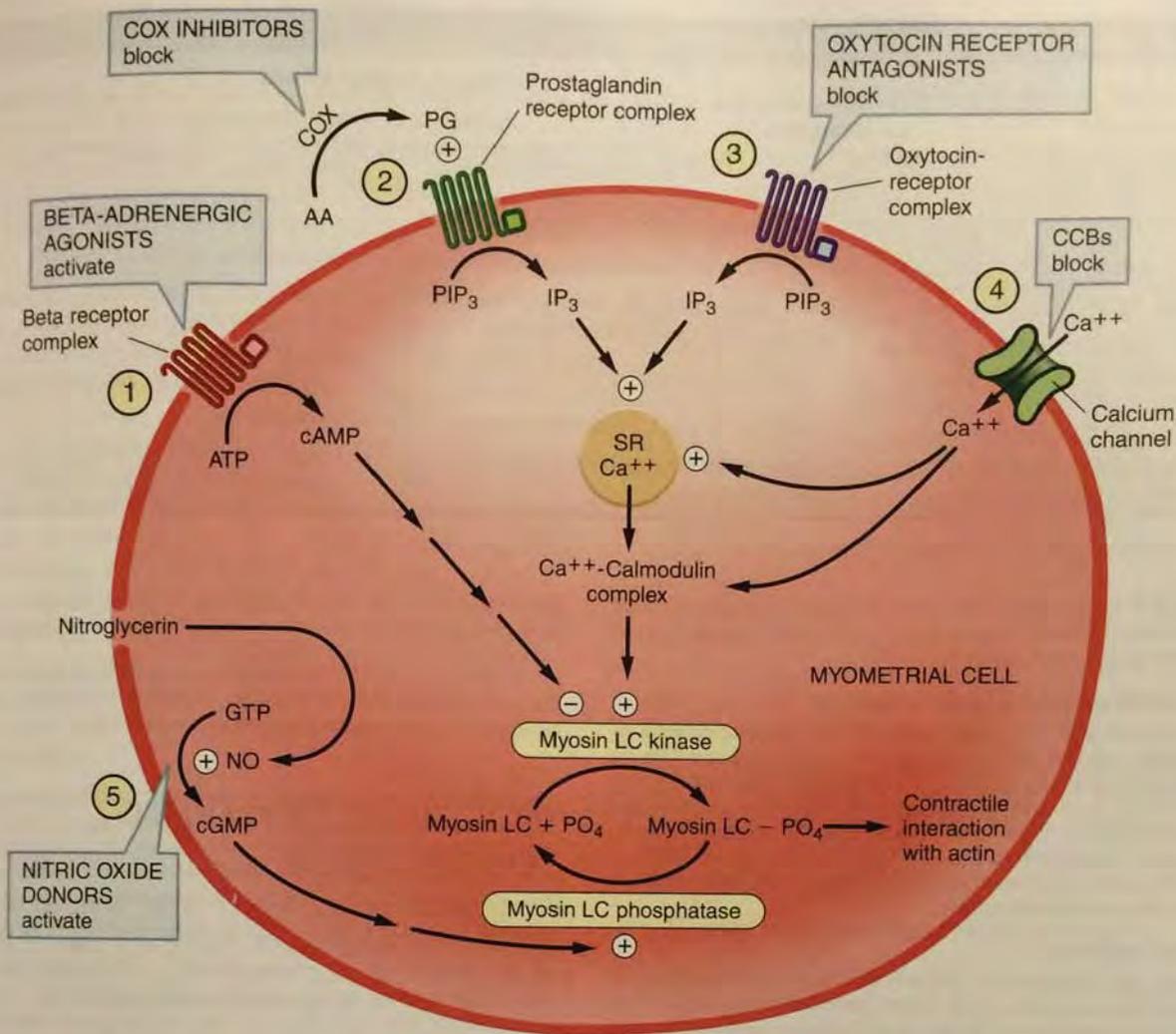


Figure 64-1 ■ Control of myometrial contraction and the actions of tocolytic drugs.

The figure shows five pathways that regulate availability of myosin LC phosphate (myosin LC PO_4), the form of myosin needed for contractile interaction with actin. Note that two enzymes—myosin LC kinase and myosin LC phosphatase—play central roles. Four classes of tocolytic drugs (numbers 1, 2, 3, and 4 in the figure) work to reduce the activity of myosin LC kinase, and thereby reduce production of myosin LC phosphate. A fifth class—the nitric oxide donors—increases the activity of myosin LC phosphatase, and thereby stimulates conversion of myosin LC phosphate to its inactive (dephosphorylated) form. Note also the important role played by calcium in controlling the activity of myosin LC kinase. (AA = arachidonic acid, ATP = adenosine triphosphate, cAMP = cyclic adenosine monophosphate, CCBs = calcium channel blockers, cGMP = cyclic guanosine monophosphate, COX = cyclooxygenase, GTP = guanosine triphosphate, IP_3 = inositol triphosphate, LC = light-chain, NO = nitric oxide, PG = prostaglandin, PIP_3 = phosphatidylinositol triphosphate, PO_4 = phosphate, SR = sarcoplasmic reticulum.)

lingual) is followed by maintenance doses (10 or 20 mg PO) every 4 to 6 hours. The basic pharmacology of calcium channel blockers is discussed in Chapter 45.

Indomethacin, a Cyclooxygenase Inhibitor

Indomethacin [Indocin] is a second-line tocolytic agent generally reserved for women who go into labor extremely early. The drug is as effective as terbutaline, but carries a higher risk of neonatal complications. Indomethacin suppresses labor by inhibiting synthesis of prostaglandins, local hormones that promote uterine contraction by increasing release of calcium from the SR. Adverse neonatal outcomes include prolonged renal insufficiency, bronchopulmonary dysplasia, necrotizing enterocolitis, and periventricular leu-

komalacia (white matter injury caused by reduced blood flow in the brain). In addition, indomethacin can cause *in utero* closure of the ductus arteriosus. Adverse maternal effects include nausea, gastric irritation, interstitial nephritis, and, rarely, increased postpartum bleeding. Tocolytic treatment is initiated with a loading dose (50 or 100 mg, usually rectal) followed by maintenance doses (25 to 50 mg PO) given every 4 to 8 hours for 2 to 3 days.

Nitroglycerin, a Nitric Oxide Donor

Nitroglycerin, administered by transdermal patch, appears similar in efficacy to terbutaline. Benefits derive from release of nitric oxide, which then stimulates production of cyclic GMP (cGMP), a mediator that leads to enhanced activity of myosin light-chain phosphatase. As a result, availability of phosphorylated myosin declines. Major side effects are hypotension and headache

TABLE 64-2 ■ Adverse Effects of Tocolytic Drugs

Drug	Major Adverse Effects	
	Maternal	Fetal/Neonatal
Terbutaline, a beta ₂ agonist	Pulmonary edema, tachycardia, palpitations, chest pain, myocardial ischemia, hypotension, tremors, hypokalemia, hyperglycemia	Fetal tachycardia, hypotension, ileus, hyperinsulinemia with hypoglycemia, hyperbilirubinemia, hypocalcemia
Nifedipine, a calcium channel blocker	Tachycardia, hypotension, hepatotoxicity	Hypotension
Indomethacin, a cyclooxygenase inhibitor	Nausea, gastric irritation, interstitial nephritis, prolonged postpartum bleeding (rarely)	Prolonged renal insufficiency, bronchopulmonary dysplasia, necrotizing enterocolitis, periventricular leukomalacia, <i>in utero</i> closure of ductus arteriosus
Nitroglycerin, a nitric oxide donor	Hypotension, headache, dizziness, flushing	Hypotension
Atosiban, an oxytocin-receptor antagonist	Allergic reactions, injection-site reactions, headache, nausea	Increased rate of fetal or infant death when used before 28 weeks' gestation

in the mother, and hypotension in the infant. Dosing consists of one 10-mg patch applied every 12 hours for up to 48 hours. The basic pharmacology of nitroglycerin is discussed in Chapter 51.

Atosiban, an Oxytocin Receptor Antagonist

Atosiban [Antocin] suppresses uterine contractions by blocking oxytocin receptors on the myometrium, resulting in reduced release of calcium from the SR. The drug is licensed in Europe but not in the United States. Some experts say the drug works as well as the beta agonists; others disagree. Principal maternal side effects are hypersensitivity reactions and short-lasting headache and nausea. Significant fetal side effects have not been noted. However, when used very early in gestation—before 28 weeks—atosiban appears to increase fetal and neonatal mortality.

Magnesium Sulfate

Opinion on the role of magnesium sulfate in preterm labor is changing. Although the drug has been popular in the United States (but not in Europe), there seems to be little to recommend its use. Why? First and foremost, the drug doesn't work: high-dose magnesium sulfate does not prevent or even delay preterm birth. Second, high-dose treatment has been associated with increased infant mortality. However, recent data indicate that, when used in low doses, magnesium may protect against cerebral palsy, without increasing the risk of mortality. The bottom line? High-dose magnesium is both ineffective and dangerous, and therefore should not be used. In contrast, low-dose magnesium may offer the benefit of neuroprotection, even though it won't delay delivery.

How does magnesium sulfate suppress contractions? It inhibits release of acetylcholine at neuromuscular junctions (NMJs), both in the uterus and in skeletal muscle. At high doses, the drug can cause profound muscle weakness and respiratory arrest.

Magnesium sulfate can cause a variety of maternal adverse effects. Initial reactions include transient hypotension, flushing, headache, dizziness, lethargy, dry mouth, and a feeling of warmth. High doses may cause hypothermia and paralytic ileus. Pulmonary edema, which can be fatal, is seen in 2% of patients. This complication is managed by discontinuing magnesium and giving a diuretic to accelerate magnesium excretion. Magnesium sulfate is contraindicated in patients with myasthenia gravis (because the disease causes muscle weakness), renal failure (because magnesium is eliminated entirely by the kidneys), and hypocalcemia (because hypocalcemia intensifies magnesium-induced suppression of neurotransmitter release).

Magnesium readily crosses the placenta and is associated with increased infant mortality. The drug may also cause hypotonia (muscle weakness) and sleepiness in the newborn. Because elimination of magnesium by neonatal kidneys is slow, hypotonia may persist 3 to 4 days. During this time, mechanical assistance of ventilation may be required.

The risk of adverse effects can be reduced by monitoring (1) magnesium levels; (2) renal function (because renal impairment will cause magnesium levels to rise); (3) fluid balance (because fluid retention increases the risk of pulmonary edema); and (4) deep tendon reflexes (because loss of deep tendon reflexes is an early sign that magnesium levels are rising dangerously high).

In clinical trials testing magnesium sulfate for neuroprotection, two low-dose protocols have been used. In one, dosing consisted of a 4-g IV loading bolus infused over 20 minutes, followed by a maintenance infusion of 1 gm/hr lasting for 24 hours or until delivery, whichever came first. In the other

protocol, dosing was limited to a single IV bolus. By way of comparison, high-dose therapy consists of an initial IV bolus (4 to 6 gm), followed by infusion of 2 to 3 gm/hr for 48 to 72 hours.

In addition to its use for preterm neuroprotection, magnesium sulfate is the preferred drug for prevention and treatment of seizures associated with eclampsia and severe preeclampsia (see Chapter 47).

DRUGS USED TO PREVENT PRETERM LABOR

As discussed above, we can arrest preterm labor (albeit briefly) with tocolytics, but is there any way we can prevent it? Yes—at least for some women. Two drug interventions may help: hydroxyprogesterone and antibiotics.

Hydroxyprogesterone Caproate

Therapeutic Use. In 2011, the FDA approved hydroxyprogesterone caproate [Makena] for reducing the risk of preterm labor, making it the first and only drug approved for this use. The drug is indicated only for women with a singleton pregnancy and a history of at least one preterm birth. It is not approved for women with multiple pregnancy or other risk factors for preterm birth. Hydroxyprogesterone is a weakly active, naturally occurring progesterone derivative. The mechanism underlying prevention of preterm birth is unknown.

Efficacy of hydroxyprogesterone was demonstrated in a randomized, controlled trial that enrolled 463 pregnant women at high risk of preterm delivery (because of a spontaneous preterm delivery in the past). After random assignment to placebo or treatment groups, one-third of the women were given weekly IM injections of placebo, and two-thirds were given weekly IM injections of hydroxyprogesterone. Injections began at 16 to 20 weeks of gestation and continued until delivery or until 36 weeks of gestation. The result? The rate of preterm delivery was 54.9% in the placebo group, but only 36.3% in the progesterone group—a highly significant reduction. In addition, progesterone reduced the risk of low birth weight and several other complications. Progesterone-induced birth defects were not observed. Although these results are impressive, important questions remain:

- Are there any long-term risks to the child? (Experience with diethylstilbestrol, an estrogen that can cause vaginal

cancer in women exposed to it *in utero*, is a warning for caution.)

- Do these results apply to women at risk of preterm delivery for reasons other than having a history of the problem?
- Why did hydroxyprogesterone only work in some women? (Preterm delivery still occurred in nearly half of the women who were treated.)

Adverse Effects and Contraindications. In clinical trials, the most common adverse effects were injection-site reactions (pain, swelling, itching), hives, nausea, and diarrhea. Serious events were rare: One woman had an injection-site infection, and one had a pulmonary embolism. If thrombosis or thromboembolism occurs, hydroxyprogesterone should be stopped. Hydroxyprogesterone can promote glucose intolerance, clinical depression, and fluid retention. Accordingly, monitoring is indicated for women with diabetes, a history of depression, or a condition that could be made worse by fluid retention (eg, preeclampsia, epilepsy, or cardiac or renal dysfunction).

Hydroxyprogesterone is contraindicated for women with uncontrolled hypertension, liver cancer, liver disease, a history of thrombosis, cholestatic jaundice of pregnancy, undiagnosed abnormal vaginal bleeding (unrelated to pregnancy), or known or suspected breast cancer (or any other hormone-sensitive cancer).

Preparations, Dosage, and Administration. Hydroxyprogesterone caproate [Makena] is supplied in solution (250 mg/mL) in 5-mL multidose vials for IM injection into the upper quadrant of the gluteus maximus. The solution is viscous and oily, and hence should be injected slowly (over 1 minute or more). Shots are given by the healthcare provider, not by the patient. The dosage is 250 mg once a week, beginning between 16 and 21 weeks of gestation, and continuing until week 37 or delivery, whichever comes first.

Makena is expensive, costing \$690/dose (\$13,800 for 20 weekly doses). However, generic hydroxyprogesterone acetate can be obtained from a compounding pharmacy for much less: \$10 to \$20 per dose (\$200 to \$400 for 20 weekly doses).

Antibiotics

In women with bacterial vaginosis, antibiotics can reduce the incidence of preterm labor, as shown in two randomized, double-blind, placebo-controlled trials. Why were these studies conducted? Because there is an association between abnormal genital tract flora and preterm delivery, suggesting that normalizing genital tract flora might reduce risk.

In the first study, involving 409 pregnant women with abnormal genital tract flora (suggesting bacterial vaginosis), subjects were given a 3-day course of either 2% clindamycin vaginal cream or a placebo vaginal cream, beginning at 13 to 20 weeks of gestation. If abnormal flora were still present 3 weeks later, subjects received a longer (7-day) course of clindamycin or placebo. The result? Preterm delivery occurred in 10% of the placebo group, compared with only 4% of the clindamycin group.

In the second study, involving 494 pregnant women with abnormal genital tract flora, subjects were given a single, 5-day oral course of either clindamycin (300 mg twice daily) or placebo. Dosing was done during weeks 12 to 22 of pregnancy. Preterm delivery occurred in 16% of placebo recipients, but only 5% of clindamycin recipients.

Taken together, these antibiotic studies suggest a simple method for preventing some preterm deliveries: early screening for and treatment of asymptomatic bacterial vaginosis.

DRUGS FOR CERVICAL RIPENING AND INDUCTION OF LABOR

The goal of labor induction is to stimulate uterine contractions prior to the spontaneous onset of labor, and thereby produce a vaginal delivery. In the United States, more than 22% of deliveries are induced. Induction is considered appropriate when the

benefits of the procedure outweigh the risks of continued pregnancy and the risks of induction itself. An evidence-based practice guideline—*Induction of Labor: ACOG Practice Bulletin No. 10*—released in 2010 by the American College of Obstetricians and Gynecologists (ACOG), summarizes the indications and contraindications for induction, and discusses the benefits and risks of the drugs and procedures employed. Much of what follows is based on these guidelines.

When should labor be induced? Only when continued pregnancy constitutes a greater risk to the mother and fetus than does the risk of induction itself. As a rule, induction should be reserved for pregnancy that has continued beyond term (ie, beyond 42 weeks), and for pregnancy in which early vaginal delivery is likely to decrease morbidity and mortality for the mother or infant. Post-term pregnancy is the most common reason for induction. Indications for *early* induction include:

- Abruptio placentae (separation of the placenta from the uterus)
- Premature rupture of the membranes
- Gestational hypertension
- Preeclampsia or eclampsia
- Maternal medical conditions, including diabetes, renal disease, chronic pulmonary disease, and chronic hypertension
- Fetal compromise, including severe fetal growth restriction, isoimmunization (development of maternal antibodies directed against fetal red blood cells), and oligohydramnios (deficiency of amniotic fluid)
- Fetal demise (fetal death)

Contraindications to induction include:

- Umbilical cord prolapse
- Transverse fetal position
- Active genital herpes infection
- Previous cesarean delivery
- History of myomectomy (surgical removal of uterine fibroids)
- Placenta previa (growth of the placenta in the lowest part of the uterus, such that the placenta covers the opening to the cervix.)

Before labor can be safely induced, *cervical ripening* must occur. During pregnancy, the cervix is elongated, rigid, and constricted. When ripening takes place, the cervix shortens, softens, and dilates, thereby permitting the fetus to pass through the birth canal. If induction is attempted in the absence of ripening, maternal and fetal injury can result. Accordingly, if labor is to be induced before natural ripening has occurred, ripening must be facilitated, either with drugs (dinoprostone or misoprostol) or with a mechanical dilator (eg, saline-filled Foley catheter).

Three drugs used for cervical ripening and/or labor induction are discussed below. One of these drugs—oxytocin—is used only for induction. The other two—dinoprostone and misoprostol—can promote cervical ripening, and can also induce labor.

Prostaglandins: Dinoprostone and Misoprostol

Two prostaglandins—dinoprostone and misoprostol—act on the cervix to promote ripening, and act on the uterus to promote contractions. Because of these dual actions, treatment

with a prostaglandin alone may be sufficient to both ripen the cervix and induce labor. If contractions are inadequate with a prostaglandin alone, then oxytocin is given to strengthen contractions.

Dinoprostone

Dinoprostone [Prepidil, Cervidil, Prostin E2[◆]] is the most widely used agent for cervical ripening. The drug is a synthetic prostaglandin identical in structure to endogenous prostaglandin E₂ (PGE₂), a compound produced by fetal membranes and the placenta. Endogenous PGE₂ has two roles in the birthing process: It promotes cervical ripening, and later it stimulates uterine contractions. Cervical ripening results from activation of collagenase, an enzyme that breaks down the collagen network that makes the cervix rigid. When used to promote ripening, dinoprostone shortens the duration of labor, allows a reduction in oxytocin dosage, and decreases the need for cesarean delivery. Because it can stimulate uterine contractions, dinoprostone may induce labor as well as promote cervical ripening. As discussed in Chapter 62, dinoprostone is also used to induce abortion, owing to its ability to stimulate intense uterine contractions. For promotion of cervical ripening, dinoprostone is available in two formulations: a gel and a vaginal insert.

Dinoprostone Gel. Dinoprostone gel [Prepidil, Prostin E2[◆]] is available in single-dose, pre-filled syringes that contain 0.5 mg dinoprostone/2.5 mL gel. Administration is intracervical, using the syringe and endocervical catheter (10- or 20-mm tip) supplied by the manufacturer. To prevent leakage, the patient should lie supine during administration and for at least 30 minutes after. If the desired response has not occurred within 6 hours, a second 0.5-mg dose can be given, followed 6 hours later by a third, if needed. (Most women need at least two doses, and 50% need a third.) Because dinoprostone can stimulate uterine contractions, and may thereby cause fetal distress, uterine activity and fetal heart rate should be monitored continuously. Monitoring should start before each dose and continue for at least 2 hours after. Oxytocin is given 6 to 12 hours after the last dose of dinoprostone. The major adverse effect of dinoprostone is uterine *tachysystole*,* which occurs in 1% of patients using the gel. Rarely, systemic absorption results in nausea, vomiting, diarrhea, and fever. Dinoprostone gel is unstable and must be stored refrigerated, between 2°C and 8°C (36°F and 46°F). Treatment is moderately expensive: Each 0.5-mg dose costs about \$150, making the total cost \$450 for women who require three doses.

Dinoprostone Vaginal Inserts. Dinoprostone vaginal inserts [Cervidil] consist of a pouch, containing 10 mg of the drug, to which a long tape is attached. The purpose of the tape is to permit rapid removal of the pouch. Following insertion in the posterior fornix of the vagina, the pouch releases dinoprostone slowly (0.3 mg/hr) for 12 hours. The patient should remain supine for at least 2 hours after pouch insertion. The pouch is removed when active labor occurs or when 12 hours have elapsed, whichever comes first. If oxy-

tocin is needed, administration can begin 30 minutes after removing the pouch. As with dinoprostone gel, the major adverse effect is uterine tachysystole, which develops in 5% of patients (compared with only 1% of those receiving the gel). To minimize harm, uterine activity and fetal heart rate should undergo continuous monitoring while the insert is in place and for at least 15 minutes after it is removed. Compared with dinoprostone gel, the insert has two advantages. First, treatment is almost always cheaper. Second, because inserts can be easily removed, drug delivery can be stopped as soon as (1) labor starts (thereby avoiding unnecessary drug exposure) or (2) uterine tachysystole develops (thereby minimizing uterine contractions and related fetal distress). The vaginal inserts are unstable and must be stored frozen, between -10°C and -20°C (14°F and -4°F). The cost of one insert is about \$175, compared with \$150 for one dose of the gel. Nonetheless, treatment with the inserts is generally less expensive. Why? Because most women require two or three doses of the gel (total cost: \$300 to \$450), but only one insert (total cost: \$175).

Misoprostol

Misoprostol [Cytotec] is an attractive alternative to dinoprostone for promoting cervical ripening, although misoprostol is not approved for this use. Compared with dinoprostone, misoprostol is more effective, more convenient (stores at room temperature versus refrigerated), and *much* less expensive (treatment costs about \$1 versus \$175 to \$450). Unfortunately, misoprostol also causes a higher incidence of uterine tachysystole, and hence is contraindicated in women with a history of major uterine surgery or cesarean delivery. To induce cervical ripening, a 25-mcg dose (one-fourth of a 100-mcg tablet) is inserted into the posterior fornix of the vagina. Dosing is repeated every 4 hours as needed. In women given misoprostol, delivery occurs faster than in those given dinoprostone, and there is less need for oxytocin. To minimize risk from tachysystole, fetal heart rate and uterine activity should be monitored continuously. Like dinoprostone, misoprostol can induce labor following cervical ripening, and hence use of oxytocin may not be needed. In addition to its use for cervical ripening/labor induction, misoprostol is used to induce abortion (see Chapter 62) and to protect against peptic ulcers (see Chapter 78).

Oxytocin

Oxytocin [Pitocin] is a peptide hormone produced by the posterior pituitary. Physiologically, this hormone promotes uterine contraction during parturition and stimulates the milk-ejection reflex. The primary therapeutic use of oxytocin is induction of labor near term, a procedure for which oxytocin is the agent of choice. As discussed below under *Drugs for Postpartum Hemorrhage*, oxytocin is also a drug of choice for stopping postpartum bleeding.

Physiologic and Pharmacologic Effects

Uterine Stimulation. Oxytocin can increase the force, frequency, and duration of uterine contractions. The ability of the uterus to respond to oxytocin depends on the stage of gestation: Early in pregnancy, uterine sensitivity to oxytocin is low; as pregnancy proceeds, the uterus becomes progressively more responsive; and just prior to term, a large and

*Current ACOG guidelines use the term *uterine tachysystole* in preference to *uterine hyperstimulation* or *uterine hypercontractility*, which have been used extensively in the past. Tachysystole is a high rate of uterine contractions, defined as more than 5 contractions in 10 minutes (averaged over a 30-minute window). The normal rate of contractions is 5 or less in 10 minutes (averaged over a 30-minute window).

abrupt increase in responsiveness develops. Sensitivity increases over time because the number of oxytocin receptors on uterine smooth muscle increases throughout pregnancy. Although uterine sensitivity to oxytocin is low early in pregnancy, oxytocin can still initiate and enhance contractions at this stage. However, the doses required are much larger than those needed at term.

Despite the profound effects of oxytocin on uterine contractility, the precise role of oxytocin in spontaneous labor and delivery has not been established. We do know that giving exogenous oxytocin can elicit contractions identical to those seen during spontaneous labor. However, we also know that parturition can take place with virtually no oxytocin present—although labor will be prolonged. Furthermore, during normal labor or during labor induced artificially (through rupture of the membranes), only modest increases in plasma oxytocin occur. From these observations we can conclude that, although oxytocin is not absolutely required for parturition, the hormone probably acts to facilitate contractions. However, it is not certain that oxytocin is responsible for *initiating* labor.

Milk Ejection. Milk is produced by glandular tissue of the breast and is later transferred, via small channels, into large sinuses where it is readily accessible to the suckling infant. Transfer to the sinuses is brought about by the milk-ejection reflex: When the infant sucks on the breast, neuronal stimuli are sent to the posterior pituitary, causing release of oxytocin; oxytocin then causes contraction of the smooth muscle surrounding the small milk channels, thereby forcing milk into the large sinuses. In the absence of oxytocin, milk ejection does not occur.

Water Retention. Oxytocin is similar in structure to antidiuretic hormone (ADH), which acts on the kidney to decrease excretion of water. Although less potent than ADH, oxytocin can nonetheless promote renal retention of water.

Pharmacokinetics

Oxytocin is administered IV or IM. The plasma half-life is short, ranging from 12 to 17 minutes. Elimination is by hepatic metabolism and renal excretion.

Use for Induction of Labor

Preinduction Preparation. Induction should not be done if the fetal lungs have not matured, or if the cervix is not ripe. Accordingly, prior to induction, if the fetal lungs are still immature, maturation should be hastened with a glucocorticoid (see Chapter 107). Likewise, if the cervix is not yet ripe, ripening should be induced with dinoprostone or misoprostol. Alternatively, cervical ripening can be induced mechanically (with a cervical dilator) or by membrane stripping (ie, by separating the chorioamniotic membranes from the internal surface of the uterus).

Precautions and Contraindications. Improper use of oxytocin can be hazardous. Uterine rupture may occur, posing a risk of death for the mother, the infant, or both. The likelihood of trauma is especially high in cases of cephalopelvic disproportion, fetal malpresentation, placental abnormalities, umbilical cord prolapse, previous uterine surgery, and fetal distress. Oxytocin is contraindicated in pregnancies with any of these characteristics. In addition, oxytocin is contraindicated in women with active genital herpes. Induction of labor in women of high parity (five or more pregnancies) carries a

high risk of uterine rupture, and hence oxytocin must be used with great caution in these women.

Adverse Effect: Water Intoxication. When administered in large doses, oxytocin exerts an antidiuretic effect. If large volumes of fluid have been administered along with oxytocin, retention of water may produce intoxication. However, at the doses employed to induce labor, water intoxication is rare.

Dosage and Administration. For induction of labor, oxytocin is administered by intravenous infusion. Solutions should be dilute (10 milliunits/mL), and administered with an infusion pump that allows precise flow-rate control. Either of two regimens may be used: low dose or high dose. The low-dose regimen produces less tachysystole than the high-dose regimen. However, the high-dose regimen works faster and is associated with less chorioamnionitis, and less need for cesarean delivery. The two regimens consist of the following:

- **Low-Dose Regimen:** Start the infusion at 0.5 to 2 milliunits/min, and then gradually increase the rate by 1 to 2 milliunits/min every 15 to 40 minutes
- **High-Dose Regimen:** Start the infusion at 6 milliunits/min, and then gradually increase the rate by 3 to 6 milliunits/min every 15 to 40 minutes.

With both regimens, the dose is gradually increased until uterine contractions resembling those of spontaneous labor have been produced (ie, contractions every 2 to 3 minutes and lasting 45 to 60 seconds).

During the infusion, constant monitoring is required. The mother should be monitored for blood pressure, pulse rate, and uterine contractility (frequency, duration, and intensity). The fetus should be monitored for heart rate and rhythm. In the event of significant maternal or fetal distress, the infusion should be stopped; contractions will diminish rapidly. Complications that usually require interruption of the infusion are (1) elevation of resting uterine pressure above 15 to 20 mm Hg, (2) contractions that persist for more than 1 minute, (3) contractions that occur more often than every 2 to 3 minutes, and (4) pronounced alteration in fetal heart rate or rhythm.

Additional Therapeutic Uses

Augmentation of Labor. Oxytocin may be employed if labor is dysfunctional. However, patients must be judiciously selected, and dosage must be regulated with special care. As a rule, oxytocic agents should not be used to promote labor that is already in progress, even if labor is proceeding slowly: By intensifying the force of contractions, oxytocin may cause uterine damage (laceration or rupture) or trauma to the infant.

Postpartum Use. Oxytocin can be administered IM or IV following placental delivery to control bleeding or hemorrhage and to increase uterine tone. Dosage for postpartum hemorrhage is given below.

Abortion. Oxytocin has been employed during the second trimester to manage incomplete abortion. Intravenous infusion of 10 units at a rate of 10 to 20 milliunits/min is often effective in emptying the uterus. However, oxytocin is not a method of choice.

DRUGS FOR POSTPARTUM HEMORRHAGE

Postpartum hemorrhage is the second leading cause of maternal mortality (preeclampsia/eclampsia is first.) Morbidity and mortality result directly from blood loss. How much loss constitutes hemorrhage? Traditionally, postpartum hemorrhage has been defined as blood loss exceeding 500 mL during vaginal delivery or 1000 mL during cesarean delivery. How-

ever, a more workable definition is bleeding of any amount sufficient to cause hemodynamic instability.

Why does postpartum hemorrhage occur? Normally, the uterus contracts following delivery, allowing the placenta to separate from the uterine surface. After expulsion of the placenta, the uterus continues to contract, causing blood vessels that supplied the placenta to squeeze shut. As a result, bleeding stops. If the uterus does not contract enough, bleeding will continue. In about 80% of cases, postpartum hemorrhage results from *uterine atony* (failure of the uterus to contract). Most of the remaining cases result from lacerations, maternal coagulopathies, or retention of placental tissue.

Drugs that promote uterine contraction (uterotonic drugs) can reduce bleeding caused by uterine atony. Two of these drugs—oxytocin and carboprost—are discussed above under *Drugs for Cervical Ripening and Induction of Labor*. Three additional drugs—ergonovine, methylergonovine, and carboprost tromethamine—are introduced below. Of all these drugs, oxytocin is considered the agent of first choice for control of postpartum hemorrhage.

Oxytocin and Misoprostol

Oxytocin [Pitocin] and misoprostol [Cytotec] are powerful uterotonic agents, and hence can stop postpartum hemorrhage resulting from uterine atony. For misoprostol, the dosage is 600 to 1000 mcg administered rectally. Principal side effects are shivering (50%) and pyrexia (5% to 10%). For oxytocin, dosing may be done IM or IV. The IM dosage is 10 to 20 units given as a single injection. Intravenous dosing is done by infusing an oxytocin solution (20 milliunits/mL) at a rate sufficient to control uterine atony (usually 200 to 600 mL/hr). The pharmacology of oxytocin and misoprostol is discussed above.

Carboprost Tromethamine

Therapeutic Use

Carboprost tromethamine [Hemabate], also known as 15-methyl prostaglandin F₂ alpha, is a preferred agent for controlling postpartum hemorrhage. The drug suppresses bleeding primarily by causing intense uterine contractions, and partly by causing direct vasoconstriction. In most cases, bleeding can be stopped with a single 250-mcg dose, injected deep IM or into the myometrium. In addition to its postpartum use, carboprost is used to induce abortion (see Chapter 62).

Adverse Effects

As with other prostaglandins, GI reactions are very common. The underlying cause is stimulation of smooth muscle of the gut. Vomiting and diarrhea occur in up to 60% of patients. Nausea is also common. Gastrointestinal reactions can be reduced by pretreatment with antiemetic and antidiarrheal medications.

Fever is common. If body temperature rises, it is important to differentiate between drug-induced fever and pyrexia resulting from endometritis.

Like other prostaglandins, carboprost causes vasoconstriction and constriction of the bronchi. As a result, treatment carries a risk of hypertension and impaired respiration.

Precautions and Contraindications

Carboprost is contraindicated for women with acute pelvic inflammatory disease and active disease of the heart, lungs, kidneys, or liver. The drug should be used with caution in women with a history of asthma, hypertension, diabetes, or uterine scarring.

Ergot Alkaloids: Ergonovine and Methylergonovine

Ergot is a dried preparation of *Claviceps purpurea*, a fungus that grows on rye plants. The ergot alkaloids are compounds present in ergot. Ergot is capable of inducing powerful uterine contractions, a fact known to midwives for centuries. Analysis of ergot has revealed the presence of several pharmacologically active constituents. Of these, *ergonovine* [Ergotrate] is the most effective uterine stimulant. A derivative of ergonovine—*methylergonovine* [Methergine]—has been synthesized and produces effects much like those of ergonovine. Because the actions of ergonovine and methylergonovine are very similar, we will consider these agents jointly.

In obstetrics, the ergot alkaloids are used primarily to control postpartum bleeding. However, because they carry a high risk of severe hypertension, they are generally reserved for women who have not responded to safer agents: oxytocin, misoprostol, or carboprost tromethamine.

Pharmacologic Effects

Ergot alkaloids produce their effects by stimulating a variety of receptors (adrenergic, dopaminergic, serotonergic). These drugs exert their most profound effects on uterine and vascular smooth muscle.

Effects on the Uterus. Ergot alkaloids stimulate uterine contraction. In small doses, they produce contractions of moderate strength that alternate with uterine relaxation of normal degree and duration. With large doses, the force and frequency of contractions are greatly increased, and the extent of uterine relaxation is reduced; sustained contraction is not uncommon. Because contractions may be prolonged, ergot alkaloids are not employed to induce labor.

Vascular Effects. Ergot alkaloids can cause constriction of arterioles and veins. This ability underlies the use of two agents—ergotamine and dihydroergotamine—to treat migraine headache (see Chapter 30). Vasoconstriction may also contribute to control of postpartum bleeding.

Pharmacokinetics

Regardless of the route employed, ergonovine and methylergonovine act rapidly. Uterine contractions begin within 60 seconds of IV injection, and within 10 minutes of oral or IM administration. Effects persist for several hours.

Therapeutic Uses

Postpartum Use. The ergot alkaloids may be used postpartum and postabortion to increase uterine tone and decrease bleeding. The ability to induce sustained uterine contraction makes them very effective for these purposes. Administration is usually delayed until after delivery of the placenta. The patient should be monitored for blood pressure, pulse rate, and uterine contractility. Cramping occurs as part of the therapeutic response, but may also indicate overdose. Owing

to a high risk of severe hypertension, many physicians reserve the ergot alkaloids for patients who have not responded to safer alternatives (ie, oxytocin, misoprostol, or carboprost tromethamine).

Augmentation of Labor. Because contractions may be both intense and prolonged, ergot alkaloids are not recommended for use during labor. If they are given during labor, excessive uterine tone can cause trauma to the mother, fetus, or both. Placental blood flow may be reduced, resulting in fetal hypoxia and uterine rupture. In addition, cervical laceration may occur.

Migraine. Ergot alkaloids relieve migraine in part by constricting dilated cerebral blood vessels. Two preparations are employed: ergotamine and dihydroergotamine. The pharmacology of these drugs and their use in migraine are discussed in Chapter 30 (Drugs for Headache).

Adverse Effects

When ergot alkaloids are given orally or IM, significant adverse effects are rare. In contrast, IV administration frequently causes *hypertension*. Hypertension can be severe and may be associated with nausea, vomiting, and headache; convulsions and even death have occurred. Accordingly, IV administration should be reserved for emergencies. Furthermore, patients with pre-existing hypertension should not be given these drugs. Caution should be exercised in patients with cardiovascular, renal, or hepatic disorders.

Contraindications

Ergot alkaloids are contraindicated for women who are pregnant, hypertensive, or hypersensitive to these drugs. They are also contraindicated for induction of labor and for use in the presence of threatened or ongoing spontaneous abortion.

Preparations, Dosage, and Administration

Preparations. *Ergonovine maleate* [Ergotrate] and *methylergonovine maleate* [Methergine] are both available in 0.2-mg tablets for oral dosing, and in solution (0.2 mg/mL) for IM and IV dosing.

Dosage and Administration. Parenteral. For parenteral therapy, ergonovine and methylergonovine are usually administered IM; intravenous administration is hazardous and should be reserved for emergency control of postpartum hemorrhage. Treatment is usually initiated only after passage of the placenta. With both drugs, the dosage for postpartum hemorrhage is 0.2 mg initially (either IM or IV), repeated every 2 to 4 hours as needed.

Oral. The dosage for *methylergonovine* (to promote involution of the uterus) is 0.2 mg every 6 to 8 hours for up to 1 week. The dosage for *ergonovine* (for prevention of postpartum or postabortion hemorrhage) is 0.2 to 0.4 mg every 6 to 12 hours until the danger of uterine atony has passed (usually 48 hours).

DRUGS FOR MENORRHAGIA

Menorrhagia—heavy menstrual bleeding—is a common disorder that affects about 1 in 5 premenopausal women. The condition is characterized by excessive and/or prolonged bleeding associated with an otherwise normal cycle. In a normal cycle, bleeding lasts an average of 7 days, and total blood flow is between 25 and 80 mL. Menorrhagia is diagnosed if bleeding lasts more than 7 days, or if blood loss exceeds 80 mL. Left untreated, the condition can result in iron deficiency anemia. Excessive bleeding can be reduced with drugs or by endometrial ablation, using surgical or nonsurgical techniques. Drugs for menorrhagia are discussed below.

Tranexamic Acid

Therapeutic Uses

Menorrhagia. In 2009, the FDA approved tranexamic acid (TA) [Lysteda] for oral therapy of cyclic heavy menstrual bleeding, making TA the first nonhormonal product *approved** for this disorder. In clinical trials, TA has reduced bleeding by as much as 50%. Although use of TA for menorrhagia is new in the United States, the drug has been used for menorrhagia in Europe for decades.

Trauma Patients. Intravenous TA can save lives following traumatic injury, as shown in a recent study known as CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage 2). When given within 8 hours of injury to patients who were bleeding or at risk of bleeding, TA reduced the incidence of bleeding-related deaths without increasing the incidence of vaso-occlusive events. The results indicate that, for every 67 patients treated, 1 life would be saved. Importantly, TA is inexpensive, costing only \$100 for the dosage used in CRASH-2. Seems like a small price to pay to save a life.

Hemophilia. As discussed in Chapter 54, intravenous TA, marketed as *Cyklokapron*, is used to reduce bleeding in patients with hemophilia.

Mechanism of Action

Tranexamic acid, a derivative of lysine, inhibits plasmin, the enzyme that dissolves the fibrin meshwork of blood clots. How does TA inhibit plasmin? It binds to lysine receptor sites on plasmin, and thereby prevents plasmin from binding to lysine molecules in fibrin. Because plasmin is unable to dissolve fibrin, uterine hemostasis is preserved, and menstrual bleeding is greatly reduced.

Pharmacokinetics

For treatment of menorrhagia, TA is administered by mouth. Bioavailability is 45% in the absence of food, and slightly higher in the presence of food. Plasma levels peak about 3 hours after dosing. Metabolism is minimal. Most of each dose (95%) is excreted unchanged in the urine.

Adverse Effects and Interactions

Tranexamic acid is generally well tolerated. In clinical trials, the most common side effects were headache, back pain, joint pain, muscle cramps, migraine, fatigue, and sinus and nasal symptoms. However, with the exception of sinus and nasal symptoms, the incidence of side effects was about the same as in patients taking placebo.

The greatest concern with TA is possible venous or arterial *thrombosis*, including thrombosis in the veins and arteries of the retina. Accordingly, women who experience visual changes should discontinue TA immediately and undergo an eye exam to rule out possible vessel blockage. Women with a history of thrombosis or thromboembolic disease should not use this drug. Because combination oral contraceptives also pose a risk of thrombotic events, women using these contraceptives should not use TA.

Preparations, Dosage, and Administration

For treatment of *heavy menstrual bleeding*, tranexamic acid [Lysteda] is supplied in 650-mg tablets for oral dosing, with or without food. Tablets should be swallowed whole, without crushing or chewing. For women with normal

*Other nonhormonal drugs, specifically, nonsteroidal anti-inflammatory drugs, are also used for menorrhagia, but are not *approved* for this application.

renal function, the dosage is 1300 mg 3 times a day, taken for a maximum of 5 days during monthly menstruation. Dosage should be reduced in women with renal impairment.

For patients experiencing *traumatic injury*, the dosage used in CRASH-2 was 1 gm infused IV over 10 minute followed by 1 more gm infused IV over 8 hours.

For IV treatment of *hemophilia*, TA is available in solution (100 mg/mL) marketed as *Cyklokapron* (see Chapter 54).

Other Drugs for Menorrhagia

Nonsteroidal Anti-inflammatory Drugs. The nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen [Anaprox, Naprosyn] and diclofenac [Cataflam], are considered first-line therapy of menorrhagia. On average, these agents can decrease bleeding by 20% to 46%. In addition, they can reduce painful cramping. Dosing is limited to the 5 days in the menstrual cycle when bleeding is heaviest. As a result, side effects are limited. How do NSAIDs reduce bleeding? They inhibit cyclooxygenase, and thereby suppress pro-

duction of prostacyclin, a compound that (1) indirectly promotes menstrual bleeding and (2) is produced in excessive amounts in the menorrhagic endometrium. The basic pharmacology of the NSAIDs is discussed in Chapter 71.

Combination Oral Contraceptives. For women who desire contraception, combination oral contraceptives (OCs) are a first-line therapy for menorrhagia. Benefits equal those of NSAIDs. Combination OCs reduce bleeding by causing endometrial atrophy. As a result, when endometrial breakdown occurs, there is less blood to lose. The basic pharmacology of combination OCs is discussed in Chapter 62.

Levonorgestrel-Releasing Intrauterine System. Like the combination OCs, the *Mirena* levonorgestrel-releasing intrauterine system is considered first-line therapy for menorrhagia in women who also want contraception. Benefits derive from levonorgestrel-induced endometrial involution. Menstrual blood flow is reduced by up to 97%. The *Mirena* system is discussed further in Chapter 62.

KEY POINTS

- Tocolytic drugs suppress contraction of uterine smooth muscle.
- Tocolytic drugs have only one indication: delay of preterm labor.
- On average, tocolytic drugs delay labor for 48 hours.
- All tocolytics work to decrease the availability of phosphorylated light-chain myosin, the form of myosin needed for contractile interaction with actin.
- The major tocolytic drugs—beta₂-adrenergic agonists, calcium channel blockers, and COX inhibitors—appear equally good at suppressing preterm labor, and hence selection among them is based largely on side effects.
- Only one drug—hydroxyprogesterone caproate—is approved for preventing preterm labor.
- The goal of labor induction is to stimulate uterine contractions prior to the spontaneous onset of labor, and thereby produce a vaginal delivery.
- Induction of labor is appropriate when pregnancy has continued beyond term, or when early vaginal delivery is likely to decrease morbidity or mortality for the mother or infant.
- Before labor is induced, cervical ripening must occur, either naturally or facilitated by prostaglandins or a mechanical device.
- Dinoprostone is a prostaglandin that can promote cervical ripening, and can also induce labor in some women.
- Oxytocic drugs, also known as uterotonic drugs, stimulate contraction of uterine smooth muscle.
- Oxytocin is the drug of choice for induction of labor.
- Used improperly (eg, in pregnancies with cephalopelvic disproportion), oxytocin can cause uterine rupture.
- Three oxytocic drugs—oxytocin, misoprostol, and carboprost tromethamine—are preferred agents for controlling postpartum hemorrhage.
- Because they pose a risk of severe hypertension, ergonovine and methylergonovine are generally considered second-line drugs for controlling postpartum hemorrhage.
- Menorrhagia is defined as excessive menstrual bleeding.
- Tranexamic acid, the first nonhormonal drug approved for menorrhagia, prevents destruction of fibrin, and thereby preserves uterine hemostasis.

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Summary of Major Nursing Implications

DINOPROSTONE

Preadministration Assessment

Therapeutic Goal

Dinoprostone is used to promote cervical ripening and induce labor.

Identifying High-Risk Patients

Dinoprostone is *contraindicated* for women with acute pelvic inflammatory disease and active disease of the heart, lungs, kidneys, or liver.

Use with *caution* in women with a history of asthma, hypotension, hypertension, diabetes, or uterine scarring.

Summary of Major Nursing Implications—cont'd

Implementation: Administration

Route

Vaginal insert and vaginal gel, both for intracervical instillation.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Assess the cervix for elongation, softening, and dilation. Assess for change in uterine contractions.

Minimizing Adverse Effects

GI Disturbances. Nausea, vomiting, and diarrhea can be reduced by pretreatment with antiemetic and antidiarrheal drugs.

Fever. Fever may be induced by dinoprostone or it may indicate endometritis. If fever develops, a differential diagnosis is needed.

OXYTOCIN

The implications summarized here apply only to the use of oxytocin for induction of labor, the drug's principal use.

Preadministration Assessment

Therapeutic Goal

Oxytocin is given to initiate or improve uterine contractions. Treatment is reserved for pregnancies that have gone beyond term and for pregnancies in which early vaginal delivery is likely to decrease morbidity and mortality for the mother or infant.

Baseline Data

The history should determine parity, previous obstetric problems, stillbirths, and abortions. Full maternal and fetal status should be assessed, including the degree of cervical ripening and fetal lung maturity.

Identifying High-Risk Patients

Induction of labor is *contraindicated* in the presence of cephalopelvic disproportion, fetal malpresentation, placental abnormality, umbilical cord prolapse, previous major surgery to the uterus or cervix, fetal distress, and active genital herpes.

Use with *caution* in women of high parity (five or more pregnancies).

Induction should not be conducted in the absence of cervical ripening or fetal lung maturation. If indicated, promote cervical ripening mechanically or with drugs, and promote fetal lung maturation with glucocorticoids.

Implementation: Administration

Route

Intravenous.

Administration

Administer by carefully controlled infusion, using an infusion pump.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Uterine contractions of excessive intensity, frequency, and duration can cause maternal and fetal harm. Monitor uterine contractility (frequency, duration, and intensity), maternal blood pressure, and fetal and maternal heart rate. Interrupt the infusion if any of the following occur: (1) resting intrauterine pressure rises above 15 to 20 mm Hg, (2) individual contractions persist longer than 1 minute, (3) contractions occur more often than every 2 to 3 minutes, and (4) fetal heart rate or rhythm changes significantly.

ERGOT ALKALOIDS: ERGONOVINE AND METHYLERGONOVINE

Preadministration Assessment

Therapeutic Goal

Prevention and treatment of postpartum and postabortion hemorrhage.

Identifying High-Risk Patients

Ergot alkaloids are *contraindicated* during pregnancy, for induction of labor, in women with hypertension or allergy to ergot alkaloids, and in the presence of threatened or ongoing spontaneous abortion.

Implementation: Administration

Routes

Oral and IM. Preferred.

Intravenous. Hazardous; reserve for hemorrhagic emergencies.

Administration

As a rule, administer after passage of the placenta. Perform IV injections slowly (over 60 seconds or more).

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor blood pressure, pulse rate, and uterine activity. Report sudden increases in blood pressure, excessive uterine bleeding, and insufficient uterine tone. Cramping is normal but may also indicate overdose.

Minimizing Adverse Effects

Significant adverse effects—*hypertension, nausea, vomiting, headache, convulsions, and death*—usually occur only with IV administration. To minimize risk, infuse slowly (over 60 seconds or more) and reserve IV administration for emergencies.

Testosterone

Biosynthesis and Secretion

Mechanism of Action

Physiologic and Pharmacologic Effects

Clinical Pharmacology of the Androgens

Classification

Therapeutic Uses

Adverse Effects

Androgen Preparations for Male Hypogonadism

Androgen (Anabolic Steroid) Abuse by Athletes

Si Box 65-1. Testosterone Replacement: Can It Enhance Sexuality in Men? Or Women?

Androgen hormones are produced by the testes, ovaries, and adrenal cortex. The major endogenous androgen is testosterone. Androgens are noted most for their ability to promote expression of male sex characteristics. However, androgens also influence sexuality in females. In addition, androgens have significant physiologic and pharmacologic effects unrelated to sex. The primary clinical application of the androgens

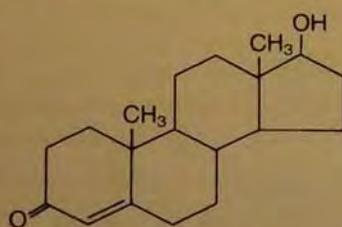
is management of androgen deficiency in males. Principal adverse effects are virilization and hepatotoxicity.

TESTOSTERONE

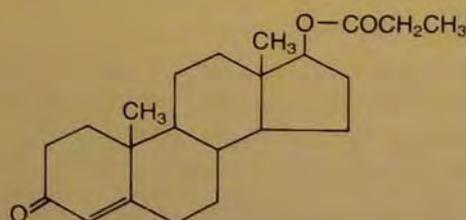
Testosterone is the prototype of the androgen hormones. This compound is the principal endogenous androgen in both males and females. In addition to its physiologic role, testosterone is representative of the androgens employed clinically. The structural formula of testosterone is shown in Figure 65-1.

Biosynthesis and Secretion

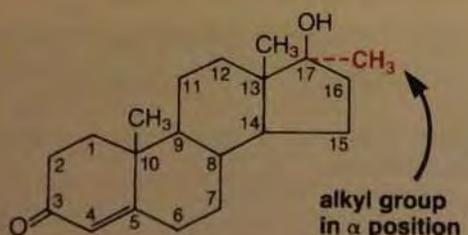
Males. Testosterone is made by Leydig cells of the testes. Daily production in men ranges from 2.5 to 10 mg. Synthesis is promoted by two hormones of the anterior pituitary: follicle-stimulating hormone (FSH) and luteinizing hormone (LH), also known as interstitial cell-stimulating hormone. Production of testosterone is regulated by negative feedback control: Rising plasma levels of testosterone act on the pituitary to suppress further release of FSH and LH, thereby decreasing the stimulus for further testosterone formation.

TESTOSTERONE AND A TESTOSTERONE ESTER

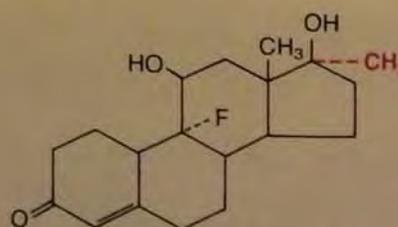
Testosterone



Testosterone Propionate

17-ALPHA-ALKYLATED ANDROGENS

Methyltestosterone



Fluoxymesterone

Figure 65-1 • Structural formulas of representative androgens.

Some of the testosterone present in plasma is produced by the adrenals. However, androgenic activity of adrenal origin is much less than that of testicular origin. Hence, in males, adrenal androgens have minimal functional significance.

Testosterone production changes over time. Peak production occurs around age 17. Production then remains steady until age 30 or 40, after which it slowly declines. By the time a man reaches 80, testosterone production is only half what it was in his youth.

Females. In women, preandrogens (precursors of testosterone) are secreted by the adrenal cortex and ovaries. Conversion into testosterone takes place in peripheral tissues. Synthesis of preandrogens by the adrenals is regulated by adrenocorticotropic hormone (ACTH), whereas synthesis of preandrogens by the ovaries is regulated by LH. Daily testosterone production is about 300 mcg (150 mcg from the ovaries and 150 mcg from the adrenals). The total is 10 to 40 times less than the amount produced in men. In the event of ovarian or adrenocortical pathology (eg, adenoma, carcinoma, hyperplasia), secretion of androgens can increase greatly, and may be sufficient to produce virilization. At menopause, testosterone production decreases.

Mechanism of Action

Effects of testosterone on its target tissues are mediated by specific receptors located in the cell cytoplasm. Following binding of testosterone to its receptor, the hormone-receptor complex migrates to the cell nucleus, and then acts on DNA to promote synthesis of specific messenger RNA molecules. These, in turn, serve as templates for production of specific proteins, which then mediate testosterone effects. It should be noted that in some tissues—prostate, seminal vesicles, and hair follicles—androgen receptors do not interact with testosterone itself. Rather, they interact with dihydrotestosterone, a testosterone metabolite.

Physiologic and Pharmacologic Effects

Effects on Sex Characteristics in Males

Pubertal Transformation. Increased production of testosterone promotes the transformations that signal puberty in males. Under the influence of testosterone, the testes enlarge, after which the penis and scrotum enlarge. Pubic and axillary hair appear, and hair on the trunk, arms, and legs assumes adult male patterns. Testosterone stimulates growth of bone and skeletal muscle, causing height and weight to increase rapidly. Testosterone also accelerates epiphyseal closure, causing bone growth to cease within a few years. The larynx enlarges, thereby deepening the voice. Sebaceous glands increase in number, causing the skin to become oily; acne results if the glands become clogged and infected. The final pubertal change is beard development. Several years are required for all of these changes to occur.

Spermatogenesis. Androgens are necessary for production of sperm by the seminiferous tubules, and for maturation of sperm as they pass through the epididymis and vas deferens. Androgen deficiency causes sterility.

Effects on Sex Characteristics in Females

Under physiologic conditions, endogenous androgens have only moderate effects in females. Principal among these are promotion of clitoral growth and, perhaps, maintenance of normal libido. However, when production of androgens becomes

excessive (eg, in girls with congenital adrenal hyperplasia), virilization can take place. Virilization can also occur in response to therapeutic use of androgens or to androgen abuse.

Anabolic Effects

Testosterone promotes growth of skeletal muscle. This anabolic effect results from binding of androgens to the same type of receptor that mediates androgen actions in other tissues. Effects in young males, and in females of any age, can be dramatic. In contrast, effects in healthy adult males are modest. Why? Because the testes of adult males already produce enough testosterone to cause near-maximal stimulation of the musculature. Hence, in adult males, the increment in muscle mass that can be achieved with exogenous androgens is relatively small.

Erythropoietic Effects

Testosterone promotes synthesis of erythropoietin, a hormone that acts on bone marrow to increase production of erythrocytes (red blood cells). This action of testosterone, together with the high levels of testosterone present in males, explains why men have a higher hematocrit than women. When women are given testosterone, the hematocrit rises and hemoglobin levels increase by an average of 4.3 gm/dL. In contrast, since men have high testosterone levels to begin with, the increase in plasma hemoglobin that can be elicited with exogenous androgens is smaller—only 1 gm/dL.

CLINICAL PHARMACOLOGY OF THE ANDROGENS

In addition to testosterone, a few other androgens are employed clinically. All of these agents can bind to androgen receptors, and therefore all can elicit similar responses. Major differences among individual androgens pertain to route of administration, pharmacokinetics, adverse effects, and specific applications.

Classification

The androgens used clinically fall into two basic groups: (1) testosterone and testosterone esters, and (2) 17-alpha-alkylated compounds (noted for their hepatotoxicity). Androgens belonging to each group are listed in Table 65-1.

When speaking of testosterone-like compounds, it is traditional to distinguish between “androgens” and “anabolic steroids.” However, we will not make this distinction. Why? Because it is now clear that the receptor type that mediates the androgenic actions of the androgens is the same receptor type that mediates the anabolic actions of these hormones. Consequently, it has not been possible to separate anabolic activity from androgenic activity. Virtually all anabolic hormones are also androgenic. Accordingly, rather than creating two categories—androgens versus anabolic steroids—and assigning some agents to one category and some to the other, we will simply refer to all of the testosterone-like drugs as androgens.

Therapeutic Uses

Individual androgens differ in their applications. No single androgen is employed for all of the uses discussed below. Specific applications of individual androgens are summarized in Table 65-1.

TABLE 65-1 • Approved Uses of Individual Androgens

Androgen	Indications			
	Hypogonadism (Male)	Replacement Therapy (Male)	Delayed Puberty (Male)	Catabolic States
Testosterone and Testosterone Esters				
Testosterone	✓	✓	✓	
Testosterone cypionate	✓	✓		
Testosterone enanthate	✓	✓	✓	
17-Alpha-Alkylated Androgens				
Fluoxymesterone	✓	✓	✓	
Methyltestosterone	✓	✓	✓	
Oxandrolone				✓

Male Hypogonadism. Hypogonadism in males is the principal indication for androgens. In this condition, the testes fail to produce adequate amounts of testosterone, and hence replacement therapy is required. Male hypogonadism may be hereditary or it may result from other causes, including pituitary failure, hypothalamic failure, and primary dysfunction of the testes.

When complete hypogonadism occurs in boys, puberty cannot take place—unless exogenous androgens are supplied. To induce puberty, a long-acting parenteral preparation (*testosterone enanthate* or *testosterone cypionate*) is chosen. Injections are given IM every 2 to 4 weeks for 3 to 4 years. Under the influence of these androgens, the normal sequence of pubertal changes occurs: growth is accelerated, the penis enlarges, the voice deepens, and other secondary sex characteristics become expressed. As in normal males, these changes take place over several years.

Replacement Therapy. Androgen replacement therapy is beneficial when testicular failure occurs in adult males. Treatment restores libido, increases ejaculate volume, and supports expression of secondary sex characteristics. However, treatment will not restore fertility. The principal drugs employed for testosterone replacement are testosterone itself and two testosterone esters: testosterone enanthate and testosterone cypionate. Preparations and dosages for replacement therapy are summarized in Table 65-2 and discussed below under *Androgen Preparations for Male Hypogonadism*. Replacement therapy in older males is discussed further in Box 65-1.

Delayed Puberty. In some boys, puberty fails to occur at the usual age (ie, prior to 15 years). Most often, this failure reflects a familial pattern of delayed puberty and does not indicate pathology. Puberty can be expected to occur spontaneously, but later than usual. Hence, although androgen therapy can be employed, treatment is not an absolute necessity. However, although therapy is not required, the psychologic pressures of delayed sexual maturation are sometimes greater than a boy (or his parents) can tolerate. In these cases, a limited course of androgen therapy is indicated. If delayed puberty is the result of true hypogonadism, long-term replacement therapy is indicated.

Replacement Therapy in Menopausal Women. Testosterone replacement therapy can alleviate some menopausal symptoms, especially fatigue, reduced libido, and reduced genital sensitivity. Testosterone is not approved for replacement in women in the United States, although it is approved in the United Kingdom. Testosterone replacement in women is discussed in Box 65-1.

Wasting in Patients with AIDS. Testosterone levels often decline in patients with AIDS, putting them at risk of wasting and loss of muscle mass. Testosterone therapy decreases this risk.

Anemias. Androgens may be used in men and women to treat anemias that have been refractory to other therapy. Anemias that may respond include aplastic anemia, anemia associated with renal failure, Fanconi's anemia, and anemia caused by cancer chemotherapy. Androgens help relieve anemia by promoting synthesis of erythropoietin, the renal hormone that stimulates production of red blood cells. Androgens may also stimulate production of white blood cells and platelets.

Adverse Effects

Virilization in Women, Girls, and Boys. Virilization is the most common complication of androgen therapy. When taken in high doses by women, androgens can cause acne, deepening of the voice, proliferation of facial and body hair, male-pattern baldness, increased libido, clitoral enlargement, and menstrual irregularities. Clitoral growth, hair loss, and lowering of the voice may be irreversible. Masculinization can also occur in children. Boys may experience growth of pubic hair, penile enlargement, increased frequency of erections, and even priapism (persistent erection). In girls, growth of pubic hair and clitoral enlargement may occur. To prevent irreversible masculinization, androgens must be discontinued when virilizing effects first appear.

Premature Epiphyseal Closure. When given to children, androgens can accelerate epiphyseal closure, thereby decreasing adult height. To evaluate androgen effects on the epiphyses, radiographic examination of the hand and wrist should be performed every 6 months.

Hepatotoxicity. Androgens can cause *cholestatic hepatitis* and other disorders of the liver. Clinical *jaundice* may occur, but is rare. Patients receiving androgens should undergo periodic tests of liver function. If jaundice develops, it will reverse

TABLE 65-2 • Products for Androgen Replacement Therapy in Hypogonadal Males

Formulation	Drug	Trade Name	Dosage	CSA Schedule	Comments
Oral Tablet	Fluoxymesterone Methyltestosterone	Androxy Methitest, Testred, Virilon	5–20 once daily 10–50 mg once daily	III	These 17- α -alkylated androgens are hepatotoxic and androgenic effects are erratic. Oral therapy is not generally recommended.
Intramuscular Injection	Testosterone cypionate Testosterone enanthate	Depo-Testosterone Delatestryl	50–400 mg every 2–4 wk 50–400 mg every 2–4 wk	III	Safe, but require an office visit every 2–4 wk. Blood levels fluctuate widely (high after dosing and low before the next dose) and thereby cause variations in libido, energy, and mood.
Transdermal Patch	Testosterone	Androderm	One patch/day (delivers 2, 2.5, 4, or 5 mg/24 hrs)	III	Applied to the arm, back, abdomen, or thigh, but <i>not</i> the scrotum. Causes local irritation.
Transdermal Gel	Testosterone	AndroGel, Testim Fortesta	5–10 gm of 1% gel once daily (delivers 50– 100 mg/day) 40–70 mg of 2% gel once daily	III	Apply AndroGel to upper arm, shoulder, or abdomen, but <i>not</i> the scrotum. Apply Testim only to upper arm or shoulder. Apply Fortesta to the front and inner thigh. Easier to use and better tolerated than testosterone patches. Can transfer to others via intimate contact.
Transdermal Underarm Solution	Testosterone	Axiron	60–180 mg once daily	III	Apply to one or both armpits at the same time each morning. Easier to use and better tolerated than testosterone patches. Can transfer to others via intimate contact.
Implantable Pellets	Testosterone	Testopel	150–450 mg (2–6 pellets) subQ every 3–4 mo	III	Implanted subQ. Long lasting. Produce steady blood levels.
Buccal System	Testosterone	Striant	One buccal system (30 mg) every 12 hr	NR	Provides fairly steady testosterone levels, but may cause mouth or gum irritation.

CSA = Controlled Substances Act, NR = not regulated as a controlled substance.

following discontinuation of androgen use. Androgens may also be carcinogenic: *Hepatocellular carcinoma* has developed in some patients following prolonged use of these drugs.

It must be emphasized that not all androgens are hepatotoxic: Liver damage is associated primarily with the 17- α -alkylated androgens. As indicated in Figure 65-1 (see methyltestosterone), these androgens all share a structural feature in common: an alkyl group substituted on carbon 17 of the steroid nucleus. Because of their capacity to cause liver damage, the 17- α -alkylated compounds should not be used long term. In contrast to the 17- α -alkylated androgens, testosterone and the testosterone esters (testosterone cypionate, testosterone enanthate) are not associated with liver disease.

Effects on Cholesterol Levels. Androgens can lower plasma levels of high-density lipoprotein (HDL) cholesterol (“good cholesterol”) and elevate plasma levels of low-density

lipoprotein (LDL) cholesterol (“bad cholesterol”). These actions may increase the risk of atherosclerosis and related cardiovascular events.

Use in Pregnancy. Because of their ability to induce masculinization of the female fetus, androgens are contraindicated during pregnancy. Potential fetal changes include vaginal malformation, clitoral enlargement, and formation of a structure resembling the male scrotum. Virilization is most likely when androgens are taken during the first trimester. Women who become pregnant while using androgens should be informed about the possible impact on the fetus. Androgens are classified in Food and Drug Administration (FDA) Pregnancy Risk Category X: The ability to cause fetal harm outweighs any possible therapeutic benefit.

Prostate Cancer. Androgens do not cause prostate cancer, but they can promote the growth of this cancer once it

TESTOSTERONE REPLACEMENT: CAN IT ENHANCE SEXUALITY IN MEN? OR WOMEN?

In Men

More and more elderly men are taking testosterone, despite limited information on efficacy and safety. Why? Because they want to alleviate aging-related symptoms—specifically, erectile dysfunction, loss of libido, hot flashes, fatigue, muscle atrophy, and depression and other mood disturbances. Unfortunately, there's little proof that testosterone replacement can help. In fact, there's not even proof that low testosterone is the cause: Although these symptoms can occur in men with low testosterone levels, they can also occur in older men with normal levels.

In an effort to document the benefits and risks of testosterone replacement, a committee of the Institute of Medicine (IOM) conducted a systematic review of the medical literature. Unfortunately, the committee was unable to reach any firm conclusions. Why? Because even the best relevant studies were of short duration (most covered less than 12 months) and had few subjects (typically less than 50), and most were not placebo controlled. Hence, the committee couldn't say with certainty that testosterone replacement is either safe or effective. To generate more reliable information, the committee recommended performing (1) short-term, randomized, placebo-controlled trials to evaluate the potential benefits of testosterone, followed by (2) long-term trials to evaluate potential risks.

Although the existing data on testosterone replacement are generally weak, do they tell us anything useful at all? According to the IOM committee, available data suggest—but don't prove—that testosterone may enhance both libido and sexual function. There's also pretty good evidence that testosterone can reduce body fat and increase muscle mass, although it may not increase muscle strength. Testosterone may also improve mood, increase energy, and promote a sense of well-being, but does not seem to improve cognition or memory. The IOM committee also identified potential risks. Testosterone stimulates production of red blood cells, and may thereby cause polycythemia. Testosterone can also increase LDL cholesterol (bad cholesterol) and reduce HDL cholesterol (good cholesterol), and may thereby promote cardiovascular disease. Perhaps the greatest concern is prostate cancer. Although testosterone doesn't cause cancer, it can promote growth of prostate cancer cells.

Given our limited understanding of testosterone therapy, how should replacement be conducted? As with all other treatments, we want to balance benefits and risks. However, since we don't know what the benefits and risks really are, a cautious approach would seem prudent. According to a recent Endocrine Society clinical practice guideline—*2010 Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes*—the following principles should be observed:

- Androgen deficiency should be diagnosed only in men with unquestionably low testosterone levels (below 220 ng/dL) plus classic symptoms and signs of testosterone deficiency.
- Testosterone therapy is recommended only for symptomatic men with classic androgen deficiency syndromes.
- The goal of testosterone therapy is to induce and sustain secondary sex characteristics and to improve sexual func-

tion, sense of well-being, muscle mass, muscle strength, and bone mineral density.

- Testosterone dosage should be adjusted to achieve serum testosterone levels in the mid-normal range (300 to 450 ng/dL).
- Testosterone therapy is *not* recommended for men expecting to improve fertility or for men with breast cancer, prostate cancer, a palpable prostate nodule, or poorly controlled heart failure.

These principles represent an interim approach. Once long-term studies on safety and efficacy have been conducted, development of more detailed guidelines should be possible.

In Women

Can testosterone replacement enhance the sex lives of menopausal women? Yes. But the benefits are often modest, and only some women respond. Furthermore, the long-term risks are unknown. Nonetheless, testosterone has been used by millions of menopausal women for decades, and continues to be used by millions today.

Why do menopausal women take testosterone? When menopause occurs—either naturally or following oophorectomy (surgical removal of the ovaries)—many women experience a decline in libido. Reduced testosterone is believed to be the cause. Prior to menopause, women produce about 300 mcg of testosterone daily—half is made by the adrenals and half by the ovaries. After menopause, ovarian production stops, and hence testosterone levels drop about 50%. As a result, women may experience a decline in sexual desire, genital sensitivity, and sense of well-being, even with estrogen therapy.

What's the effect of testosterone therapy? To answer this question, the manufacturer of *Intrinsa* (a testosterone patch designed for women) conducted clinical trials in women with low testosterone owing to bilateral oophorectomy. All of the women were receiving estrogen replacement and all were in monogamous sexual relationships. And they all suffered from documented hypoactive sexual desire disorder (HSDD), which began after surgically induced menopause. (HSDD is characterized by a persistent reduction in sexual desire that causes significant personal distress.) The testosterone trial was double-blinded, and the women were randomly assigned to receive either a placebo patch or *Intrinsa*, which delivers low-dose testosterone (only 300 mcg a day). The result? Women using *Intrinsa* had more sex and were happier about it. Testosterone increased the frequency of sexually satisfying encounters (from a baseline of three encounters per month up to five per month, versus four per month with placebo). In addition, testosterone increased sexual arousal, pleasure, responsiveness, and orgasms; decreased distress regarding sexual encounters; and improved self-image. Benefits began after 4 weeks of treatment, and reached a maximum by week 12. Results of other large studies mirrored those of the *Intrinsa* trials.

Is low-dose testosterone safe? In the *Intrinsa* trials, side effects from *short-term* use were common but generally mild. About 30% of users had application-site reactions. Less com-

BOX 65-1 ■ SPECIAL INTEREST TOPIC—cont'd

mon effects were hirsutism (7.3% with Intrinsa vs. 5.9% with placebo), acne (6.7% vs. 5.1%), alopecia (4.2% vs. 2.9%), voice deepening (2.7% vs. 2.2%), migraine (2.7% vs. 1.5%), and weight gain (2% vs. 1.5%). There were no clinically significant effects on cardiovascular parameters, including serum lipid levels, coagulation, blood pressure, and hematology.

What about long-term safety? No one knows. Testing to date has not ruled out the possibility that testosterone therapy could increase the risk of stroke, heart disease, breast cancer, and other disorders. The absence of information on long-term safety is of special concern in light of data from the Women's Health Initiative, which revealed that long-term estrogen therapy is less beneficial than previously believed—and more dangerous.

Who is a candidate for testosterone replacement? In 2005, after considering this study and many others, the North American Menopause Society (NAMS) issued a position statement on the role of testosterone therapy in women following spontaneous or surgically induced menopause. The statement notes that testosterone can have a positive effect on sexual function—primarily desire, arousal, and orgasmic response—and that women with no other identifiable cause of decreased desire may be candidates for testosterone therapy, provided that estrogen is taken as well. In 2006, The Endocrine Society released its own publication—*Androgen Therapy in Women: An Endocrine Society Clinical Practice Guideline*—which cautioned against generalized use of testosterone in women, but did recognize that

occurs. Accordingly, androgens are contraindicated for men with diagnosed prostate cancer. Men without diagnosed prostate cancer should be monitored for emergence of covert cancer.

Edema. Edema can result from androgen-induced retention of salt and water. This complication is a concern for patients with heart failure and for those with a predisposition to developing edema from other causes. Treatment consists of discontinuing the androgen, and giving a diuretic, if needed.

Gynecomastia. Breast enlargement may occur in males receiving androgen replacement therapy. This effect results from converting certain androgens into estrogen.

Abuse Potential. As discussed below, androgens are frequently misused (abused) to enhance athletic performance. Because of their abuse potential, nearly all androgens are regulated as Schedule III controlled substances.

Androgen Preparations for Male Hypogonadism

Treatment options for androgen replacement therapy have expanded in recent years. In the past, IM therapy with a long-acting testosterone ester was the major treatment mode. Today, we have five attractive alternatives: transdermal patches, transdermal gels, a transdermal underarm liquid, buccal tablets, and implantable subcutaneous pellets. Table 65-2 presents a summary of these and other androgen preparations used for replacement therapy in hypogonadal males. With the exception of buccal tablets, all of these formulations are regulated as Schedule III controlled substances. The buccal tablets are not regulated under the Controlled Substances Act.

Oral Androgens

Only two androgens are approved for oral therapy of male hypogonadism. Both drugs—*flacymesterone* and *methyltestosterone*—are 17- α -alkylated androgens, and therefore pose a risk of hepatotoxicity. Accordingly,

testosterone can be appropriate for *specific* women, namely those with HSDD resulting from spontaneous or surgically induced menopause.

If a woman, after consultation with her prescriber, wants to try testosterone therapy, what options are available? In the United States, we have no formulations approved for women, and all of the formulations approved for men deliver more testosterone than women need. (Remember, the goal is to mimic premenopausal testosterone production—about 300 mcg/day.) What about Intrinsa? The patch is approved for use in countries in the European Union, but has been denied approval in the United States. Why? Because members of the Reproductive Health Drugs Advisory Committee of the FDA felt that the benefits of Intrinsa were only modest, and that there are concerns regarding possible long-term risks. If not Intrinsa, what can be used? Women still have several options. These include subdermal implantation of a testosterone pellet (eg, 50 mg every 4 to 6 months), IM injection with a long-acting testosterone ester, and use of a topical formulation custom made by a compounding pharmacist. Formulations for topical therapy include testosterone propionate (1% to 2%) in petrolatum and 2% micronized testosterone gel. The testosterone propionate formulation is applied to the genital mucosa. The micronized formulation is applied to the skin of the arm, thigh, or abdomen. For both formulations, the initial daily dosage is one-quarter teaspoon or less. Over time, the frequency of topical administration (genital or dermal) can be reduced to 3 or 4 times per week.

they should not be used long term, and hence are not first-line agents. Oral androgens are used only rarely.

Transdermal Testosterone

Testosterone is available in three transdermal formulations: patches, gels, and a liquid. With all three formulations, testosterone is absorbed through the skin and then slowly absorbed into the blood.

Patches. Testosterone patches [Androderm] are indicated for male hypogonadism. Four strengths are available, delivering 2, 2.5, 4, or 5 mg of testosterone in 24 hours. Patches are applied once daily to the upper arm, thigh, back, or abdomen. The principal adverse effect is rash at the site of application.

Gels. Testosterone is available in three gel formulations, sold as *AndroGel*, *Testim*, and *Fortesta*. AndroGel and Testim contain 1% testosterone; Fortesta contains 2% testosterone. All three gels are applied once daily to treat male hypogonadism. After the gel is applied, testosterone is absorbed rapidly into the skin, and then slowly into the blood over the next 24 hours. Compared with transdermal patches, the gels have three advantages: they (1) cause less local irritation, (2) can't fall off, and (3) produce more consistent testosterone levels.

The principal disadvantage of the gels is that testosterone can be transferred to others by skin-to-skin contact. This is possible because only 10% of an applied dose is absorbed; the other 90% remains on the skin after the gel dries. In one study, blood levels of testosterone were doubled in female partners of gel users following 15 minutes of intimate contact that occurred 2 to 12 hours after the gel had been applied. Testosterone transfer is a concern because the drug can cause virilization of female partners and can also cause fetal harm. In children, contact transfer can cause genital enlargement (penis or clitoris), premature development of pubic hair, advanced bone age, increased libido, and aggressive behavior. In most cases, these effects regress after testosterone exposure stops. To reduce the risk of unintended gel transfer, the following guidelines should be followed:

- Gel users should wash their hands with soap and warm water after every application.
- Gel users should cover the application site with clothing once the gel has dried.

- Gel users should wash the application site prior to anticipated skin-to-skin contact with another person.
- Women and children should avoid skin-to-skin contact with application sites on gel users.
- Women and children who make accidental contact with a gel application site should wash contaminated skin immediately.

AndroGel is supplied in unit-dose foil packets (2.5 and 5 gm). The 2.5-gm packet contains 25 mg of testosterone (of which 2.5 mg becomes absorbed) and the 5-mg packet contains 50 mg of testosterone (of which 5 mg becomes absorbed). The gel is applied once daily (preferably in the morning) to clean, dry skin of the shoulders, upper arms, or abdomen—but *not* the genitalia. Instruct patients to squeeze the entire contents of the packet into the palms, and then immediately apply the gel to the skin and rub it in. To prevent the transfer of testosterone to others, patients should wash their hands and, once the gel has dried, keep the treated area covered with clothing. Because testosterone can be washed off, patients should wait 5 to 6 hours before showering or swimming. To ensure safe and effective dosing, blood levels of testosterone should be measured 14 days after initiating therapy and periodically thereafter.

Testim is available in 5-gm tubes that contain 50 mg of testosterone, of which 10% (5 mg) gets absorbed. The usual dosage is 1 or 2 tubes (50 or 100 mg) applied once daily to skin of the shoulders or upper arms, but not to the abdomen or scrotum. As with *AndroGel*, patients should wash their hands immediately and keep the treated area covered. They should also avoid showering for at least 2 hours. Testosterone levels should be checked after 14 days and periodically thereafter.

Fortesta is supplied in a metered-dose pump that delivers 10 mg of testosterone per actuation. The recommended starting dose is 40 mg once daily, and the maximum dose is 70 mg once daily. All doses are applied to the front or inner thigh. As with *AndroGel*, patients should wash their hands immediately and keep the treated area covered. Also, they should avoid swimming or showering for at least 2 hours. *Fortesta* is a flammable, alcohol-based formulation, and hence patients should avoid flames or smoking until the gel has dried. Testosterone levels should be checked after days 14 and 35, and periodically thereafter.

Underarm Liquid. Testosterone underarm liquid [*Axiron*], approved in 2010, is much like the testosterone gels. The principal difference is the application site: *Axiron* liquid is formulated specifically for application to the axilla (armpit, underarm), whereas *Testim* is applied to the shoulder or upper arm, and *AndroGel* is applied to the shoulder, upper arm, or abdomen. Following application, testosterone is absorbed rapidly into the skin, and then slowly into the blood. Steady-state levels are reached in 14 days. Once application stops, blood levels take 7 to 10 days to decline to baseline.

Axiron is supplied as an alcohol-based solution in a metered-dose pump that delivers 30 mg of testosterone per actuation. Dosing is done by pumping the liquid onto an applicator (supplied with the pump), and then applying the liquid to clean, dry, intact skin of the underarm—and not to anyplace else. Patients should not swim or bathe for 2 hours after application. If an underarm deodorant or antiperspirant is used, it should be applied before applying testosterone (in order to avoid contaminating the deodorant or antiperspirant dispenser). Because of its alcohol content, *Axiron* liquid is flammable. Accordingly, users should stay away from flames until the solution has dried.

The initial dosage is 60 mg once a day, delivered as 30 mg applied to each armpit at the same time every morning. After 14 days or longer, blood levels of testosterone are measured, and dosage is adjusted up or down as indicated.

Like the testosterone gels, testosterone underarm liquid can be transferred to others through skin-to-skin contact, posing a risk to women and children. Accordingly, the same guidelines noted above should be followed. That is, *Axiron* users should wash their hands after every application, cover the application site with clothing once the gel has dried, and wash the application site prior to anticipated skin-to-skin contact with another person. Women and children should avoid contact with skin where *Axiron* was applied, and should wash contaminated skin if accidental contact with an application site occurs.

Implantable Testosterone Pellets

Testosterone pellets [*Testopel*] are long-acting formulations indicated for male hypogonadism and delayed puberty. The pellets are implanted subdermally in the abdominal wall lateral to the umbilicus. Each pellet contains 75 mg of testosterone. The usual dosage is 150 to 450 mg (2 to 6 pellets) every 3 to 4 months. About one-third of the dose is absorbed the first month, one-quarter the second month, and one-sixth the third month. For patients

switching from IM testosterone propionate or IM testosterone enanthate, the recommended dosage is 2 pellets for each 25 mg of IM testosterone used weekly. For example, a patient receiving 75 mg of IM testosterone enanthate each week would switch to 6 pellets every 3 to 4 months.

Testosterone Buccal Tablets

Testosterone buccal tablets [*Striant*], approved for male hypogonadism, produce steady blood levels of testosterone. Tablets are applied to the gum area just above the incisor tooth, and are designed to stay in place until removed. To ensure good adhesion, tablets should be held in place (with a finger over the lip) for 30 seconds. The recommended dosage is 1 tablet every 12 hours, alternating sides of the mouth with each dose. If a tablet falls out before 8 hours, it should be replaced with a new one for the remainder of the dosing interval. If a tablet falls out after 8 hours, it should be replaced with a new one, and the next scheduled dose should be skipped (ie, the replacement tablet should remain in place for 16 hours or so). The tablets are not affected by eating, drinking, chewing gum, or toothbrushing. Adverse effects, which are usually transient, include local irritation, bitter taste, and taste distortion. Treatment for up to 1 year has not caused serious gum changes.

Intramuscular Testosterone Esters

Two IM testosterone esters are available: *testosterone cypionate* [*Depo-Testosterone*] and *testosterone enanthate* [*Delatestryl*]. Both drugs are formulated in oil, and both are long acting. Following IM injection, these drugs are slowly absorbed and then hydrolyzed to release free testosterone. For replacement therapy in hypogonadal males, the usual dosage for both is 50 to 400 mg IM every 2 to 4 weeks. Unfortunately, these preparations produce testosterone blood levels that vary widely: Testosterone levels are higher than normal immediately after dosing, and decline to lower than normal before the next dose. As a result, patients may experience significant variations in libido, energy, and mood.

ANDROGEN (ANABOLIC STEROID) ABUSE BY ATHLETES

Many athletes take androgens (anabolic steroids) and androgen precursors to enhance athletic performance. The potential benefits of this practice, although substantial, are accompanied by significant risks. Drugs commonly used by athletes include nandrolone, stanozolol, and methenolone. All of these drugs are regulated as controlled substances, making their use by athletes illegal.

Who takes steroids? Steroid use is especially prevalent among baseball players, football players, weight lifters, discus throwers, shot-putters, and bodybuilders. These drugs are also used by sprinters and athletes in endurance sports (eg, cycling, Nordic skiing). Steroids are used by athletes of all ages. This includes professionals as well as athletes in college, high school, and junior high. Use is not limited to males: Some females also take them, despite masculinizing effects.

What can anabolic steroids do for the athlete? The answer depends partly on age and gender, and partly on whether an athlete or a scientist is answering the question. Scientists and athletes have agreed for years that steroids can increase muscle mass in *young males* and in *females of all ages*. However, it was not until 1996 that scientists finally demonstrated what athletes have claimed for years: Exogenous androgens can significantly increase muscle mass and strength in *sexually mature males*. In order to demonstrate these effects, scientists gave normal men *large* daily injections of testosterone enanthate for 10 weeks. Some subjects did regular strength training while receiving the drug, and some did not. As indicated in Table 65-3, testosterone treatment produced a 7-pound increase in muscle mass in the subjects who did not exercise, and a 13-pound increase in the subjects who exercised along

TABLE 65-3 ■ Impact of Testosterone on Muscle Mass and Strength in Normal Men

Regimen	Increase in Muscle Mass (pounds)	Increase in Bench Press (pounds)
Testosterone* alone	7	20
Exercise alone	4	20
Testosterone* + exercise	13	48

*Testosterone dosage = 600 mg testosterone enanthate, IM, daily for 10 weeks.

Data from Bhasin S, Storer TW, Berman N: The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 335:1, 1996.

with taking the drug. In contrast, exercise in the absence of exogenous testosterone produced only a 4-pound increase in muscle mass. Similar increases were shown in the subjects' ability to bench-press weights (see Table 65-3). Why did it take so long for scientists to agree with the athletes? The principal reason is that, in studies performed prior to 1996, the doses of androgens employed were too small to elicit a clear response. When sufficiently large doses were finally given, the results were unequivocal. (In the 1996 study, the testosterone dosage was equivalent to 6 to 8 times the amount produced by the testes.)

The potential for adverse effects of androgens is substantial. Salt and water retention can lead to hypertension. When administered in the high doses used by athletes, androgens suppress release of LH and FSH, resulting in testicular shrinkage, sterility, and gynecomastia (breast development). Acne is common. Reduction of HDL cholesterol and elevation of LDL cholesterol may accelerate development of atherosclerosis (although no effect was seen on lipids in the study just noted). Because most of the androgens that athletes take are 17-alpha-alkylated compounds, hepatotoxicity (cholestatic hepatitis, jaundice, hepatocellular carcinoma) is an ever-present risk. Most recently, androgens have been linked with kidney damage. In females, androgens can cause menstrual irregularities and virilization (growth of facial hair, deepening of the voice, decreased breast size, uterine atrophy, clitoral enlargement, and male-pattern baldness); hair loss, growth of facial hair, and voice change may be irreversible. In boys and girls, androgens promote premature epiphyseal closure, thereby reducing attainable adult height. In boys, androgens can induce premature puberty.

What about psychologic effects? Interestingly, although androgens are reputed to cause depression, manic episodes,

and aggressiveness ('roid rage), none of these effects was observed in the 1996 study. The authors suggested that, if an athlete is mentally healthy, testosterone will not make him into a beast. On the other hand, if an athlete is already psychologically unbalanced, it is possible that steroids could intensify aggressive behavior.

Long-term androgen use can lead to an "abuse" or "addiction" syndrome. Characteristics include preoccupation with androgen use and difficulty in stopping use. When androgens finally are discontinued, an abstinence syndrome can develop similar to that produced by withdrawal of alcohol, opioids, and cocaine.

Because of their abuse potential, nearly all androgen preparations are regulated under an amendment to the Controlled Substances Act, known as the *Anabolic Steroid Control Act of 2004*, which updates the *Anabolic Steroid Control Act of 1990*. Under the 2004 legislation, most androgens are classified as Schedule III substances. The new act covers anabolic steroids as well as their precursors, and lists a large number of currently available drugs, including tetrahydrogestrinone (THG), 1-testosterone, and 4-hydroxytestosterone. In addition, it has a provision for regulating new anabolic steroids as they become available, hence new agents can be subject to regulation even though they are not specifically identified in the 2004 Act.

For more information on drug abuse in sports, a good place to start is www.wada-ama.org, the web site of the World Anti-Doping Agency. This organization, created in 1999, is dedicated to promoting, coordinating, and monitoring the fight against use of anabolic steroids and other banned substances in sports of all forms. Other good resources include the United States Anti-Doping Agency (www.usantidoping.org) and the National Center for Drug-Free Sport (www.drugfreesport.com).

KEY POINTS

- Testosterone is the principal endogenous androgen.
- Important physiologic effects of androgens are pubertal transformation in males, maintenance of adult male sexual characteristics, promotion of muscle growth, and stimulation of erythropoiesis.
- The major indication for androgens is male hypogonadism.
- The major side effects of androgens are edema, virilization in females, premature epiphyseal closure in children, and liver toxicity (in people taking 17-alpha-alkylated androgens).
- Androgens are contraindicated during pregnancy, owing to a risk of injury to the female fetus.
- Large doses of androgens can increase muscle mass and strength in athletes. However, athletic use of androgens is illegal and can cause significant harm.

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Summary of Major Nursing Implications*

ANDROGENS

Fluoxymesterone
Methyltestosterone
Oxandrolone
Testosterone
Testosterone cypionate
Testosterone enanthate

Preadministration Assessment

Therapeutic Goals

Males. Treatment of hypogonadism and delayed puberty.

Females. Relief of menopausal symptoms, especially fatigue, decreased libido, and decreased genital sensitivity.

Males and Females. Treatment of anemias and catabolic states.

Identifying High-Risk Patients

Androgens are *contraindicated* for pregnant women, for males who have prostate cancer or breast cancer, and for enhancing athletic performance.

Implementation: Administration

Routes

PO, IM, buccal, subQ (implantable pellets), and transdermal (gel, patch, underarm liquid).

Administration

Oral. Advise patients to take oral androgens with food if GI upset occurs.

Transdermal Gel and Underarm Liquid. Advise patients to wash their hands after applying the gel, and to cover the site of application with clothing (to reduce the risk of transferring testosterone to others). Advise patients not to shower or swim for several hours (to avoid washing the drug off). Advise users of the underarm liquid to avoid flames until the liquid has evaporated.

Buccal. Instruct patients to apply buccal tablets to the gum just above the upper incisor tooth, and to apply pressure (using a finger on the lip) to ensure good adhesion.

Implantable Pellets. Pellets are implanted subdermally (under local anesthesia) in the abdominal wall lateral to the umbilicus.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Virilization. Virilization may occur in women, girls, and boys. Inform female patients about signs of virilization (deepening of the voice, acne, changes in body and facial hair, menstrual irregularities), and instruct them to notify the prescriber if these occur. Irreversible changes may be avoided if androgens are withdrawn early.

Premature Epiphyseal Closure. Accelerated bone maturation in children can decrease attainable adult height. Monitor effects on epiphyses with radiographs of the hand and wrist twice yearly.

Hepatotoxicity. The 17-alpha-alkylated androgens can cause cholestatic hepatitis, jaundice, and other liver disorders. Rarely, liver cancer develops. Obtain periodic tests of liver function. Inform patients about signs of liver dysfunction (jaundice, malaise, anorexia, fatigue, nausea), and instruct them to notify the prescriber if these occur. Liver function normalizes following cessation of drug use. Avoid long-term use of 17-alpha-alkylated preparations.

Edema. Salt and water retention may result in edema. Inform patients about signs of salt and water retention (swelling of the extremities, unusual weight gain), and instruct them to notify the prescriber if these occur. Treatment consists of androgen withdrawal and, if necessary, use of a diuretic.

Teratogenesis. Androgens can cause masculinization of the female fetus. Rule out pregnancy prior to androgen use. Warn women against becoming pregnant while taking androgens.

Prostate Cancer. Avoid androgens in men with diagnosed prostate cancer. In men without diagnosed prostate cancer, monitor for exacerbation of pre-existing but covert prostate cancer.

Injury from Skin-to-Skin Transfer of Topical Testosterone. Topical testosterone—applied as a gel or underarm liquid—can transfer to others through intimate contact.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Transfer of testosterone to women can cause masculinization, as well as fetal harm if the woman is pregnant. Transfer to children can cause genital enlargement (penis or clitoris), premature development of pubic hair, advanced bone age, increased libido, and aggressive behavior. **To minimize the risk of accidental skin-to-skin transfer, advise users of testosterone gel or testosterone underarm liquid to (1) wash**

their hands after every application, (2) cover the application site with clothing once the gel has dried, and (3) wash the application site prior to anticipated skin-to-skin contact with another person. Also, advise women and children to avoid contact with skin where testosterone was applied, and advise them to wash contaminated skin if accidental contact with an application site should occur.

*Patient education information is highlighted as **blue text**.

Drugs for Erectile Dysfunction and Benign Prostatic Hyperplasia

ERECTILE DYSFUNCTION

Physiology of Erection

Oral Drugs for ED: PDE5 Inhibitors

Sildenafil

Vardenafil and Tadalafil

Nonoral Drugs for ED

Papaverine Plus Phentolamine

Alprostadil (Prostaglandin E₁)

BENIGN PROSTATIC HYPERPLASIA

Pathophysiology and Overview of Treatment

Drug Therapy of BPH

5-Alpha-Reductase Inhibitors

Alpha₁-Adrenergic Antagonists

Alpha₁ Blocker/5-Alpha-Reductase Inhibitor Combination

Tadalafil, a PDE5 Inhibitor

Other Drugs for BPH

ERECTILE DYSFUNCTION

Erectile dysfunction (ED), also known as impotence, is defined as a persistent inability to achieve or sustain an erection suitable for satisfactory sexual performance. In the United States, ED affects up to 30 million men, and accounts for 525,000 physician visits each year. ED is commonly associated with chronic illnesses, especially diabetes, hypertension, and depression. The cause of ED may be the illness itself or the drugs used for treatment. Among men with diabetes, the incidence of ED is between 35% and 75%. Some of the drugs that can cause ED are listed in Table 66-1.

The risk of ED increases with advancing age. According to the Massachusetts Male Aging Study, among men ages 40 to 70, 52% have some degree of ED, and among men over 70, 67% suffer from ED. Of the men in the 40- to 70-year-old group, 17% report minimal ED, 25% report moderate ED, and 10% report complete ED (ie, no erection at all). Only 48% report their erections are OK.

First-line treatments for ED are lifestyle measures (weight loss, increased exercise, smoking cessation), changing drug regimens that may cause ED, and drug therapy with sildenafil [Viagra] or another drug in its class. Other interventions include psychotherapy and surgical implantation of a penile prosthesis.

PHYSIOLOGY OF ERECTION

Before discussing drugs for ED, we need to review the physiology of erection. As indicated in Figure 66-1, the process begins with sexual arousal, which increases parasympathetic nerve traffic to the penis, causing local release of nitric oxide. Nitric oxide then activates guanylyl cyclase, an enzyme that makes cyclic guanosine monophosphate (cGMP). Through a series of steps, cGMP promotes relaxation of arterial and trabecular smooth muscle. The resultant arterial dilation increases local blood flow and blood pressure, which, in combination with relaxation of trabecular smooth muscle, causes expansion and engorgement of sinusoidal spaces in the corpus cavernosum. This, in turn, causes venous occlusion and thereby reduces venous outflow. The combination of increased arterial pressure and arterial inflow plus reduced venous outflow causes sufficient engorgement to produce erection. Erection subsides when cGMP is removed by phosphodiesterase type 5 (PDE5), an enzyme that converts cGMP into guanosine monophosphate.

ORAL DRUGS FOR ED: PDE5 INHIBITORS

Drugs for ED fall into two major groups: oral agents and nonoral agents. The oral agents—PDE5 inhibitors—are by far the most common treatments for ED, and hence constitute our primary focus. The nonoral agents—papaverine plus phentolamine, alprostadil—are considered briefly.

Three PDE5 inhibitors are available: sildenafil, tadalafil, and vardenafil. All three are considered first-line therapy for ED. Current guidelines recommend that, in the absence of a specific contraindication, all men with ED be offered one of these drugs. Which drug is preferred? Only a few trials have compared them head-to-head, and hence there is insufficient evidence to recommend one over the others. Accordingly, selection among them should be based on patient preference and prescriber judgment.

Sildenafil

Sildenafil [Viagra] was introduced in 1998 as the first oral treatment for ED. The drug is reliable and easy to use. Benefits derive from enhancing the natural response to sexual stimuli; sildenafil does not cause erection directly. Although sildenafil is generally well tolerated, it can be dangerous for men taking certain vasodilators, specifically alpha-adrenergic

TABLE 66-1 ■ Some Drugs That Can Cause Sexual/Erectile Dysfunction

Drug Class	Representative Drug	Incidence of SD/ED*
Renal/Cardiovascular Drugs		
Cardiac Glycosides	Digoxin [Lanoxin]	36%
Adrenergic Neuron Blockers	Reserpine	24%–40%
Central Alpha ₂ -Adrenergic Agonists	Methyl dopa	20%–30%
Beta Blockers	Propranolol [Inderal]	10%–15%
Thiazide Diuretics	Hydrochlorothiazide	10%–20%
Aldosterone Antagonists	Spirolactone [Aldactone]	4%–30%
CNS Drugs		
Selective Serotonin Reuptake Inhibitors	Fluoxetine [Prozac]	Up to 70%
Monoamine Oxidase Inhibitors	Isocarboxazid [Marplan]	16%–31%
Tricyclic Antidepressants	Amitriptyline [Elavil]	7%–30%
Antipsychotics	Chlorpromazine [Thorazine]	30%–60%
Mood Stabilizers	Lithium [Lithobid]	5%–50%
Social Lubricant/Intoxicant	Alcohol [Johnny Walker]	50%–75%
Urogenital Drugs		
5-Alpha-Reductase Inhibitors	Finasteride [Proscar]	33%

*Values for sexual dysfunction/erectile dysfunction (SD/ED) incidence are estimates based on patient reports, not on carefully controlled trials.

blockers, and nitroglycerin and other nitrates used for angina pectoris. In addition to ED, sildenafil is approved for pulmonary arterial hypertension (PAH) (see Chapter 107).

Sildenafil has been wildly popular. First-year sales were the hottest in pharmaceutical history. By now, tens of millions of men in over 100 countries have used the drug.

The erection-enhancing effects of sildenafil were discovered by accident. The drug was developed as a cardiac medicine, but benefits were minimal. However, in the course of testing, some men noticed a surprising side effect: Their impotence had been cured. The rest, as they say, is history.

As discussed in Chapter 107, sildenafil, sold as *Revatio*, is also used for pulmonary arterial hypertension (PAH).

Mechanism of Action

Sildenafil causes selective inhibition of PDE5. By doing so, it increases and preserves cGMP levels in the penis, thereby making the erection harder and more long lasting. Please note that the drug only enhances the normal erectile response to sexual stimuli (eg, erotic imagery, fantasies, physical contact). In the absence of sexual stimuli, nothing happens.

Pharmacokinetics

Sildenafil is well absorbed following oral administration. Bioavailability is about 40%. In fasting subjects, plasma levels peak about 1 hour after dosing. A high-fat meal slows absorption. As a result, plasma levels peak in 2 hours (rather than 1), and the peak concentration is reduced. Sildenafil is metabolized in the liver, primarily by the 3A4 isozyme of cytochrome P450 (CYP3A4). Both the parent drug and its major metabolite (*N*-desmethyl sildenafil) are biologically active. Both compounds are eliminated primarily in the feces (80%) and partly in the urine (13%). For both compounds, the half-life is 4 hours. Clearance of both

is delayed in men older than 65 and in men with hepatic impairment or severe renal insufficiency, causing drug levels to rise higher and persist longer.

Sexual Benefits

In Men with ED. Sildenafil has been evaluated in several thousand men (ages 19 to 87) with ED of organic, psychogenic, or mixed-cause origin. At least some improvement in erection hardness and duration was seen in 70% of men taking the drug, compared with 20% taking placebo. Benefits were dose related and lasted up to 4 hours, although they began to fade after 2 hours. Sildenafil was able to help a wide range of patients, including those with ED resulting from diabetes, spinal cord injury, and transurethral prostate resection, as well as ED of no known physical cause.

In Men Without ED. Despite anecdotal reports to the contrary, sildenafil has little or no effect on erection quality or duration in men who do not have ED. After all, there's a limit to how good an erection can get. Sildenafil cannot improve on that limit. Any apparent benefits in healthy men are likely the result of a placebo response (or perhaps wishful thinking).

In Women. Sildenafil is not approved for use in women and probably won't be. Although several large-scale studies showed the drug is safe in women, they failed to show much enhancement of sexual arousal. Hence, the manufacturer decided not to seek Food and Drug Administration (FDA) approval for treating female hypoactive sexual desire disorder or any other condition in women.

Adverse Effects

Hypotension. At recommended doses, sildenafil produces a small (8.4/5.5 mm Hg) reduction in blood pressure. However, in men taking nitrates or alpha blockers (see below), severe hypotension can develop.

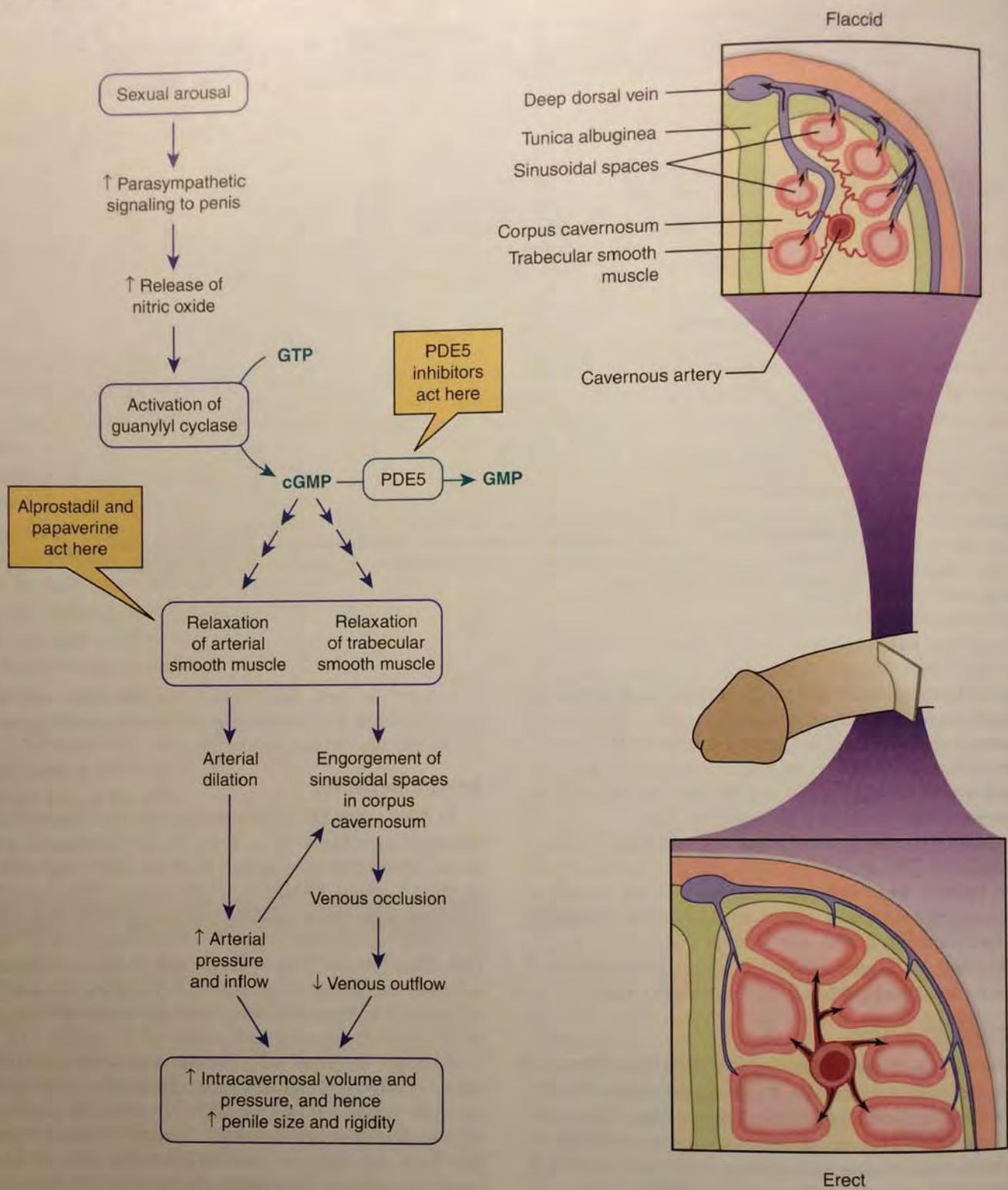


Figure 66-1 ■ Physiology of penile erection.

In the flaccid state, there is free outflow of venous blood and restricted inflow of arterial blood. During sexual arousal, cGMP relaxes arterial and trabecular smooth muscle, thereby permitting free inflow of arterial blood and subsequent engorgement of sinusoidal spaces, whose expansion compresses penile veins, thereby restricting blood outflow. The resultant accumulation of blood at elevated pressure increases penile size and rigidity. Removal of cGMP by PDE5 restores penile sine monophosphate, GMP = guanosine monophosphate, GTP = guanosine triphosphate, PDE5 = phosphodiesterase type 5.)

Priapism. A few cases of priapism (painful erection lasting more than 6 hours) have been reported. If an erection persists more than 4 hours, immediate medical intervention is required. Left untreated, priapism can damage penile tissue, thereby causing permanent loss of potency. Persistent erection can be relieved by aspirating blood from the corpus cavernosum followed by irrigation with a solution containing a vasoconstrictor (eg, epinephrine, phenylephrine, metaraminol).

Nonarteritic Ischemic Optic Neuropathy (NAION). Very rarely, men taking sildenafil have developed NAION, resulting in irreversible blurring or loss of vision. The cause is blockage of blood flow to the optic nerve. In most cases, there were underlying anatomic or vascular risk factors for NAION. Also, although NAION developed during sildenafil use, a direct causal relationship has not been established. Nonetheless, patients with NAION in one eye should not use sildenafil, owing to a potential risk of developing NAION in the other eye.

Sudden Hearing Loss. Very rarely, men taking sildenafil have experienced sudden hearing loss, usually in one ear, sometimes in association with dizziness, vertigo, and tinnitus (ringing in the ears). Hearing loss may be partial or complete. Hearing returned by the time the loss was reported in one-third of cases, but had not returned in the remaining two-thirds. To date, a direct causal relationship between sildenafil and hearing loss has not been established. Nonetheless, the drug is suspected because (1) sudden hearing loss is unusual and (2) it developed when sildenafil was taken. Men who experience sudden hearing loss should discontinue the drug—but only if they are taking it for ED; men taking the drug for PAH should continue treatment.

Other Adverse Effects. The most common adverse effects are headache (16%), flushing (10%), and dyspepsia (7%). Sildenafil may also cause nasal congestion (4%), diarrhea (3%), rash (2%), and dizziness (2%). About 3% of patients experience mild transient visual disturbances (blue color tinge to vision, increased sensitivity to light, blurring). In addition, sildenafil may intensify symptoms of obstructive sleep apnea (perhaps by relaxing pharyngeal muscles and/or dilating pulmonary blood vessels).

Drug Interactions

Nitrates. Both sildenafil and nitrates (eg, nitroglycerin, isosorbide dinitrate) promote hypotension, and they both do so by increasing cGMP (nitrates increase cGMP formation and sildenafil slows cGMP breakdown). If these drugs are combined, life-threatening hypotension could result. Therefore, *sildenafil is absolutely contraindicated for men taking nitrates.* At least 24 hours should elapse between the last dose of sildenafil and giving a nitrate. If elimination of sildenafil is slowed (owing to a CYP3A4 inhibitor or hepatic or renal impairment), an even longer time should elapse before nitrate use.

Alpha Blockers. Alpha-adrenergic antagonists—including doxazosin [Cardura] and other alpha blockers used for prostatic hypertrophy (see below)—dilate arterioles, and can thereby lower blood pressure. Combined use with sildenafil has caused symptomatic postural hypotension. Accordingly, these combinations should be used with caution.

Inhibitors of CYP3A4. Inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, erythromycin, cimetidine, saquinavir,

ritonavir, grapefruit juice) can suppress metabolism of sildenafil, thereby increasing its levels. These combinations should be used with caution.

Is Sildenafil Safe for Men with CHD?

Reports of adverse cardiovascular events, including at least 130 cardiac deaths, raised concern about the safety of sildenafil in men with coronary heart disease (CHD). However, there was a question as to what caused the adverse events: sildenafil or the sexual activity that sildenafil permitted. When attempting to answer this question, researchers made two important observations: First, giving sildenafil to resting men with severe CHD produced no harmful effects on coronary blood flow or any other hemodynamic parameter. Second, in men with stable CHD who were performing exercise, sildenafil had no effect on CHD symptoms, exercise tolerance, or exercise-induced ischemia. Taken together, these results suggest that, in men with CHD, sexual activity—and not sildenafil—is the likely cause of ischemic events. However, even though sildenafil itself appears safe for men with CHD, sexual activity may not be. Accordingly, the drug should be used with caution by men with the following conditions:

- Myocardial infarction, stroke, or life-threatening dysrhythmia within the last 6 months
- Resting hypotension (blood pressure below 90/50 mm Hg)
- Resting hypertension (blood pressure above 170/110 mm Hg)
- Heart failure
- Unstable angina

In addition, *sildenafil should not be used at all by men taking nitroglycerin or any other drug in the nitrate family.*

To reduce the risk of adverse events, candidates for sildenafil therapy should undergo a careful evaluation of cardiovascular function. Those with impaired function should be counseled about the risks posed by sexual activity and all other moderate to intense physical activity.

Preparations, Dosage, and Administration

For treatment of ED, sildenafil is available in 25-, 50-, and 100-mg tablets sold as Viagra. The usual dose is 50 mg taken 1 hour before sexual activity. The dosage range is 25 to 100 mg taken 30 minutes to 4 hours before sexual activity. A low dose (25 mg) should be considered for men older than 65, men with hepatic dysfunction or severe renal dysfunction, and men taking alpha blockers or drugs that inhibit CYP3A4. Dosing should not be done more than once a day.

Vardenafil and Tadalafil

Vardenafil and tadalafil are very similar to sildenafil. All three drugs inhibit PDE5, and all three are approved for oral therapy of ED. Vardenafil is unique in that it prolongs the QT interval, and tadalafil is unique in that its effects last 36 hours. Otherwise, the clinical effects of all three drugs appear about equal, although some patients may respond better to one than to the others. Properties of all three are summarized in Table 66-2.

Vardenafil

Actions and Use. Vardenafil [Levitra, Staxyn], approved in 2003, was the second selective PDE5 inhibitor released for ED. As with sildenafil, benefits derive from relaxing arterial and trabecular smooth muscle in the penis. Effects begin about 60 minutes after dosing, and persist about 4 hours. There is no evidence that vardenafil works faster, longer, or better than sildenafil.

Pharmacokinetics. Oral bioavailability is low (15%), and is decreased further by a high-fat meal. Plasma levels peak about 1 hour after dosing, or after 2 hours if dosing is done with a high-fat meal. Vardenafil undergoes extensive metabolism by hepatic CYP3A4, followed by excretion primarily in the feces. The drug's half-life is 4 to 5 hours.

TABLE 66-2 • Comparison of PDE5 Inhibitors

Parameter	Drug		
	Sildenafil [Viagra]	Tadalafil [Cialis]	Vardenafil [Levitra, Staxyn]
Date approved	3/27/1998	11/21/2003	8/19/2003
Dosing schedule	PRN only	PRN <i>or</i> once daily	PRN only
Dosing with food	May be taken without regard to meals—but high-fat meals delay absorption and reduce peak levels	May be taken without regard to meals	May be taken without regard to meals—but high-fat meals delay absorption and reduce peak levels
Median time to peak level	1 hr	2 hr	1 hr
Half-life	4 hr	17.5 hr	4–5 hr
Duration of action	4 hr	36 hr	4 hr
Major mode of metabolism	CYP3A4	CYP3A4	CYP3A4
Drug interactions			
Nitrates	Contraindicated: Wait 24 hr before giving a nitrate	Contraindicated: Wait 48 hr before giving a nitrate	Contraindicated: Wait 24 hr before giving a nitrate
Alpha blockers	Use with caution	Contraindicated (except for tamsulosin, 0.4 mg once daily)	Contraindicated
CYP3A4 inhibitors	Reduce sildenafil dosage	Reduce tadalafil dosage to no more than 10 mg every 72 hr	Reduce vardenafil dosage
Class I and class III antidysrhythmic drugs	No interaction	No interaction	Vardenafil prolongs the QT interval—avoid class I and class III antidysrhythmics

Adverse Effects. The most common adverse effects are headache (15%), flushing (11%), rhinitis (9%), and dyspepsia (4%). Like other PDE5 inhibitors, vardenafil can lower blood pressure. Like sildenafil, vardenafil can cause visual changes, and has been associated with sudden hearing loss and vision loss from NAION.

Vardenafil can prolong the cardiac QT interval, and might thereby pose a risk of serious dysrhythmias. However, dysrhythmias have not been reported. Nonetheless, to reduce risk, vardenafil should be used with caution in patients taking other drugs that cause QT prolongation.

Drug Interactions. Vardenafil is contraindicated for use with alpha-adrenergic blockers, and with nitroglycerin and other nitrates. Plasma levels can be increased by inhibitors of CYP3A4 (eg, ketoconazole, ritonavir), and hence such combinations must be used with caution. As noted, caution is needed in patients taking drugs that prolong the QT interval.

Preparations, Dosage, and Administration. Vardenafil is available in two formulations: standard tablets (2.5, 5, 10, and 20 mg) sold as Levitra, and orally disintegrating tablets (10 mg) sold as Staxyn. The usual dose is 10 mg taken 60 minutes before intercourse. The maximum dose is 20 mg. Doses should be reduced in men older than 65, men with hepatic impairment, and men taking inhibitors of CYP3A4. Dosing should be done no more than once a day.

Tadalafil

Actions and Uses. Tadalafil [Cialis], approved in 2003, was the third PDE5 inhibitor to hit the market. Like sildenafil and vardenafil, the drug is indicated for oral therapy of ED. As with other PDE5 inhibitors, benefits derive from relaxation of penile arterial and trabecular smooth muscle brought on by accumulation of cGMP. On average, therapeutic levels of the drug are reached by 2 hours after dosing and persist about 36 hours—much longer than with sildenafil or vardenafil. As a result, timing of dosing and sexual activity needn't

be tightly coupled. Furthermore, in addition to being approved for PRN dosing (like sildenafil and vardenafil), tadalafil is also approved for *daily* dosing (but only for men who anticipate sexual activity at least twice a week).

As discussed below, tadalafil is also used for benign prostatic hypertrophy. In addition, like sildenafil, tadalafil, sold as Adcirca, is used for PAH. (see Chapter 107).

Pharmacokinetics. Absorption rate is variable, but unaffected by food. Plasma levels peak 0.5 to 6 hours after dosing, and then slowly decline. Tadalafil undergoes metabolism by hepatic CYP3A4, followed by excretion primarily in the feces. The drug's half-life is 17.5 hours.

Adverse Effects. The most common adverse effects are headache (11%), dyspepsia (8%), back pain (5%), myalgia (4%), limb pain (3%), flushing (3%), and nasal congestion (3%). Like other PDE5 inhibitors, tadalafil can lower blood pressure. Very rarely (0.1%), the drug alters color vision. A few cases of NAION and sudden hearing loss have been reported, but a causal relationship has not been established. Because tadalafil has a long duration of action, adverse effects may persist for many hours.

Drug Interactions. Tadalafil is contraindicated for use with nitrates or alpha blockers (except tamsulosin [Flomax], 0.4 mg once daily). As with sildenafil and vardenafil, CYP3A4 inhibitors can cause levels of tadalafil to rise. To avoid toxicity, men taking CYP3A4 inhibitors should limit tadalafil dosage to 10 mg every 72 hours.

Preparation and Dosage. Tadalafil [Cialis] is available in tablets (2.5, 5, 10, and 20 mg) for dosing with or without food. Two dosing schedules are approved: PRN and daily.

PRN Dosing. The usual initial dose is 10 mg. The dosage range is 5 to 20 mg, taken no more than once a day. The manufacturer does not identify a minimum time between dosing and sexual activity. However, since blood levels peak more slowly than with sildenafil or vardenafil, allowing at least

1 hour for absorption would seem reasonable. Dosage should be reduced in men with moderate renal or hepatic insufficiency. Men with severe hepatic insufficiency should not use the drug. For men taking CYP3A4 inhibitors, the maximum dosage is 10 mg every 72 hours.

Daily Dosing. The approved dosage is 2.5 or 5 mg once a day. Daily dosing is recommended only for men who anticipate getting lucky at least twice a week.

NONORAL DRUGS FOR ED

Unlike the PDE5 inhibitors, which are administered PO, the drugs discussed in this section—papaverine, phentolamine, and alprostadil—are administered by nonoral routes. Specifically, they are administered either by injection into the penis, or by insertion into the urethra. Because of this inconvenient dosing, these drugs are second-line agents for ED.

Papaverine Plus Phentolamine

Therapeutic Use. The combination of papaverine (a smooth muscle relaxant) plus phentolamine (an alpha-adrenergic blocking agent) can counteract impotence when injected directly into the corpus cavernosum. Erection develops within 10 minutes and lasts 2 to 4 hours. In clinical trials, erection suitable for intercourse was produced in 65% to 100% of males with impotence of neurologic or vascular origin. For men who do not respond to papaverine plus phentolamine, addition of alprostadil may help (see below).

Mechanism of Action. Papaverine and phentolamine produce erection by increasing arterial inflow to the penis and decreasing venous outflow. Arterial inflow is augmented by alpha-adrenergic blockade (causing arterial dilation) and by the direct relaxant action of papaverine on arterial smooth muscle. Why is venous outflow reduced? Probably because relaxation of trabecular smooth muscle results in occlusion of the venules that drain the corporal spaces.

Adverse Effects. Priapism (persistent erection lasting more than 6 hours) occurs in about 10% of patients. Development of painless fibrotic nodules in the corpus is common. Other adverse effects include orthostatic hypotension with dizziness, transient paresthesias, ecchymosis (extravasation of blood into subcutaneous tissue), and difficulty in achieving orgasm or ejaculation. The injections are nearly painless.

Dosage and Administration. For men with psychogenic or neurogenic impotence, erection can be achieved by injecting as little as 0.1 mL of a solution containing 30 mg of papaverine/mL and 1 mg of phentolamine/mL. A 1-mL syringe with a 27- or 28-gauge, 3/8-inch needle is used. Injections are made directly into the corpus cavernosum through the lateral aspect of the shaft of the penis. These injections are nearly painless and can be administered by the patient.

Alprostadil (Prostaglandin E₁)

Intracavernous. Like the combination of phentolamine plus papaverine, alprostadil [Caverject, Caverject Impulse, Edex] can produce erection when injected directly into the corpus cavernosum. The response is rapid and the injections are relatively painless. As with papaverine, erection results from relaxation of smooth muscle (arterial, venous, and trabecular), causing arterial inflow to increase and venous outflow to decrease. Dosages range from 5 to 40 mcg and should be determined in the prescriber's office. The dosing endpoint is an erection that is sufficient for intercourse, but that does not last for more than 1 hour. Alprostadil should be used no more than 3 times a week and not more than once in 24 hours. Acute adverse effects are burning sensations (37%), prolonged erection (4%), and priapism (erection lasting more than 6 hours; 0.4%). Penile fibrosis may develop with continued use.

Transurethral. Alprostadil pellets [Muse], inserted into the urethra, are an alternative to intracavernous injections. Administration is accomplished by loading a pellet into a small plastic applicator, which is then inserted an inch and a half into the urethra. The procedure is painless. Erection develops 7 to 10 minutes after drug insertion and lasts 30 to 60 minutes. Alprostadil pellets are available in four strengths: 125, 250, 500, and 1000 mcg. Dosage should be determined in the prescriber's office; the objective is to employ the smallest dose required to produce an erection sufficient for intercourse. Alprostadil pellets should be used no more than twice every 24 hours. The most common adverse effect, dull ache in the penis, occurs in 11% of users. Priapism and penile fibrosis, which have developed with alprostadil injections, have not been reported with the pellets.

BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is a common condition that develops in more than 50% of men by age 60, and 90% by age 85. The disorder accounts for 1.7 million physician visits each year and leads to 300,000 prostatectomies. The total annual cost exceeds \$2 billion. Although BPH and prostate cancer can coexist, there is no evidence that one predisposes to the other.

PATHOPHYSIOLOGY AND OVERVIEW OF TREATMENT

Pathophysiology

The prostate is a heart-shaped gland that surrounds the urethra. Its major function is to produce fluids that contribute to ejaculate volume. In healthy men, the prostate is walnut sized and weighs between 4 and 20 gm. In men with BPH, prostate mass may reach 50 to 80 gm.

BPH is a nonmalignant prostate enlargement caused by excessive growth of epithelial (glandular) cells and smooth muscle cells. Overgrowth of epithelial cells causes *mechanical obstruction* of the urethra, whereas overgrowth of smooth muscle causes *dynamic obstruction* of the urethra. In men with BPH, the ratio of epithelium to smooth muscle varies from 1:3 to 4:1—in general, the larger the prostate, the higher the percentage of epithelium.

Signs and symptoms of BPH include urinary hesitancy, urinary urgency, increased frequency of urination, dysuria, nocturia, straining to void, postvoid dribbling, decreased force and caliber of the urinary stream, and a sensation of incomplete bladder emptying. There is no direct correlation between symptoms and prostate size. Hence, some men with only moderate enlargement may be highly symptomatic, whereas others with substantial enlargement may have no symptoms. Long-term complications of BPH include obstructive nephropathy, bladder stones, and recurrent urinary tract infections.

Treatment Modalities

BPH can be managed in three ways: invasive treatments, drug therapy, and "watchful waiting." Invasive options include transurethral resection of the prostate, laser prostatectomy, transurethral electrovaporization of the prostate, and transurethral microwave therapy. These procedures are most appropriate for men with severe symptoms or the complications noted above. Drugs are indicated for men with moderate symptoms. Watchful waiting, which consists of reassurance and annual re-evaluation, is appropriate for men with minimal symptoms.

DRUG THERAPY OF BPH

BPH can be treated with two major classes of drugs: 5-alpha-reductase inhibitors and alpha₁-adrenergic antagonists. With both, the goal is to relieve bothersome urinary symptoms and delay disease progression. As discussed below, 5-alpha-reductase inhibitors are most appropriate for men with very large prostates (mechanical obstruction), whereas alpha blockers are preferred for men with relatively small

TABLE 66-3 • Drugs for Benign Prostatic Hypertrophy

Generic Name	Trade Name	Actions in BPH	Adverse Effects
5-Alpha-Reductase Inhibitors			
Dutasteride	Avodart	Reduce dihydrotestosterone production, which causes the prostate to shrink, which reduces mechanical obstruction of the urethra. May also delay BPH progression. Benefits take months to develop.	Decreased ejaculate volume and libido. Teratogenic to the male fetus.
Finasteride	Proscar		
Alpha₁ Blockers			
Selective Alpha_{1a} Blockers			
Silodosin	Rapaflo	Blockade of alpha _{1a} receptors relaxes smooth muscle in the bladder neck, prostate capsule, and prostatic urethra, and thereby decreases dynamic obstruction of the urethra. Benefits develop rapidly.	Abnormal ejaculation (ejaculation failure, reduced ejaculate volume, retrograde ejaculation). Risk of floppy-iris syndrome during cataract surgery.
Tamsulosin	Flomax		
Nonselective Alpha₁ Blockers			
Alfuzosin	Uroxatral, Xatral	Same as the selective alpha _{1a} blockers.	Hypotension, fainting, dizziness, somnolence, and nasal congestion (from blocking alpha ₁ receptors on blood vessels)
Doxazosin	Cardura		
Terazosin	Hytrin		
Alpha_{1a} Blocker/5-Alpha-Reductase Inhibitor			
Tamsulosin/ dutasteride	Jalyn	Combination of the effects of 5-alpha-reductase inhibitors and selective alpha _{1a} blockers, as summarized above	Decreased libido and abnormal ejaculation (ejaculation failure, reduced ejaculate volume, retrograde ejaculation)
Tadalafil	Cialis	Smooth muscle relaxation in the bladder, prostate, and urethra	Hypotension, priapism

prostates (dynamic obstruction). Major drugs for BPH are summarized in Table 66-3.

5-Alpha-Reductase Inhibitors

Two 5-alpha-reductase inhibitors are available: finasteride and dutasteride. Both drugs can reduce prostate size, although several months are required for a noticeable effect. There is no proof that one drug works better than the other.

Finasteride. Finasteride [Proscar] acts in reproductive tissue to inhibit 5-alpha reductase, an enzyme that converts testosterone to dihydrotestosterone (DHT), the active form of testosterone in the prostate. Treatment reduces levels of DHT in blood by 70% (but does not decrease testosterone levels). By decreasing DHT availability, finasteride promotes regression of prostate epithelial tissue, and thereby decreases *mechanical obstruction* of the urethra. Since the percentage of epithelial tissue is highest in very large prostates, finasteride is most effective in men whose prostates are highly enlarged. Conversely, the drug confers less benefit if the degree of enlargement is small. Be aware that prostate shrinkage occurs slowly—over a period of 6 to 12 months.

By reducing levels of DHT, finasteride can protect against prostate cancer—but only cancers classified as low grade. Finasteride does not protect against high-grade prostate cancer. In fact, when given to healthy men to prevent prostate cancer, finasteride actually *increased* the likelihood of a high-

grade tumor. Accordingly, in 2010, the Oncologic Drugs Advisory Committee of the FDA recommended against allowing the manufacturer to label finasteride as a drug for prostate cancer prevention.

Finasteride is generally well tolerated. However, in 5% to 10% of patients, it decreases ejaculate volume and libido. In addition, gynecomastia (breast enlargement) develops in some men.

Finasteride is teratogenic to the male fetus, and hence is classified in FDA Pregnancy Risk Category X. When given to pregnant rats, the drug reduced the weight of the prostate gland and seminal vesicles in the male offspring, and also caused hypospadias (a malformation in which the opening to the urethra is on the underside of the penis, rather than at the tip). Finasteride is contraindicated for women who are pregnant or may become pregnant. In addition, because finasteride can be absorbed through the skin, pregnant women should not handle tablets that have been broken or crushed.

Finasteride decreases serum levels of prostate-specific antigen (PSA), a marker for prostate cancer. The expected decline is 30% to 50%. PSA levels should be determined prior to treatment and 6 months later. If PSA levels do not fall as expected, the patient should be evaluated for cancer of the prostate.

For treatment of BPH, finasteride is available in 5-mg tablets sold as *Proscar*. (As discussed in Chapter 105, the drug is also available in 1-mg tablets, sold as *Propecia*, for treatment

of male-pattern baldness.) For men with BPH, the usual dosage is 5 mg once a day, taken with or without food. Treatment continues for life.

Dutasteride. Dutasteride [Avodart] is similar to finasteride in most respects. However, there are two important differences. First, with dutasteride, the reduction in circulating DHT is more complete. And second, dutasteride has an extremely long half-life (about 5 weeks), and hence it takes months to clear the drug after dosing has stopped.

Like finasteride, dutasteride inhibits 5- α reductase, and thereby suppresses production of DHT. However, whereas finasteride inhibits only the form of 5- α reductase found in reproductive tissues, dutasteride also inhibits the form found in the skin and liver. As a result, dutasteride produces a greater reduction in circulating DHT (93% vs. 70%). Whether this translates to a greater clinical response has not been established (dutasteride and finasteride have not been directly compared).

Dutasteride is generally well tolerated. However, like finasteride, dutasteride reduces ejaculate volume and libido in some men, and causes a decline in PSA in all men.

Animal studies indicate that dutasteride can inhibit development of the external genitalia in the male fetus. Accordingly, like finasteride, the drug is classified in FDA Pregnancy Risk Category X. Dutasteride can be absorbed through the skin, and hence pregnant women should not handle the drug. Men should not donate blood while using dutasteride or for at least 6 months after stopping it (to avoid transmission to women via an infusion).

Like finasteride, dutasteride can reduce the likelihood of a low-grade prostate tumor, but it increases the likelihood of a high-grade prostate tumor. Accordingly, the drug should not be used for prostate cancer prevention.

Dutasteride is available alone in 0.5-mg capsules sold as Avodart, and in a fixed-dose combination with tamsulosin sold as Jalyn. The dosage is 0.5 mg once a day, taken with or without food. As with finasteride, treatment continues indefinitely.

Alpha₁-Adrenergic Antagonists

Five alpha₁ blockers are approved for BPH: *alfuzosin* [Uroxatral, Xatral♦], *terazosin* [Hytrin], *doxazosin* [Cardura], *silodosin* [Rapaflo], and *tamsulosin* [Flomax]. These drugs have not been directly compared in clinical trials, and hence we can't say if one is more effective than the others. However, two newer ones—silodosin and tamsulosin—may be better tolerated. The basic pharmacology of these drugs is presented in Chapter 18. Discussion here is limited to their use in BPH.

Mechanism of Action. Blockade of alpha₁ receptors relaxes smooth muscle in the bladder neck (trigone and sphincter), prostate capsule, and prostatic urethra, thereby decreasing *dynamic obstruction* of the urethra. Symptomatic *dynamic obstruction* and increased urinary flow develop *rapidly*. Because dynamic obstruction is the major contributor to symptoms in patients with relatively mild prostatic enlargement, alpha blockers are preferred to 5- α -reductase inhibitors for these men. To maintain benefits, alpha blockers must be taken lifelong. Unlike the 5- α -reductase inhibitors, the alpha₁ blockers do not reduce prostate size.

Receptor Specificity and Impact on Blood Pressure. The alpha blockers differ regarding specificity of receptor blockade and resultant impact on blood pressure. Specifically, whereas silodosin and tamsulosin are *selective for alpha_{1A} receptors* (the type of alpha₁ receptors found in the prostate), alfuzosin, terazosin, and doxazosin are *nonselective alpha₁ blockers*, and hence block alpha₁ receptors in blood vessels as well as alpha_{1A} receptors in the prostate. By blocking alpha₁ receptors in blood vessels, the three nonselective agents promote vasodilation, and can thereby lower blood pressure. In fact, two of these drugs—doxazosin and terazosin—were developed as antihypertensive agents; their use in BPH came later. Because of their impact on blood pressure, the nonselective

alpha₁ blockers are especially useful for patients who have hypertension in addition to BPH—but may be dangerous for men with reduced blood pressure. Conversely, because silodosin and tamsulosin have little or no effect on blood pressure, they are of no benefit to men with hypertension—but are preferred if reducing blood pressure would be a problem.

Adverse Effects. The alpha₁ blockers are generally well tolerated. For the nonselective agents (alfuzosin, doxazosin, and terazosin), principal adverse effects are hypotension, fainting, dizziness, somnolence, and nasal congestion. Because *silodosin* and *tamsulosin* have minimal effects on vascular smooth muscle, these drugs are less likely to cause hypotension, fainting, dizziness, or nasal congestion. However, silodosin and tamsulosin *can* cause abnormal ejaculation (ejaculation failure, reduced volume, retrograde ejaculation), whereas the nonselective agents do not. In contrast to dutasteride and finasteride, the alpha blockers do not reduce levels of PSA.

For men undergoing cataract surgery, alpha blockade increases the risk of intraoperative *floppy-iris syndrome*, a complication that can increase postoperative pain, delay recovery, and reduce the hoped-for improvement in vision acuity. In severe cases, the syndrome can cause sight-threatening defects to the iris. Men anticipating cataract surgery should postpone alpha blocker therapy until after the procedure. Men already taking an alpha blocker should be sure to tell their ophthalmologist.

Drug Interactions. Exercise caution when combining nonselective alpha blockers with other drugs that lower blood pressure; excessive hypotension could result. Drugs of concern include organic nitrates (eg, nitroglycerin), antihypertensive drugs, and PDE5 inhibitors used for ED (eg, sildenafil [Viagra]).

Strong inhibitors of CYP3A4 (an isozyme of cytochrome P450) can dramatically increase levels of alfuzosin and silodosin. Accordingly, alfuzosin and silodosin must not be combined with these drugs. Among them are erythromycin, itraconazole, nefazodone, and HIV protease inhibitors (eg, ritonavir).

Use in Women. Tamsulosin and other alpha blockers are being used off-label to treat women with urinary hesitancy or urinary retention associated with bladder outlet obstruction or insufficient contraction of the bladder detrusor muscle. Benefits derive from relaxing smooth muscle in the bladder neck and urethra. Maximal improvement may take several weeks to develop.

Dosage and Administration. All of the alpha blockers are taken orally. Dosages for BPH are as follows:

- *Doxazosin* [Cardura]—Start with 1 mg once daily and gradually increase to a maximum of 8 mg once daily.
- *Terazosin* [Hytrin]—Start with 1 mg once daily at bedtime and gradually increase to a maximum of 10 mg once daily.
- *Alfuzosin* [Uroxatral, Xatral♦]—Treat with 10 mg once daily, taken immediately after the same meal each day.
- *Silodosin* [Rapaflo]—For men with normal renal function, dosage is 8 mg once daily, taken with the same meal each day. For men with moderate renal impairment, dosage is reduced to 4 mg once daily. And for men with severe renal impairment, silodosin should be avoided.
- *Tamsulosin* [Flomax]—Treat with 0.4 mg once daily, taken about 30 minutes after the same meal each day.

Note that dosages of terazosin and doxazosin must be titrated, whereas dosages for alfuzosin, silodosin, and tamsulosin are fixed. Titration is done to minimize hypotension.

Alpha₁ Blocker/5-Alpha-Reductase Inhibitor Combination

In clinical trials, combining an alpha blocker with a 5-alpha-reductase inhibitor has been superior to treatment with either agent alone. For example, in a study known as MTOPS, men with moderate BPH were given either (1) finasteride (a 5-alpha-reductase inhibitor), (2) doxazosin (an alpha blocker), (3) both drugs, or (4) placebo. The result? After 4 years, the incidence of disease progression was 17% among men taking the placebo, 10% among men taking one drug, and only 5% among men taking both drugs. In another study, involving men with more advanced BPH, the combination of two newer drugs—dutasteride and tamsulosin—was again superior to either agent alone. Since alpha blockers and 5-alpha-reductase inhibitors work by different mechanisms, it is not surprising that combining them can be helpful: The alpha blocker can provide rapid symptomatic relief (by relaxing prostate-related smooth muscle), while, over time, the 5-alpha-reductase inhibitor can provide additional symptomatic relief (by shrinking the prostate), and may also delay disease progression.

Although use of an alpha blocker with a 5-alpha-reductase inhibitor has been common practice for years, it was not until 2008 that a specific combination—tamsulosin plus dutasteride—was given FDA approval for use in BPH. In 2010, these two drugs became available as *Jalyn* capsules, a fixed-dose combination (0.4 mg tamsulosin/0.5 mg dutasteride) for once-daily dosing 30 minutes after the same meal each day. Presumably, other combinations of an alpha blocker with a 5-alpha-reductase inhibitor would be effective too.

Tadalafil, a PDE5 Inhibitor

In 2011, the FDA approved tadalafil [Cialis] for men who have BPH by itself or BPH combined with ED. (The drug was approved for ED in 2003.) In men with BPH, tadalafil produces a modest decrease in symptoms (urinary frequency, urinary urgency, straining), but does not improve urine flow rate.

Furthermore, only 1 in 6 men benefit. Initial improvement is seen in 2 weeks. How does tadalafil help? Possibly by relaxing smooth muscle in the prostate, bladder, and urethra. Although tadalafil is the only PDE 5 inhibitor approved for ED, other PDE5 can reduce symptoms too. Owing to the risk of hypotension, tadalafil should be used with caution in men taking an alpha blocker, and should be avoided in men taking nitrates. The recommended dosage is 5 mg once a day. In men taking an alpha blocker, dosing should start at 2.5 mg once a day, and then increase to 5 mg once a day as needed and tolerated. The basic pharmacology of tadalafil, and its use in ED, are discussed above.

Other Drugs for BPH

Saw Palmetto. Saw palmetto is an herbal preparation used widely to treat BPH. The active ingredient, if any, has not been identified. How effective is saw palmetto? Not very. In fact, according to a 2006 report in the *New England Journal of Medicine*, saw palmetto is not effective at all: The herb had no effect on maximal urinary flow rate, prostate size, residual volume after voiding, or quality of life. Since this study was randomized, double-blinded, and placebo-controlled, the results are hard to ignore—even though they conflict with the results of earlier, less rigorous trials. Saw palmetto is discussed further in Chapter 108 (Dietary Supplements).

Tolterodine. Tolterodine [Detrol] is a muscarinic antagonist developed for urge incontinence (see Chapter 14). When used alone or combined with tamsulosin (an alpha blocker), tolterodine can improve urinary symptoms associated with BPH.

Botulinum Toxin. *Botulinum toxin* [Botox, others], a well-known remedy for facial wrinkles (see Box 105-1 in Chapter 105), can also help men with BPH. A single injection into the prostate can relieve urinary symptoms for up to 1 year. Benefits derive in part from blocking release of acetylcholine from neurons that innervate urinary tract smooth muscle. However, since the drug also reduces both prostate size and blood levels of PSA, other mechanisms must also be involved.

KEY POINTS

- Erectile dysfunction (ED) is defined as a persistent inability to achieve or sustain an erection suitable for satisfactory sexual performance.
- Sildenafil [Viagra] is the prototype of the PDE5 inhibitors, the only oral drugs for ED.
- The PDE5 inhibitors are first-line drugs for ED, and should be offered to all men with ED, except for men with a specific contraindication.
- By inhibiting PDE5, sildenafil prevents conversion of cGMP to GMP, and thereby preserves erection.
- Sildenafil is contraindicated for men taking organic nitrates, because the combination poses a risk of life-threatening hypotension.
- Sildenafil does not increase the risk of cardiovascular events in patients with coronary heart disease—although the sexual activity that sildenafil permits may.
- Sildenafil and other PDE5 inhibitors have been associated with rare cases of sudden hearing loss and vision loss from NAION, although a causal relationship has not been established.
- Symptoms of benign prostatic hyperplasia (BPH) result from (1) mechanical obstruction of the urethra (secondary to overgrowth of epithelial cells), and (2) dynamic obstruction of the urethra (secondary to overgrowth of smooth muscle).
- Two 5-alpha-reductase inhibitors—finasteride [Proscar] and dutasteride [Avodart]—shrink prostate epithelial tissue, and thereby decrease mechanical obstruction of the urethra. Since the percentage of epithelial tissue is highest in very large prostates, these drugs are most effective in men whose prostates are highly enlarged.
- In addition to reducing BPH symptoms, 5-alpha-reductase inhibitors may delay BPH progression.
- Tamsulosin [Flomax] and other alpha₁ blockers relax smooth muscle in the prostate capsule, prostatic urethra, and bladder neck (trigone and sphincter), and thereby decrease dynamic obstruction of the urethra. These drugs do not decrease prostate size.
- In men with BPH, beneficial effects of the alpha₁ blockers develop quickly (in days to weeks), whereas benefits of 5-alpha-reductase inhibitors develop more slowly (over several months).
- For men with BPH, combined therapy with an alpha blocker plus a 5-alpha-reductase inhibitor is more effective than therapy with either drug alone.

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Summary of Major Nursing Implications*

PDE5 INHIBITORS

Sildenafil
Tadalafil
Vardenafil

The nursing implications summarized below pertain only to the use of PDE5 inhibitors for ED, not for their use in pulmonary arterial hypertension (PAH).

Preadministration Assessment

Therapeutic Goal

PDE5 inhibitors are used to enhance both the hardness and duration of erection in men with ED.

Baseline Data

Evaluate patients for cardiovascular disorders, including stroke, hypotension, hypertension, heart failure, unstable angina, myocardial infarction, and recent history of a severe dysrhythmia.

Identifying High-Risk Patients

PDE5 inhibitors are *contraindicated* for men taking nitrates (eg, nitroglycerin), and should generally be avoided by men taking alpha blockers. Avoid *vardenafil*—but not sildenafil or tadalafil—in men taking class I or class III antidysrhythmic drugs.

Use PDE5 inhibitors with *caution* in men taking CYP3A4 inhibitors and in those with nonarteritic ischemic optic neuropathy (NAION), coronary heart disease, and other cardiovascular disorders.

Implementation: Administration

Route

Oral.

Administration

Dosing with Food. Inform patients that dosing may be done with or without food, although a high-fat meal will delay absorption of sildenafil or vardenafil (but not tadalafil).

PRN Dosing. All PDE5 inhibitors may be used PRN. Advise patients to take these drugs about 1 hour before sexual activity.

Daily Dosing. Only *tadalafil* is approved for daily dosing. Warn men that the maximum dosage is 5 mg once a day.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Cardiac Risk. Inform men with pre-existing cardiovascular disease about the cardiac risk of sexual activity (not the PDE5 inhibitor). Advise men who experience symptoms

(eg, anginal pain, dizziness) during sex to refrain from further sexual activity and discuss the event with their prescriber.

Priapism. PDE5 inhibitors can cause priapism (persistent erection), which can result in permanent impotence owing to local tissue damage. Advise patients to seek immediate medical attention if an erection lasts more than 4 hours. Treatment involves aspiration of blood from the corpus cavernosum followed by irrigation with a vasoconstrictor.

Nonarteritic Ischemic Optic Neuropathy. Very rarely, men taking PDE5 inhibitors have developed NAION with resultant irreversible blurring of vision or blindness. Advise patients to stop their PDE5 inhibitor and seek immediate medical attention if they experience sudden loss of vision in one or both eyes.

Sudden Hearing Loss. Very rarely, men taking PDE5 inhibitors have developed sudden loss of hearing, sometimes associated with dizziness, vertigo, and tinnitus. Advise men with ED to discontinue the drug if hearing loss develops. (Men taking sildenafil for PAH should not interrupt treatment.)

Minimizing Adverse Interactions

Nitrates. Combining a PDE5 inhibitor with a nitrate (eg, nitroglycerin) can cause a severe drop in blood pressure, and hence concurrent use of these drugs is contraindicated. Instruct patients to avoid nitrates for at least 24 hours after taking sildenafil or vardenafil, and for at least 48 hours after taking tadalafil.

Alpha-Adrenergic Blockers. Combining a PDE5 inhibitor with an alpha blocker (eg, doxazosin) can cause a serious drop in blood pressure. To avoid harm, use caution when combining *sildenafil* with an alpha blocker; do not combine *tadalafil* with any alpha blockers except tamsulosin (0.4 mg once daily); and do not combine *vardenafil* with any alpha blockers at all.

Inhibitors of CYP3A4. Agents that inhibit CYP3A4 (eg, ketoconazole, ritonavir, grapefruit juice) can raise PDE5 inhibitor levels. To avoid harm, dosage of the PDE5 inhibitor should be reduced.

Antidysrhythmic Drugs. Avoid *vardenafil* in men taking class I or class III antidysrhythmic drugs. Vardenafil prolongs the QT interval, and can thereby cause a severe dysrhythmia when combined with these agents.

*Patient education information is highlighted as blue text.

Introduction to the Immune System**Natural Immunity Versus Specific Acquired Immunity****Cell-Mediated Immunity Versus Antibody-Mediated (Humoral) Immunity****Introduction to Cells of the Immune System****Antibodies****Antigens****Characteristic Features of Immune Responses****Phases of the Immune Response****Major Histocompatibility Complex Molecules****Cytokines, Lymphokines, and Monokines****Antibody-Mediated (Humoral) Immunity****Production of Antibodies****Antibody Effector Mechanisms****Cell-Mediated Immunity****Delayed-Type Hypersensitivity****Cytolytic T Lymphocytes**

Life is a constant battle, and the immune system is the army that helps us prevail. This system protects us from invading organisms (viruses, bacteria, fungi, and parasites) and can destroy cancer cells before they destroy us. Unfortunately, the army does not always act in our best interest: It can attack transplanted organs and tissues and, when it runs amok, can turn on the cells it normally protects.

To study the immune system, we begin with an overview. After that, we discuss the two major types of specific immune responses: antibody-mediated immunity (humoral immunity) and cell-mediated immunity.

INTRODUCTION TO THE IMMUNE SYSTEM

Our objective in this section is to establish an overview of immune system components and how they function. Much of the information introduced here is amplified later.

Natural Immunity Versus Specific Acquired Immunity

Our bodies can mount two types of immune responses, referred to as *natural immunity* (innate or native immunity) and *specific acquired immunity*. Factors that confer natural immunity include physical barriers (eg, skin), phagocytic cells, and natural killer cells. All of these factors are present prior to exposure to a particular infectious agent and all respond non-

specifically. In contrast, specific acquired immune responses occur only after exposure to a foreign substance. The foreign substances that induce specific responses are called *antigens*, and the objective of the immune response is to destroy them. With each succeeding re-exposure to a particular antigen, the specific immune response to that antigen becomes more rapid and more intense. Specific immune responses are possible because certain cells of the immune system (T lymphocytes and B lymphocytes) possess receptors that can recognize individual antigens. In this chapter, our focus is on specific acquired immunity, not on natural immunity.

Cell-Mediated Immunity Versus Antibody-Mediated (Humoral) Immunity

Specific acquired immune responses can be classified as either cell mediated or humoral. *Cell-mediated immunity* refers to immune responses in which targets are attacked directly by immune system cells—specifically, cytolytic T cells and macrophages. *Humoral immunity* refers to immune responses that are mediated by *antibodies*. (The term *humoral*—defined as “pertaining to elements dissolved in blood or body fluids”—simply connotes that antibodies are present dissolved in the blood.)

Introduction to Cells of the Immune System

Immune responses are mediated by several types of cells, some of which play a bigger role than others. The major actors are the *lymphocytes* (B cells, cytolytic T cells, helper T cells), *macrophages*, and *dendritic cells*. Accessory cells include neutrophils and basophils. With the exception of some dendritic cells, all of the cells involved in the immune response arise from pluripotent stem cells in the bone marrow (Fig. 67-1) and, for at least part of their life cycle, circulate in the blood. Defining characteristics of individual immune system cells are summarized in Table 67-1.

B Lymphocytes (B Cells). B lymphocytes have the job of making *antibodies*. Hence, B cells mediate humoral immunity. As discussed below, antibody specificity is determined by the structure of highly specific receptors found on the surface of B cells. Like all other lymphocytes, B cells circulate in the blood and lymph. B cells are so named because in chickens, where B cells were discovered, these cells are produced in the *bursa of Fabricius*, a structure not found in mammals. In humans and other mammals, B cells are produced in the bone marrow.

Cytolytic T Lymphocytes (Cytolytic T Cells, CD8 Cells). Cytolytic T cells are key players in cellular immunity. These cells do not produce antibodies. Rather, they attack and kill target cells directly. Specificity of attack is determined by the

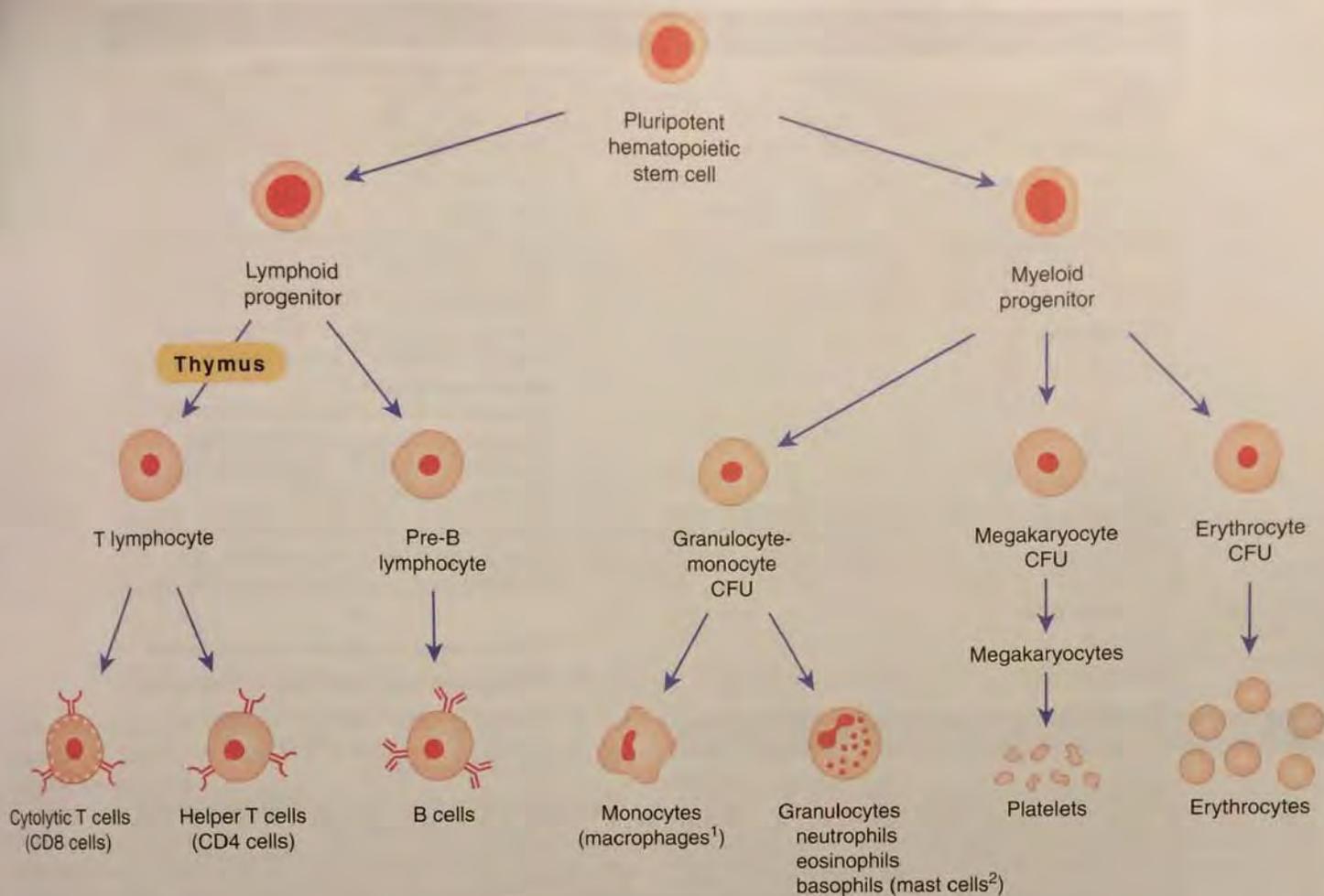


Figure 67-1 ■ Maturation of blood cells.

With the exception of platelets and erythrocytes, all of the mature blood cells shown participate in immune responses. However, only cells of lymphoid origin (cytolytic T cells, helper T cells, B cells) possess receptors that can recognize specific antigens. (CFU = colony-forming unit.)

¹Monocytes that have moved into tissues are called macrophages.

²Basophils that have moved into tissues are called mast cells.

presence of antigen molecules on the surface of the target cell and specific receptors for that antigen on the surface of the T cell. Cytolytic T cells are also known as *CD8 cells* and *cytotoxic T cells*. The designation “CD8” refers to the presence of cell-surface marker molecules known as *cell differentiation complex 8*. The “T” in T cell stands for thymus, the organ in which cytolytic T cells and helper T cells mature. Like B cells, cytolytic T cells circulate in the blood and lymph.

Helper T Lymphocytes (Helper T Cells, CD4 Cells).

Helper T cells contribute to the immune response in three ways: (1) they have an essential role in antibody production by B cells, (2) they release factors that promote delayed-type hypersensitivity (DTH), and (3) they participate in the activation of cytolytic T cells. Specificity of helper T cells is achieved through highly specific cell-surface receptors that recognize individual antigens. Like other lymphocytes, helper T cells circulate in the blood and lymph. Helper T cells carry CD4 (cell differentiation complex 4) marker molecules on their surface, and hence are referred to as *CD4 cells*.

The term *helper* is somewhat misleading, in that it connotes a useful but dispensable role. Nothing could be further from reality. Helper T cells are not simply nice to have around,

they are absolutely required for an effective immune response. The critical nature of their contribution—and the grim consequences of their absence—are manifested in people with HIV/AIDS: Helper T cells are the immune cells that HIV attacks. Because of helper T-cell loss, AIDS patients are at high risk of death from opportunistic infection.

Macrophages. Macrophages begin their existence in the bone marrow, enter the blood as monocytes, and then infiltrate tissues, where they evolve into macrophages. Macrophages are present in all organs and tissues.

The primary function of macrophages is *phagocytosis* (ie, ingestion of microbes, other foreign material, and cellular debris). In their role as phagocytes, macrophages are the principal scavengers of the body. Although their major job is phagocytosis, macrophages also have an important role in specific acquired immunity, natural immunity, and inflammation.

In specific acquired immunity, macrophages have three functions: (1) they are required for activation of T cells (both helper T cells and cytolytic T cells), (2) they are the final mediators of DTH, and (3) they phagocytize cells that have been tagged with antibodies. Of these three immune-related roles,

TABLE 67-1 • Cells of the Immune System

Cell Type	Synonyms	Primary Immune-Related Actions
Major Cell Types		
B lymphocytes	B cells	<ul style="list-style-type: none"> • Produce antibodies • Lyse target cells
Cytolytic T lymphocytes (CTLs)	Cytolytic T cells, cytotoxic T cells, CD8 cells	<ul style="list-style-type: none"> • Promote proliferation and differentiation of B cells and CTLs • Initiate delayed-type hypersensitivity
Helper T lymphocytes	Helper T cells, CD4 cells	
Macrophages		<ul style="list-style-type: none"> • Promote proliferation and differentiation of helper T cells and CTLs by serving as antigen-presenting cells • Participate in delayed-type hypersensitivity • Phagocytize cells tagged with antibodies • Phagocytize cells in the effector stage of delayed-type hypersensitivity
Dendritic cells		<ul style="list-style-type: none"> • Promote proliferation of cytolytic T cells and helper T cells by serving as antigen-presenting cells
Accessory Cells		
Mast cells		<ul style="list-style-type: none"> • Mediate immediate hypersensitivity reactions
Basophils		<ul style="list-style-type: none"> • Mediate immediate hypersensitivity reactions
Neutrophils	Polymorphonuclear leukocytes	<ul style="list-style-type: none"> • Phagocytize foreign particles (eg, bacteria), especially those tagged with IgG • Mediate inflammation
Eosinophils		<ul style="list-style-type: none"> • Attack helminths and foreign particles that have been coated with IgE • Contribute to immediate hypersensitivity reactions

IgE = immunoglobulin E, IgG = immunoglobulin G.

activation of T cells is arguably the most critical. When performing this function, macrophages are referred to as *antigen-presenting cells* (APCs). Because antigen presentation is an absolute requirement for specific immune responses (see below), you can appreciate how important macrophages are.

Dendritic Cells. Dendritic cells perform the same antigen-presenting task as do macrophages. However, unlike macrophages, dendritic cells do not also serve as scavengers. Dendritic cells are found in lymph nodes and other lymphoid tissues.

Mast Cells and Basophils. These cells mediate immediate hypersensitivity reactions. Mast cells, which are derived from basophils, are concentrated in the skin and other soft tissues. Basophils circulate in the blood. Both cell types release histamine, heparin, and other compounds that cause the symptoms of immediate hypersensitivity. Release of these mediators is triggered when an antigen binds to antibodies on the cell surface. The role of mast cells and basophils in allergic reactions is discussed further in Chapter 70 (Antihistamines).

Neutrophils. Neutrophils, also known as *polymorphonuclear leukocytes*, phagocytize bacteria and other foreign particles. As discussed below, neutrophils avidly devour cells that have been tagged with antibodies of the immunoglobulin G (IgG) class. Accordingly, neutrophils can be viewed as important effectors in humoral immunity. Neutrophils are also major contributors to inflammation.

Eosinophils. Eosinophils attack and destroy foreign particles that have been coated with antibodies of the immunoglobulin E (IgE) class. Their usual target is helminths (parasitic worms). Eosinophils also contribute to tissue injury and inflammation associated with immediate hypersensitivity reactions.

Antibodies

Antibodies are a family of structurally related glycoproteins that mediate humoral immunity. The most characteristic feature of antibodies is their ability to recognize and bind with specific antigens. Alternative names for antibodies are *immunoglobulins* and *gamma globulins*.

All antibodies are produced by B lymphocytes. Some of the antibodies that B cells produce are retained on the surface of the B cell, where they serve as the receptors whereby B cells recognize specific antigens. However, most of the antibodies that B cells produce are secreted from the cell, after which they bind to their specific antigen, thereby initiating the effector phase of humoral immunity. The process of antibody production is discussed in detail below.

All antibodies are composed of units that have the same basic structure. As shown in Figure 67-2, antibodies have four chains: two heavy chains and two light chains. Disulfide bridges connect the four chains to form a unit. Each heavy chain and each light chain has two regions, one in which the

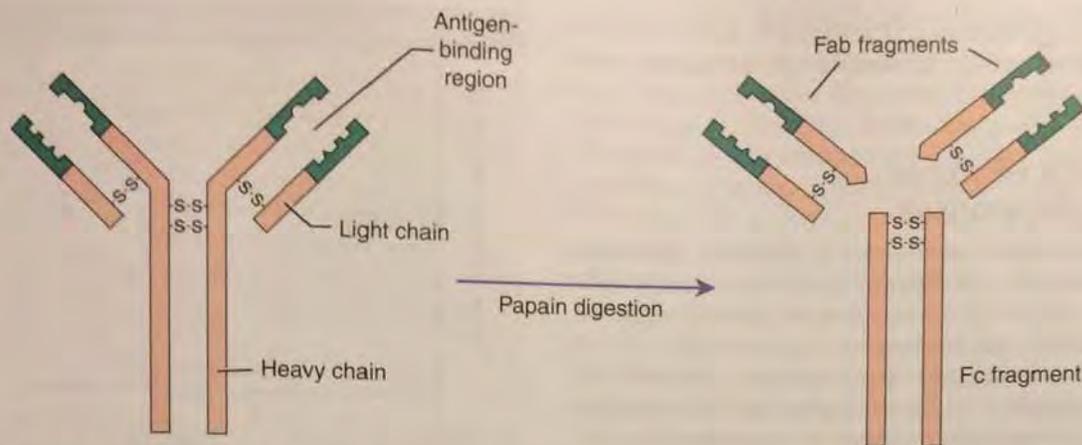


Figure 67-2 ■ Antibody structure.

The basic antibody structure depicting heavy and light chains is shown on the left. Variable regions of the heavy and light chains, which form the antigen-binding site, appear in green. As shown on the right, papain digestion of antibodies produces two types of fragments: Fab fragments, which retain the ability to bind antigen, and Fc fragments, which do not bind antigen and tend to crystallize in the test tube.

sequence of amino acids is *constant* and one in which the sequence is highly *variable*. The variable regions form the antigen-binding site.

There are five classes of antibodies (immunoglobulins), known as IgA, IgD, IgE, IgG, and IgM. All are constructed from the same basic parts just described. However, the heavy chains differ for each class. Primary functions of the five classes are summarized in Table 67-2.

When antibodies are subjected to digestion by papain in the laboratory, they break down into three pieces (see Fig. 67-2). Two of the pieces retain the ability to bind antigen, and hence are called *Fab fragments* (fragment, antigen binding). The third piece does not bind antigen and tends to form crystals in the test tube, and hence is called the *Fc fragment* (fragment, crystalline).

Antigens

Antigens are molecules that induce specific immune responses and, as a result, become the targets of those responses. By way of analogy, an antigen is like the child who pokes a stick in a hornet's nest, at once triggering a response and becoming its target. An antigen may trigger production of antibodies, cytotoxic T cells, or both—all of which can then attack the antigen.

Most antigens are large molecules. Because antigens are big, the antigen-binding region of the resultant antibodies cannot recognize and bind the entire antigen molecule. Rather, the antibodies recognize and bind selected small portions of the antigen, referred to as *epitopes* or *antigenic determinants*. All antigens have multiple epitopes. As a result, more than one antibody can bind the antigen.

In research and in clinical practice, we may want to generate antibodies to molecules that are too small to induce an immune response. To overcome this obstacle, we can link the small molecule to a larger molecule, usually a protein. When this is done, the small molecule is referred to as a

TABLE 67-2 ■ Functions of Antibody Classes

Class	Function
IgA	<ul style="list-style-type: none"> • Located in mucous membranes of the GI tract and lungs and in many secretions, where it serves as the first line of defense against microbes entering the body via these routes • Transferred to infants via breast milk; is not absorbed from the GI tract but does protect the infant against microbes <i>in</i> the GI tract
IgD	<ul style="list-style-type: none"> • Found only on the surface of mature B cells, where it serves as a receptor for antigen recognition (along with IgM)
IgE	<ul style="list-style-type: none"> • Binds to the surface of mast cells; subsequent binding of antigen to IgE stimulates release of histamine, heparin, and other mediators from the mast cells, thereby causing symptoms of allergy (eg, hives, hay fever) • Binds to parasitic worms, after which eosinophils bind to IgE and release compounds that lyse the worms
IgG	<ul style="list-style-type: none"> • Produced in copious amounts in response to antigenic stimulation, and hence is the major antibody in blood • Fixes complement and thereby promotes target-cell lysis • Binds target cells and thereby enhances phagocytosis • Transferred across the placenta to the fetal circulation, thereby providing neonatal immunity
IgM	<ul style="list-style-type: none"> • First class of antibody produced in response to an antigen • Fixes complement and thereby promotes target-cell lysis • Present on the surface of mature B cells, where it serves as a receptor for antigen recognition (along with IgD)

haptens, and the large molecule is referred to as a *carrier*. At least some of the resultant antibodies will be selective for the hapten.

Characteristic Features of Immune Responses

Cell-mediated immunity and humoral immunity share five characteristic features: specificity, diversity, memory, time limitation, and selectivity for antigens of nonself origin (ie, the ability to discriminate between self and nonself).

Specificity. Cell-mediated and humoral immune responses are triggered by specific antigens, and their purpose is to destroy the antigen that triggered the response. The ability to respond to a specific antigen (ie, the ability to make subtle distinctions among related molecules) is conferred by highly specific receptors on B cells and T cells.

Diversity. Our immune systems can respond to millions of different antigenic determinants. This is possible because our immune systems have millions of clones of B and T lymphocytes—each of which is preprogrammed to recognize a different antigenic determinant. As noted, this ability to discriminate between antigens is the result of having unique cell-surface receptors.

Memory. Exposure to an antigen affects the immune system such that re-exposure produces a faster, larger, and more prolonged response compared with the initial exposure (Fig. 67-3). Why does this happen? Because during the initial response, B and T lymphocytes that recognize the antigen undergo proliferation. Most of the new cells participate in the attack against the antigen. However, some of the new cells become *memory cells*, thereby increasing the pool of antigen-specific cells available to respond in the future. Hence, when the antigen is encountered again, the memory cells mobilize, and thereby accelerate and intensify the response.

Time Limitation. As indicated in Figure 67-3, immune responses don't last indefinitely. Rather, they are time limited. The reasons are twofold. First, as the immune response proceeds, it greatly decreases the level of antigen that initiated the response, thereby attenuating the stimulus for continuing. Second, activated B cells and T cells only function for a short time, after which they become quiescent or die. Hence, in the absence of a continuing stimulus to generate more active B cells and T cells, the immune response fades.

Selectivity for Antigens of Nonself Origin. Under normal conditions, our immune systems target only foreign antigens, leaving potentially antigenic molecules on our own cells untouched. Sparing of self is possible because, as T cells develop in the thymus, cells that are able to react with antigens of self origin are eliminated. As discussed below, this discrimination between self and nonself is made possible by *major histocompatibility complex* (MHC) molecules.

When the ability to discriminate between self and nonself fails, our immune systems can attack our own cells. The result is an *autoimmune disease*. There are many diseases of autoimmune origin, including psoriasis, multiple sclerosis, rheumatoid arthritis, myasthenia gravis, type 1 diabetes, systemic lupus erythematosus, two inflammatory bowel diseases (ulcerative colitis and Crohn's disease), and two thyroid diseases (Graves' disease and Hashimoto's thyroiditis).

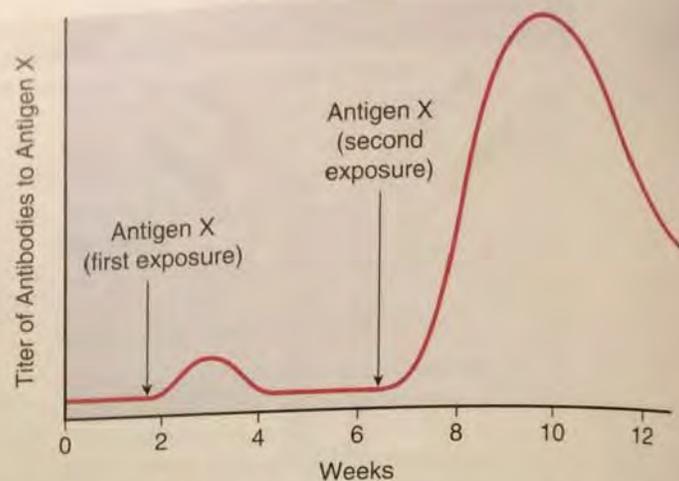


Figure 67-3 • Memory and time limitation of immune responses.

After the initial exposure to antigen X, antibody levels rise slowly, peak at a low level, and then decline rapidly. After the second exposure to antigen X, antibody levels rise more rapidly, reach a higher peak, persist longer, and then slowly decline.

Phases of the Immune Response

Specific immune responses can be viewed as having three main phases: recognition, activation, and effector.

Recognition Phase. The recognition phase occurs when a mature lymphocyte encounters its matching antigen. All specific immune responses begin with antigen recognition by B cells and T cells. Antigen recognition is possible because of antigen-specific receptors on the lymphocyte surface.

Activation Phase. Antigen recognition activates the lymphocyte, which then undergoes proliferation and differentiation. Some of the daughter cells differentiate into cells that actively participate in the immune response, attacking the source of the antigen. Other daughter cells differentiate into memory cells, thereby preparing the host for a more intense, rapid, and prolonged response in the event of antigen re-exposure.

Effector Phase. In this stage, the immune system attempts to eliminate the specific antigen that initiated the response. With cell-mediated or antibody-mediated immunity, several effector mechanisms can be involved. In cell-mediated immunity, antigen-bearing target cells can be lysed by cytotoxic T cells, or they can be ingested by macrophages. In antibody-mediated immunity, target cells may be primed for attack by phagocytes or by the complement system.

Major Histocompatibility Complex Molecules

The *major histocompatibility complex* is a group of genes that codes for *MHC molecules*, which become expressed on the surface of all cells. MHC molecules are critical to immune system function. They play a key role in the activation of helper and cytotoxic T lymphocytes; they guide cytotoxic T lymphocytes toward target cells; and they provide the basis for distinguishing between self and nonself.

There are two classes of MHC gene products, referred to as *class I MHC molecules* and *class II MHC molecules*. Class I

TABLE 67-3 ■ Functions of Selected Cytokines

Cytokine	Function
Interleukin-1	Stimulates lymphocyte progenitor cells
Interleukin-2	Stimulates proliferation and differentiation of helper T cells and cytolytic T cells
Interleukin-3	Stimulates proliferation of bone marrow lineage cells, B cells, and T cells
Interleukin-4	Activates B cells, T cells, and macrophages
Interleukin-5	Stimulates generation of eosinophils
Interleukin-6	Stimulates proliferation of bone marrow cells and plasma cells
Interleukin-7	Stimulates B cells and T cells
Interleukin-8	Attracts neutrophils, B cells, and T cells
Interleukin-9	Stimulates proliferation of mast cells
Interleukin-10	Inhibits some T cells
Interleukin-11	Enhances actions of interleukin-3
Interleukin-12	Enhances actions of interleukin-2
Interferon alpha	Activates macrophages, cytolytic T cells, and natural killer cells
Interferon gamma	Activates macrophages and T cells and enhances expression of MHC molecules
Tumor necrosis factor	Kills tumor cells; promotes inflammation
Granulocyte-macrophage colony-stimulating factor	Stimulates proliferation of monocytes, macrophages, and granulocytes (neutrophils, eosinophils, basophils)

MHC = major histocompatibility complex.

MHC molecules are found on virtually all cells except erythrocytes; class II MHC molecules are found primarily on B cells and antigen-presenting cells (macrophages and dendritic cells). As discussed below, *class I MHC molecules* on the surface of antigen-presenting cells (APCs) help initiate immune responses by “presenting” antigen to *cytotoxic T cells*. In contrast, *class II MHC molecules* on the surface of APCs help initiate immune responses by presenting antigen to *helper T cells*.

As a rule, the sequence of amino acids in MHC molecules produced by one individual differs from the sequence of amino acids in MHC molecules produced by everyone else. That is, it is rare for two individuals to have MHC molecules that are identical. As a result, MHC molecules from one individual are recognized as foreign (nonself) by the immune systems of nearly everyone else. Hence, when we attempt to transplant organs between individuals who are not identical twins, immune rejection of the transplant is likely. To reduce the risk of rejection, we can treat patients with immunosuppressant drugs (see Chapter 69).

Cytokines, Lymphokines, and Monokines

The terms *cytokine*, *lymphokine*, and *monokine* are encountered frequently when discussing the immune system and can be a source of confusion. Accordingly, clarification is in order. The term *cytokine* refers to any mediator molecule (other than an antibody) released by *any* immune system cell. A *lymphokine* is simply a cytokine released by a *lymphocyte*, and a *monokine* is simply a cytokine released by a *mononuclear phagocyte* (monocyte or macrophage). Put another way, *cytokine* is a generic term for the whole class of nonantibody mediators released by immune cells, whereas the terms *lymphokine* and *monokine* are more restrictive, referring only to nonantibody mediators released by lymphocytes and mononuclear phagocytes, respectively. Examples of cytokines and their functions are listed in Table 67-3.

ANTIBODY-MEDIATED (HUMORAL) IMMUNITY

As noted, there are two types of immune responses: humoral immunity and cell-mediated immunity. In this section, we review humoral immunity, focusing on (1) how antibodies are produced and (2) the mechanisms by which antibodies protect us. Cell-mediated immunity is discussed in the section that follows.

Production of Antibodies

Antibody production requires the cooperative interaction of three types of cells: *B cells*, which actually make the antibodies; *helper T cells* (CD4 cells), which stimulate the B cells; and an *antigen-presenting cell* (either a macrophage or a dendritic cell), which activates the CD4 cells so that they can then help the B cells. The major steps in the process are depicted in Figure 67-4.

Overview of Antibody Production

As indicated in Figure 67-4, production of antibodies begins with binding of a specific antigen (Ag) to two types of cells: a virgin B cell and an APC. The APC may be either a macrophage or a dendritic cell. After processing the Ag, the APC is able to bind with a specific CD4 cell, thereby causing the CD4 cell to proliferate and differentiate into active CD4 cells and memory CD4 cells. The active CD4 cells then bind with processed Ag on B cells, thereby causing the B cells to proliferate and differentiate into (1) plasma cells, which manufacture the antibodies; and (2) memory B cells, which await the next Ag exposure.

Specific Cellular Events in Antibody Production

B Cells. Participation of B cells in the immune response begins with recognition and binding of a *specific antigen*. The receptor that B cells employ for antigen recognition is actually an antibody (IgD or IgM). For any given B cell, this antibody (receptor) is highly specific for just one antigenic determinant. After the antigen binds the B-cell receptor, the receptor-antigen complex is internalized and the antigen is broken down into small peptide fragments. Each fragment is then complexed with a *class II MHC molecule*, after which the *antigen-MHC II complexes* are transported to the cell surface. (In Figure 67-4, only

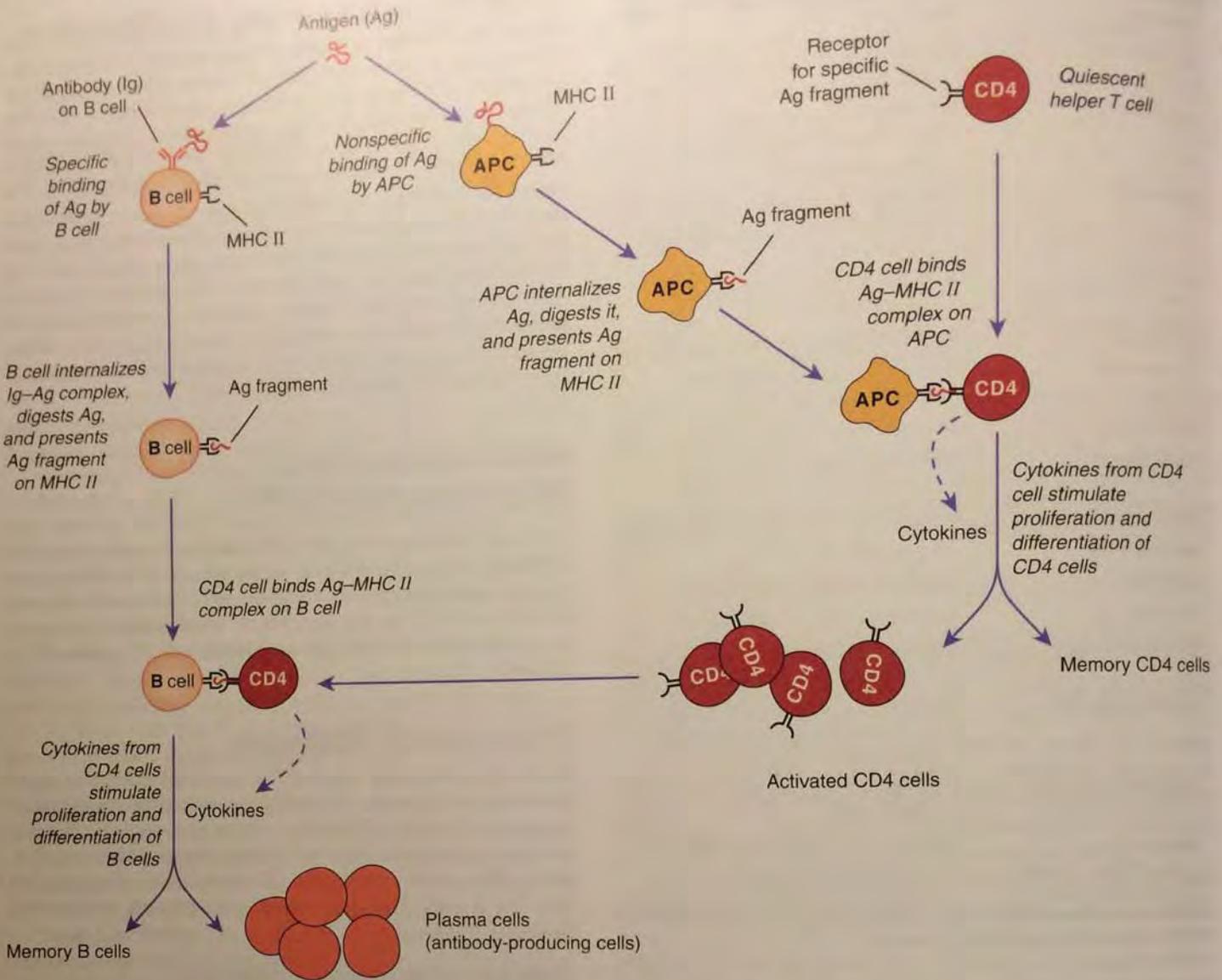


Figure 67-4 • Major events in antibody-mediated (humoral) immunity.

Humoral immunity requires three types of cells: B cells, APCs, and helper T cells (CD4 cells). Binding of a CD4 cell with an APC activates the CD4 cell, which then binds with a B cell and releases cytokines, which then stimulate the B cell. (Ag = antigen, APC = antigen-presenting cell [macrophage or dendritic cell], Ig = immunoglobulin [antibody], MHC II = class II MHC molecule.)

one such complex is shown. However, in a real cell, many such complexes, each with a different piece of the antigen, would appear on the cell surface.) The final step of B-cell activation occurs when a CD4 helper T cell recognizes and binds with an antigen-MHC II complex on the B cell. This binding causes the CD4 cell to secrete cytokines, which then stimulate the B cell to proliferate and differentiate into two types of cells: plasma cells and memory B cells. The plasma cells are the cells that make antibodies. The memory cells serve to hasten, intensify, and prolong the immune response if antigen exposure should recur.

Antigen-Presenting Cells. APCs are essential for activation of CD4 helper T cells. Why? Because CD4 cells cannot recognize antigen that is free in solution. Rather, they can only recognize antigen that has been complexed with an MHC II molecule.

Participation of APCs in the immune response begins with nonspecific binding of antigen to the APC (see Fig. 67-4). Next, as in B cells, the antigen is internalized and broken into fragments, which are then complexed with MHC II molecules and transported to the cell surface, where they are available for interaction with CD4 cells.

Helper T Cells (CD4 Cells). The job of CD4 cells in humoral immunity is to activate B cells. In the absence of activation by CD4 cells, B cells are unable to proliferate and produce antibodies.

Participation of CD4 cells in the immune response begins when these cells bind with an antigen-MHC II complex on the surface of an APC. Binding of a receptor on the CD4 cell that is specific for the particular antigen in the antigen-MHC II complex. (As noted, in order for the CD4

cell to recognize the antigen, the antigen must be complexed with an MHC II molecule, which is why the APC is essential for CD4 cell activation.) Upon binding with the antigen–MHC II complex, the CD4 cell releases cytokines, which then cause the CD4 cell itself to proliferate and differentiate into memory CD4 cells and activated CD4 cells. The activated CD4 cells then bind with their corresponding antigen–MHC II complexes on B cells, release cytokines, and thereby cause proliferation and differentiation of the B cells.

Antibody Effector Mechanisms

Antibodies are simply molecules with the ability to bind to other molecules. Antibodies have no special destructive powers. Hence, in order to rid the body of antigens, which is what antibodies are for, antibodies usually work in conjunction with other factors, namely, *phagocytic cells* and the *complement system*. The only antigens that antibodies can neutralize without help are bacterial toxins and viruses.

Oponization of Bacteria

One mechanism for ridding the body of pathogenic bacteria is phagocytosis by macrophages and neutrophils. However, because of their structures, some bacteria are difficult for phagocytes to grab hold of, and hence these bacteria are resistant to ingestion. Antibodies help promote phagocytosis of these bacteria by acting as *opsonins*. (An opsonin is a molecule that binds to a bacterium or other target particle and thereby promotes phagocytosis by providing a handle for phagocytes to grab.)

Bacterial opsonization by antibodies occurs in two steps. First, the antigen-binding region of the antibody binds with antigen on the bacterial surface, which leaves the Fc portion of the antibody projecting away from the bacterial surface. Second, phagocytes link up with the Fc portion of the antibody, which brings them in close contact with the bacterium, and hence enables them to commence phagocytosis. Phagocytes are able to bind the Fc fragment because they have high-affinity receptors for Fc on their surface. Most of the antibodies that act as opsonins belong to the IgG class.

Activation of the Complement System

The complement cascade is a complex system consisting of at least 20 serum proteins that, when activated, can cause multiple effects, including cell lysis, opsonization, degranulation of mast cells, and infiltration of phagocytes. The system can be activated in two ways, known as the *classical pathway* and the *alternative pathway*. The classical pathway is activated by *antibodies*; the alternative pathway is not. However, with both pathways, the end results are essentially the same. Consideration here is limited to the classical pathway.

The classical pathway is turned on when C1 (the first component of the complement system) encounters an antigen-antibody complex and then binds with the Fc region of the antibody. C1 will not bind with antibody that is free in solution, and hence free antibodies cannot activate the system. Activation of the complement system triggers a cascade of reactions that amplify the response at each stage. The result is production of compounds that can injure target cells.

Lysis of target cells that have been tagged with antibodies is the most dramatic effect of the complement system. Lysis

is caused by cylindrical *membrane attack complexes*, which are formed by the complement cascade. Following their insertion into the target-cell membrane, the attack complexes act as pores through which fluid can enter the cell. Fluid influx causes the target cell to swell and then burst.

Neutralization of Viruses and Bacterial Toxins

Neutralization of toxins and viruses is the only protective action that antibodies can perform unassisted. In order to hurt us, bacterial toxins must first bind with receptors on our cells. Likewise, in order to infect us, viruses must first bind with cell-surface receptors. By binding with antigenic determinants on toxins and viruses, antibodies make it impossible for toxins and viruses to bind with cellular receptors. As a result, these agents can no longer hurt us.

CELL-MEDIATED IMMUNITY

Cell-mediated immunity has two branches, one mediated by *helper T lymphocytes* (CD4 cells) plus *macrophages*, and one mediated primarily by *cytolytic T lymphocytes* (CD8 cells). In the branch mediated by CD4 cells and macrophages, the result is called *delayed-type hypersensitivity*. In the branch mediated by CD8 cells, the result is *target-cell lysis*.

Delayed-Type Hypersensitivity

The object of delayed-type hypersensitivity (DTH) is to rid the body of bacteria that replicate primarily within macrophages (eg, *Listeria monocytogenes*, *Mycobacterium tuberculosis*). For DTH to occur, two cells are needed: an *infected macrophage* and a *CD4 helper T cell*. The macrophage serves to activate the CD4 cell, which in turn activates the macrophage, thereby enabling the macrophage to kill the bacteria residing within. Hence, the same cell (ie, the macrophage) is both the activator of the CD4 cell and the recipient of the activated CD4 cell's help.

Activation of Helper T Cells. Activation of CD4 cells in DTH is essentially identical to the activation of CD4 cells in humoral immunity. As shown in Figure 67–5, the process begins when a macrophage becomes infected with intracellular bacteria. As in humoral immunity, the macrophage breaks down the antigen to small peptides, combines each peptide with a class II MHC molecule, and then presents the antigen–MHC II complexes on its surface. In the next step, a CD4 cell binds with an antigen–MHC II complex on the macrophage. As discussed above, selectivity of binding is determined by receptors on the CD4 cell that recognize a specific antigen fragment—but only when the fragment is bound to a class II MHC molecule. Binding of the CD4 cell with the APC causes the CD4 cell to release (1) cytokines that cause the CD4 cell itself to proliferate and differentiate into memory cells and (2) mediators of DTH, including interferon gamma and tumor necrosis factor.

Activation of Macrophages. *Interferon gamma*, released from the activated CD4 cell, is the major stimulus for macrophage activation. In response to interferon gamma, macrophages increase production of lysosomes and reactive oxygen. The reactive oxygen is ultimately responsible for killing bacteria inside the macrophage. In addition to ridding macrophages of bacteria, DTH produces local inflammation.

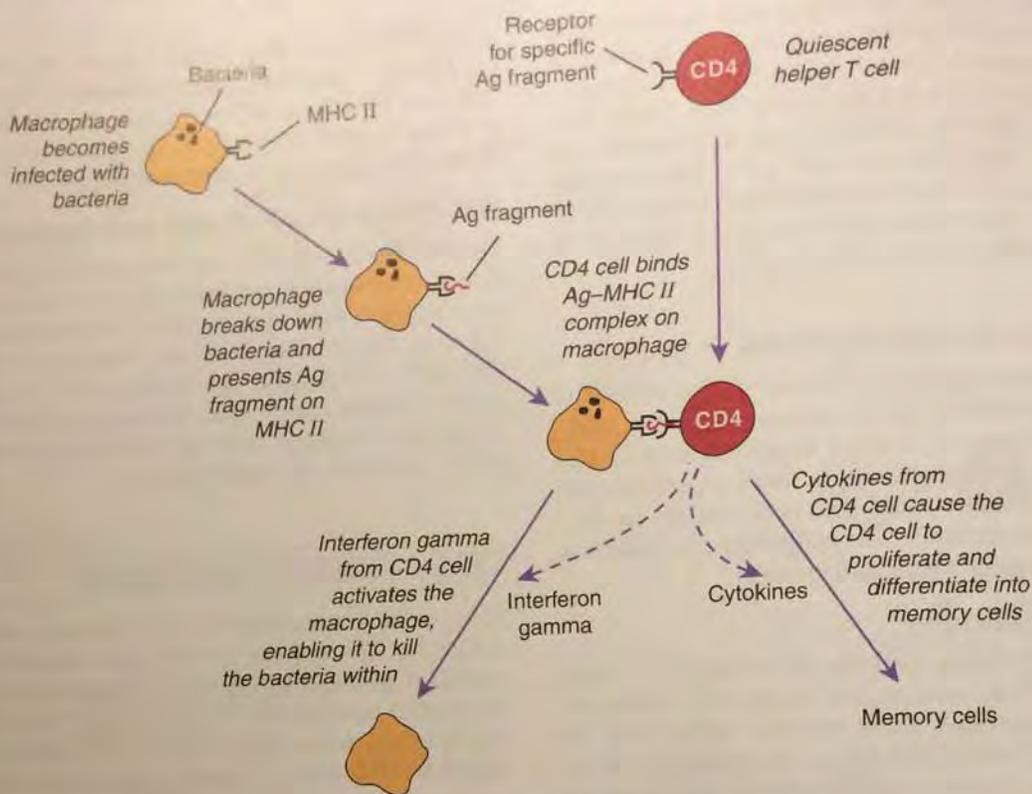


Figure 67-5 • Cell-mediated immunity: delayed-type hypersensitivity.

DTH requires two cells: an infected macrophage and a CD4 cell. Binding of the CD4 cell to the macrophage activates the CD4 cell, which then releases interferon gamma and several cytokines. Interferon gamma activates the macrophage. The cytokines cause the CD4 cell to proliferate and differentiate into memory cells. (Ag = antigen, MHC II = class II MHC molecule.)

Cytolytic T Lymphocytes

Cytolytic T lymphocytes (CTLs, CD8 cells) kill other cells. Their principal job is to kill self cells that are infected with viruses, thereby halting viral replication. In addition, CTLs participate in rejection of transplants. In this chapter, discussion is limited to killing virally infected cells.

The process by which CTLs kill other cells has two stages: activation of CTLs, followed by recognition and killing of the target cell. The overall process is depicted in Figure 67-6.

Activation of Cytolytic T Cells. Activation of CTLs requires the participation of an *antigen-presenting cell* and a *helper T cell* (CD4 cell). The process is very similar to the activation of CD4 cells discussed above. However, there is one important difference: Whereas CD4 cells specifically recognize antigen that is bound to a *class II* MHC molecule on an APC, CTLs specifically recognize antigen that is bound to a *class I* MHC molecule on an APC.

In viral infections, activation of CTLs begins with processing of viral antigens by an APC. As shown in Figure 67-6, the APC combines the antigen with a class I MHC molecule and then presents the antigen-MHC I complex on its surface. Next, a pre-CTL binds to the antigen-MHC I complex. (Like CD4 cells, each pre-CTL has receptors that are specific for a particular antigen-MHC I complex.) Linking of the pre-CTL with the APC primes the pre-CTL for the next stage of activation: stimulation by cytokines (interleukin-2, interferon gamma, and probably others) provided by an activated CD4

cell. (Activation of the CD4 cell, which is not shown in Figure 67-6, occurs when the CD4 cell encounters an APC that has a viral antigen-MHC II complex.) In response to the cytokines released by the CD4 cell, the pre-CTL undergoes proliferation and differentiation into memory CTLs and activated CTLs.

Recognition of Virally Infected Target Cells. CTLs recognize their targets by the presence of an antigen-MHC I complex. This is the same process by which CTLs recognize APCs. As noted earlier, virtually all cells in the body carry class I MHC molecules. (Class II molecules are limited to APCs and B cells.) Hence, when a cell is infected with a virus, viral antigens form intracellular complexes with MHC I molecules, after which the antigen-MHC I complexes are presented on the cell surface. As shown in Figure 67-6, activated CTLs recognize the antigen-MHC I complex, and hence bind with the target cell. Since only cells that are infected with the virus will bear viral antigens on their class I MHC molecules, attack by CTLs is limited to infected cells; all others are spared.

Mechanisms of Cell Kill. Binding of a CTL to its target cell causes the CTL to release mediators that kill the target. Two mechanisms of cell kill are involved: *lysis* and *apoptosis* (programmed cell death). The mediator of lysis is called *perforin*, a molecule that forms pores in the target-cell membrane; the resultant influx of fluid causes the cell to swell and then burst. (This mechanism is very

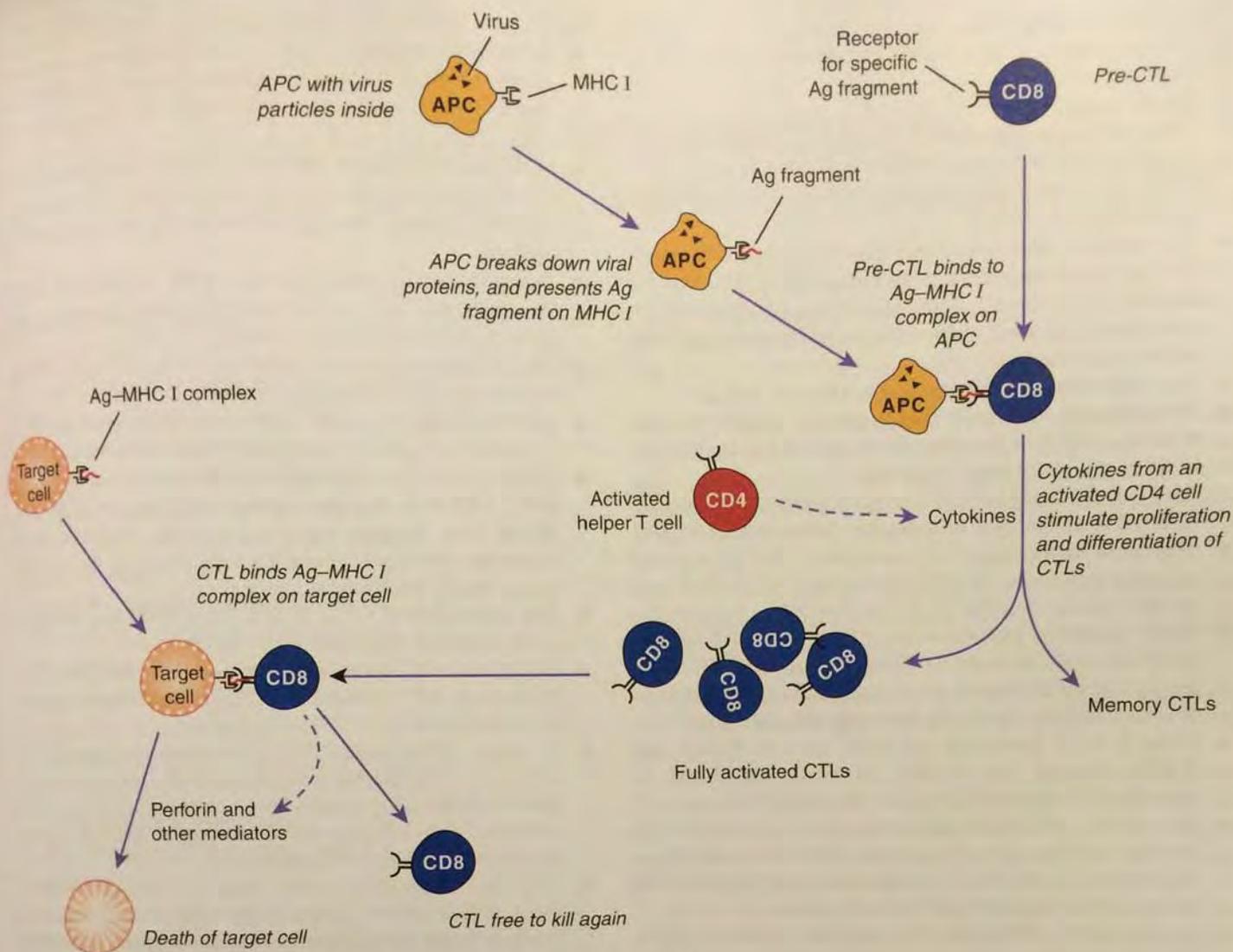


Figure 67-6 ■ Cell-mediated immunity: cytolytic T cells.

This branch of cell-mediated immunity requires three types of cells: CTLs, APCs, and CD4 cells. Binding of the pre-CTL with the APC begins the activation of the CTL. Stimulation of the CTL by cytokines from the CD4 cell completes the activation of the CTL, which then binds with and kills its target. Activation of the CD4 cells, which is not shown, takes place essentially as depicted in Figures 67-4 and 67-5. (Ag = antigen, APC = antigen-presenting cell, CTL = cytolytic T lymphocyte, MHC I = class I MHC molecule.)

similar to one by which the complement system causes cell lysis.) The mediators of apoptosis have not been identified with certainty. However, their effects are very clear. The initial effect is activation of intracellular enzymes that digest the cell's own DNA. This is followed by fragmentation

of the nucleus and cell death. Only the target cell is harmed; bystander cells and the CTL itself are not touched. In fact, after releasing its mediators, the CTL disconnects from the doomed target and goes on to seek another victim.

KEY POINTS

- The immune system helps us by attacking invading organisms (viruses, bacteria, fungi, and parasites) and cancer cells. The immune system can hurt us by attacking transplants and our own healthy cells.
- There are two basic types of immune responses: natural immunity (native or innate immunity) and specific acquired immunity.
- There are two types of specific acquired immunity: cell-mediated immunity and antibody-mediated (humoral) immunity.
- The immune system has five major types of cells: B lymphocytes (B cells), helper T lymphocytes (CD4 cells), cytolytic T lymphocytes (CD8 cells, CTLs), macrophages, and dendritic cells.

- Only lymphocytes have receptors that can recognize specific antigens.
- B cells make antibodies.
- CTLs kill target cells directly.
- Helper T cells are essential for the activation of B cells, CTLs, and the macrophages involved in delayed-type hypersensitivity (DTH).
- Macrophages have three functions in specific immunity: (1) they serve as antigen-presenting cells (APCs) in the activation of helper T cells and CTLs, (2) they are involved in DTH, and (3) they phagocytize opsonized cells in humoral immunity.
- Like macrophages, dendritic cells serve as APCs.
- An antigen is a molecule that triggers a specific immune response, and then becomes the target of that response.
- Most antigens are large molecules.
- Antibodies bind to specific, small regions of an antigen, referred to as epitopes or antigenic determinants.
- The major histocompatibility complex (MHC) is a group of genes that codes for MHC molecules, which are found on the surface of cells.
- MHC molecules have three major functions: (1) they play a key role in the activation of helper T cells and CTLs, (2) they guide CTLs toward target cells, and (3) they provide the basis for distinguishing between self and nonself.
- Class II MHC molecules are found only on B cells and APCs, whereas class I MHC molecules are found on virtually all cells (including B cells and APCs).
- It is rare for two individuals to have MHC molecules that are precisely the same. As a result, MHC molecules from one individual are usually recognized as foreign (nonself) by the immune systems of everyone else.
- A cytokine is defined as any mediator molecule (other than an antibody) released by any immune system cell.
- The most characteristic feature of antibodies is their ability to recognize specific antigens.
- Antibody production requires the cooperative interaction of three types of cells: B cells, which make the antibodies; helper T cells (CD4 cells), which stimulate the B cells; and APCs, which activate the CD4 cells so that they can then activate B cells.
- B cells have antibodies on their surface that serve as receptors for recognizing specific antigens. Binding of the antigen to the receptor is the first step in B-cell activation.
- Activation of B cells is completed when a CD4 cell binds with an antigen–MHC II complex on the B cell and then releases cytokines, which then stimulate the B cell.
- In order to activate a B cell, a CD4 cell must first become activated itself. CD4 activation is initiated by binding of the CD4 cell with an antigen–MHC II complex on an APC.
- Antibodies eliminate antigens by three mechanisms: (1) direct neutralization of toxins and viruses, (2) opsonization of bacteria, and (3) activation of the complement system.
- Opsonization (coating bacteria with antibodies) helps macrophages and neutrophils grab onto bacteria, and thereby facilitates phagocytosis.
- The complement system forms pores in the bacterial cell membrane, thereby promoting death by lysis.
- Cell-mediated immunity can result in delayed-type hypersensitivity (DTH) and lysis of target cells by CTLs.
- DTH involves two types of cells: an infected macrophage and a CD4 cell. The macrophage activates the CD4 cell, which then releases interferon gamma, which in turn stimulates the macrophage, thereby enabling the macrophage to kill the bacteria inside it.
- The major role of CTLs is to kill self cells that have become infected with viruses.
- Activation of CTLs proceeds in two steps: first, the CTL binds to an APC; second, the CTL is stimulated by cytokines provided by a CD4 cell.
- Binding of CTLs with APCs differs from binding of CD4 cells with APCs in that CTLs specifically recognize antigen that is bound to a class I MHC molecule on the APC, whereas CD4 cells specifically recognize antigen that is bound to a class II MHC molecule.
- CTLs kill target cells in two ways: (1) they release perforin, which creates pores in the cell, thereby causing death by lysis; and (2) they release compounds that cause apoptosis (programmed cell death).
- Activated CTLs attack only self cells that have antigen–MHC I complexes; all other self cells, including the CTLs, are spared.
- Specific immune responses result in production of memory T cells and memory B cells. As a result, the next time an antigen is encountered, the immune response occurs faster and with greater intensity.

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General Considerations**Definitions****Public Health Impact of Immunization****Reporting Vaccine-Preventable Diseases****Immunization Records****Adverse Effects of Immunization****Vaccine Information Statements****Childhood Immunization Schedule****Target Diseases****Measles, Mumps, and Rubella****Diphtheria, Tetanus, and Pertussis****Poliomyelitis*****Haemophilus influenzae* Type b****Varicella (Chickenpox)****Hepatitis B****Hepatitis A****Pneumococcal Infection****Meningococcal Infection****Influenza****Rotavirus Gastroenteritis****Genital Human Papillomavirus Infection****Specific Vaccines and Toxoids****Measles, Mumps, and Rubella Virus Vaccine (MMR)****Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine****Poliovirus Vaccine*****Haemophilus influenzae* Type b Conjugate Vaccine****Varicella Virus Vaccine****Hepatitis B Vaccine****Hepatitis A Vaccine****Pneumococcal Conjugate Vaccine****Meningococcal Conjugate Vaccine****Influenza Vaccine****Rotavirus Vaccine****Human Papillomavirus Vaccine**

The purpose of immunization is to protect against infectious diseases. Thanks to widespread immunization, the incidence of several infectious diseases has been dramatically reduced, and one disease—smallpox—has been eliminated from the planet. Of all the advances in medicine, none has reduced sickness and death more than immunization.

Experience has shown that the most effective way to reduce vaccine-preventable diseases (VPDs) is to create a

highly immune population. Accordingly, universal vaccination is a national goal. Although immunization carries some risk, the risks from failing to vaccinate are much greater.

In this chapter, discussion is limited to childhood immunization. Chapter 110 (Potential Weapons of Biologic, Radiologic, and Chemical Terrorism) addresses vaccines for anthrax and smallpox. And Chapter 93 (Antiviral Agents I: Drugs for Non-HIV Viral Infections) addresses a vaccine for avian flu.

GENERAL CONSIDERATIONS**Definitions**

In order to discuss immunization, we need to use special terminology. Accordingly, we begin the chapter by defining some terms.

Vaccine. A vaccine is a preparation containing whole or fractionated microorganisms. Administration causes the recipient's immune system to manufacture antibodies directed against the microbe from which the vaccine was made. Most of the preparations discussed in this chapter are vaccines.

Killed Vaccines Versus Live Vaccines. There are two major classes of vaccines: killed and live (albeit attenuated). Killed vaccines are composed of whole, killed microbes or isolated microbial components (eg, the polysaccharide of *Haemophilus influenzae* type b or the surface antigen of hepatitis B). In contrast, live, attenuated vaccines are composed of live microbes that have been weakened or rendered completely avirulent. Live vaccines can be dangerous in recipients who are immunocompromised. Why? Because these people are unable to mount an effective immune response, even against an avirulent organism.

Toxoid. A toxoid is a bacterial toxin that has been changed to a nontoxic form. Administration causes the recipient's immune system to manufacture antitoxins (ie, antibodies directed against the natural bacterial toxin). Antitoxins protect against injury from toxins, but do not kill the bacteria that produce them. In this chapter, only two toxoids are considered: tetanus toxoid and diphtheria toxoid.

Vaccination. The terms *vaccination* and *vaccine* derive from *vaccinia*, a virus whose name in turn derives from *vacca* (Latin for cow). At one time, vaccinia virus was used as a vaccine against smallpox. (Vaccinia itself causes cowpox—a mild sickness—and in the process induces synthesis of smallpox antibodies.) Hence, when the term *vaccination* was originally coined, it had the limited meaning of giving vaccinia to generate immunity against smallpox. Today, vaccination refers broadly to giving any vaccine or toxoid.

Immunization: Active Versus Passive. *Immunization* is a more inclusive term than *vaccination*, in that immunization refers to production of both active immunity and passive im-

TABLE 68-1 ■ Impact of Vaccination on the Incidence of Some Vaccine-Preventable Diseases in the United States

	Prevaccine Era: Peak Number of Cases (Year the Peak Occurred)	Vaccine Era: Number of Cases Reported in 2006	Percentage Decrease in Cases
Vaccine Introduced Before 1980			
Diphtheria	30,508 (1938)	0	100
Smallpox	110,672 (1920)	0	100
Poliomyelitis (wild)	21,269 (1952)	0	100
Rubella	488,796 (1964)	11	99.99
Measles	763,094 (1958)	55	99.99
Mumps	212,932 (1964)	6584	96.91
Pertussis	265,269 (1934)	15,632	94.11
Tetanus	601 (1948)	41	93.18
Vaccine Introduced Between 1980 and 2005			
Varicella (chickenpox)	5,358,595* (1988)	48,445	99.10
Hepatitis A	254,518* (1971)	3579	98.59
Acute hepatitis B	74,361* (1985)	4713	93.66
Invasive <i>Haemophilus influenzae</i> type B	20,000* (1984)	208	98.96
Invasive pneumococcal disease	64,400* (1999)	5169	91.97

*Estimated peak number.

Data from Roush SW, Murphy TV, and the Vaccine-Preventable Disease Table Working Group: Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA* 298:2155–2163, 2007.

munity, whereas vaccination refers to production of active immunity only.

Active immunity develops in response to infection or to administration of a vaccine or toxoid. In either case, the result is endogenous production of antibodies. Active immunity takes weeks or months to develop, but is long lasting. Discussion in this chapter is limited almost exclusively to active immunization.

Passive immunity is conferred by giving a patient *preformed* antibodies (immune globulins). Unlike active immunity, passive immunity protects immediately, but persists only as long as the antibodies remain in the body.

Specific Immune Globulins. These preparations contain a high concentration of antibodies directed against a specific antigen (eg, hepatitis B virus). Administration provides immediate passive immunity. These preparations are made from donated blood and do not transmit infectious diseases.

Public Health Impact of Immunization

Widespread vaccination has had a profound impact on public health. In the United States, vaccination has greatly reduced the incidence of some infectious diseases (eg, pertussis, mumps, tetanus) and virtually eliminated five others: diphtheria, smallpox, poliomyelitis, rubella, and measles (Table 68-1). With two diseases, results have been even more dramatic: wild-type polio is gone from the Western hemisphere, and smallpox is gone from the planet.

Despite these successes, we still have a long way to go: Although our national vaccination rate is at an all-time high,

every year 2.1 million children ages 1 to 3 years receive few or no vaccinations. In some parts of the country, more than 50% of the children are not current. The consequences of failing to vaccinate can be enormous. For example, between 1989 and 1991, a measles epidemic occurred; 55,000 cases were reported, 11,000 people were hospitalized, and more than 130 people died, half of them young children.

The Childhood Immunization Initiative, begun in 1993, is directed at preventing such epidemics in the future. The goal is to eliminate all indigenous cases of diphtheria, measles, rubella, tetanus, and *H. influenzae* type b infection from the United States. The program aims to achieve these goals by improving vaccine delivery systems, increasing community participation, reducing vaccine costs to parents, developing safer and simpler vaccines, and involving more federal agencies in providing vaccines to populations who otherwise might not have access to them. Thanks to these strategies, three of these diseases—diphtheria, rubella, and measles—are virtually gone from this country.

From a strictly economic viewpoint, vaccination is a sound investment. On average, we save \$14 in future healthcare costs for every dollar we spend on vaccination.

Reporting Vaccine-Preventable Diseases

Public health officials rely on healthcare providers to report cases of VPDs. Nearly all VPDs that occur in the United States are notifiable. Healthcare providers should report individual cases to their local or state health department. Each week, the state health departments make a report to the Cen-

TABLE 68-2 ■ Contraindications That Apply to All Vaccines and Conditions Often Incorrectly Regarded as Contraindications

True Contraindications (Vaccine Should Not Be Administered)	Not Contraindications (Vaccine May Be Administered)
Anaphylactic reaction to a specific vaccine: Contraindicates further doses of that vaccine	Mild to moderate local reaction (soreness, erythema, swelling) following a dose of an injectable vaccine
Anaphylactic reaction to a vaccine component: Contraindicates use of all vaccines that contain that substance	Mild acute illness with or without low-grade fever
Moderate or severe illnesses with or without a fever	Diarrhea
	Current antimicrobial therapy
	Convalescent phase of illnesses
	Prematurity (same dosage and indications as for normal, full-term infants)
	Recent exposure to an infectious disease
	Personal or family history of either penicillin allergy or nonspecific allergies

ters for Disease Control and Prevention (CDC). The information is used to (1) determine if an outbreak is occurring, (2) evaluate prevention and control strategies, and (3) evaluate the impact of national immunization policies and practices.

Immunization Records

The *National Childhood Vaccine Act of 1986* requires a permanent record of each mandated vaccination a child receives. The information should be recorded in either (1) the permanent medical record of the recipient or (2) a permanent office log or file. The following data are required:

- Date of vaccination
- Route and site of vaccination
- Vaccine type, manufacturer, lot number, and expiration date
- Name, address, and title of the person administering the vaccine

The purpose of these records is twofold. First, they help ensure that children receive appropriate vaccinations. Second, they help avoid overvaccination, and thereby reduce the risk of possible hypersensitivity reactions. To promote uniformity in record keeping, an official immunization card has been adopted by every state and the District of Columbia.

Adverse Effects of Immunization

Vaccines are generally very safe. Although mild reactions are common, serious events are rare. Many children experience local reactions (discomfort, swelling, and erythema at the injection site). Fever is also common. Very rare but severe effects include anaphylaxis (eg, in response to measles, mumps, and rubella virus vaccine [MMR]); acute encephalopathy (caused by diphtheria and tetanus toxoids and pertussis vaccine [DTP]); and vaccine-associated paralytic poliomyelitis (VAPP) (caused by oral poliovirus vaccine [OPV]). In 2011, the safety of vaccines was reaffirmed in a lengthy report—*Adverse Effects of Vaccines: Evidence and Causality*—issued by the Institute of Medicine of the National Academies.

Vaccinations can hurt. This pain, in turn, can lead to needle fears, procedural anxiety, and avoiding additional immuniza-

tions. Accordingly, minimizing pain is a primary goal. Strategies to reduce pain and anxiety include holding the child upright during the vaccination, applying a topical anesthetic, providing tactile stimulation, performing IM injections rapidly without prior aspiration, and injecting the most painful vaccine last. Pain can be further reduced by use of microneedles, needle-free devices, and intranasal vaccines. What about giving analgesic/antipyretics, such as acetaminophen and ibuprofen? Recent evidence indicates that giving these drugs before or shortly after vaccination can reduce the immune response. Accordingly, routine use of these drugs to prevent pain and/or fever should be discouraged.

Immunocompromised children are at special risk from live vaccines. The reason is that, in the absence of an adequate immune response, the viruses or bacteria in these normally safe vaccines are able to multiply in profusion, thereby causing serious infection. Accordingly, live vaccines should generally be avoided in children who are severely immunosuppressed. Causes of immunosuppression include congenital immunodeficiency, HIV infection, leukemia, lymphoma, generalized malignancy, and therapy with radiation, cytotoxic anticancer drugs, and high-dose glucocorticoids.

Some parents are concerned that *thimerosal*, a mercury-based preservative found in some vaccines, might cause *autism*. For two reasons, this concern is unfounded. First, several large, high-quality studies conducted in Denmark, Britain, and the United States have failed to show a causal link between childhood immunization using thimerosal-containing vaccines and development of autism. Second, thimerosal is being phased out of vaccines made here (owing to concerns about mercury exposure, not concerns about autism). At this time, the amount of thimerosal in most routinely used childhood vaccines is either zero or extremely low (less than 0.5 mcg per 0.5-mL dose). The only exceptions are certain flu vaccines, which still contain thimerosal as a preservative. However, even if these flu vaccines are used, total mercury exposure from childhood vaccination will still be well below the limit considered safe by the Food and Drug Administration (FDA) and the Environmental Protection Agency.

The risk of serious adverse reactions can be minimized by observing appropriate *precautions* and *contraindications*. Table 68-2 lists contraindications that apply to all vaccines.

Precautions and contraindications that apply to specific vaccines are discussed in the context of those preparations. Certain conditions, such as diarrhea and mild illness, may be inappropriately regarded as contraindications by some practitioners. As a result, vaccination may be needlessly postponed. Conditions that are often considered contraindications, although they are not, are also listed in Table 68-2.

Practitioners are required to report certain adverse events to the *Vaccine Adverse Event Reporting System* (VAERS). The information is used to help determine whether (1) a particular event that occurs after vaccination is actually caused by the vaccine, and (2) what the risk factors might be. In addition to reporting events that they are required to report, practitioners should report all other serious or unusual adverse events, regardless of whether they believe the event was caused by the vaccine. Forms for reporting adverse events can be obtained from the VAERS web site (www.vaers.hhs.gov) or by calling 1-800-822-7967.

The *National Vaccine Injury Compensation Program* (NVICP), established by the *National Childhood Vaccine Injury Act of 1986*, was created to provide compensation for injury or death resulting from vaccination. The program is intended as an alternative to civil litigation in that negligence need not be proved. As a provision of the law, a table was created listing the vaccines covered by the program and the injuries, disabilities, illness, and conditions—including death—for which compensation may be paid. Compensation may also be paid for injuries not listed in the table, provided that (1) a listed vaccine is involved and (2) causality can be demonstrated. Injuries related to vaccines not listed in the table are not covered under the program. Additional information can be obtained by calling the NVICP automated recording at 1-800-338-2382.

Vaccine Information Statements

The National Childhood Vaccine Injury Act requires that Vaccine Information Statements (VISs) be given to all vaccinees (or their parents or legal representatives) before certain vaccines are administered. The VISs, produced by the CDC, are one-page, two-sided documents that describe the benefits and risks of specific vaccines. For vaccines that require a series of shots, a VIS must be given *before each dose*, not just the first dose. The VISs are available in over 30 languages, and can be obtained online at www.cdc.gov/vaccines/pubs/vis/default.htm.

Childhood Immunization Schedule

Each year, the CDC's Advisory Committee on Immunization Practices (ACIP), in cooperation with the American Academy of Family Physicians and the American Academy of Pediatrics, issues revised recommendations for childhood immunization in the United States. Figures 68-1 and 68-2 (see pp. 871-872) show the recommended schedule for 2011. You can find the catch-up immunization schedule for persons ages 4 months through 18 years and the most recent updates online at www.cdc.gov/vaccines/.

TARGET DISEASES

Routine childhood vaccination is currently recommended for protection against 16 infectious diseases: diphtheria, tetanus (lockjaw), pertussis (whooping cough), measles, mumps, ru-

bella, invasive *H. influenzae* type b, hepatitis A, hepatitis B, polio, varicella (chickenpox), influenza, invasive pneumococcal disease, meningococcal disease (meningitis), rotavirus gastroenteritis, and genital human papillomavirus infection. In the discussion below, certain VPDs are considered in a group (eg, measles, mumps, rubella). Why? Because vaccination against these VPDs is traditionally done simultaneously using a combination vaccine.

Measles, Mumps, and Rubella

Measles. Measles is a highly contagious viral disease characterized by rash and high fever (103°F to 105°F). Infection is spread by inhalation of aerosolized sputum or by direct contact with nasal or throat secretions. Initial symptoms include fever, cough, headache, sore throat, and conjunctivitis. Three days later, rash develops. Rash begins at the hairline, spreads to the rest of the body in 36 hours, and then fades in a few days. Secondary infections can result in pneumonia and otitis media (inner ear infection). However, of the potential complications of measles, encephalitis is by far the most serious. Sequelae of encephalitis include blindness, deafness, and convulsions. Although encephalitis is rare (0.1% incidence), it carries a 10% risk of death. Thanks to widespread vaccination, measles is rarely seen in the Western hemisphere.

Mumps. Mumps is a viral disease that primarily affects the parotid glands (the largest of the three pairs of salivary glands). Although mumps can occur in adults, it usually occurs in children ages 5 to 15. As a rule, the first symptom is swelling in one of the parotid glands, often accompanied by local pain and tenderness. The patient may also experience fever (100°F to 104°F). Swelling increases for 2 to 3 days and then fades entirely by day 6 or 7. Swelling in the second parotid gland often develops after swelling in the first, but may also occur simultaneously or not at all. Painful *orchitis* (inflammation of the testes) develops in about one-third of adult and adolescent males. Acute *aseptic meningitis* develops in about 10% of all patients; symptoms, which resolve completely, include dizziness, headache, and vomiting. In the United States, the incidence of reported mumps cases has declined from a high of 212,932 in 1984 to only 6584 in 2006.

Rubella. Rubella, also known as German measles, is a generally mild viral infection. However, if it occurs during pregnancy, the consequences can be severe. Initial symptoms include sore throat, mild fever, and swelling in lymph nodes located behind the ears and in the back of the neck. Shortly after, a rash develops on the face and scalp, spreads rapidly to the torso and arms, and then fades in 2 or 3 days. Arthritis may also develop, mainly in women. In pregnant women, rubella can cause miscarriage, stillbirth, and congenital defects, especially if the disease occurs during the first trimester. Possible birth defects include cataracts, heart disease, mental retardation, and hearing loss. In the United States, rubella has been eliminated: Since 2002, all cases reported here have been traceable to foreigners who brought the disease from abroad.

Diphtheria, Tetanus, and Pertussis

Diphtheria. Diphtheria is a potentially fatal infection caused by *Corynebacterium diphtheriae*, a gram-positive bacillus. The bacterium colonizes the throat and nasal passages, and produces a toxin that spreads throughout the body. Initial

symptoms include sore throat, fever, headache, and nausea. Colonization of the airway begins as patches of gray or dirty-yellow membrane that eventually grow together, forming a thick coating. This coating, combined with swelling, can impede swallowing and breathing; in severe cases, a tracheostomy is needed. The toxin produced by *C. diphtheriae* can damage the heart and nerves, resulting in heart failure and paralysis. Diphtheria treatment includes giving diphtheria antitoxin and antibiotics (eg, erythromycin, penicillin G). In the United States, only 37 cases were reported between 1980 and 1992. However, of those infected, about 10% died, mainly children and the elderly. In 2006, no cases were reported.

Tetanus (Lockjaw). Tetanus, also known as lockjaw, is a frequently fatal disease characterized by painful spasm of all skeletal muscles. The cause is a potent endotoxin elaborated by *Clostridium tetani*, a gram-positive bacillus. Infection with *C. tetani* typically results from puncturing the skin with a nail, splinter, or other object that is contaminated with soil, street dust, or animal or human feces. The first symptom is often stiffness of the jaw, hence the name *lockjaw*. As infection progresses, the patient may experience stiff neck, difficulty swallowing, restlessness, irritability, headache, chills, fever, and convulsions. Eventually, spasm develops in muscles of the abdomen, back, neck, and face. The case fatality rate is 21%. The yearly incidence of tetanus peaked at 601 cases in 1948, but was only 41 cases in 2006. Treatment options include tetanus antitoxin, a booster dose of tetanus toxoid, and antibiotics (eg, penicillin G, doxycycline).

Pertussis (Whooping Cough). Pertussis, also known as *whooping cough* or the *100-day cough*, occurs primarily in infants and young children. The cause is *Bordetella pertussis*, a gram-negative bacillus. Initial symptoms include rhinorrhea, mild fever, and persistent cough. As infection worsens, coughing becomes more intense. The acute phase of the disease can last 4 to 6 weeks. During this time, infants experience difficulty eating, drinking, and breathing. Deaths have occurred. Complications of pertussis include pneumonia, seizures, ear infections, and, rarely, permanent neurologic injury. In the United States, reported cases dropped from a high of 265,269 in 1934 to 8483 in 2003. However, the rate of infant pertussis is rising. Worldwide, the disease afflicts about 60 million people, and kills 335,000 each year, mainly infants and young children. Erythromycin is the treatment of choice.

Poliomyelitis

Poliomyelitis, also known as polio or infantile paralysis, is a serious disease in which the poliovirus attacks neurons of the central nervous system that control muscle movement. The result is skeletal muscle paralysis, usually in the legs. However, muscles of respiration and muscles of the arms may be affected too. In about 10% of cases, polio is fatal. The disease is caused by three different polioviruses. Paralytic polio is usually caused by type 1 poliovirus. Polio has no cure. However, proper symptomatic treatment can improve comfort and reduce or prevent some crippling effects. Vaccination against polio has eliminated the disease from the Western hemisphere, except for eight to nine cases annually caused by the vaccine itself. To prevent vaccine-induced polio, use of the live virus vaccine (oral polio vaccine) has been discontinued in the United States. The number of cases worldwide was 1315 in 2007—nearly double the 784 cases documented in 2003.

Haemophilus influenzae Type b

Haemophilus influenzae type b is a gram-negative bacterium that can cause meningitis, pneumonia, and serious throat and ear infections. The bacterium is the leading cause of serious illness in children under the age of 5 years, and the most common cause of bacterial meningitis, which has a mortality rate of 5%. Among children who survive meningitis, between 25% and 35% suffer lasting neurologic deficits. As a result of childhood vaccination, the annual incidence of infection dropped from an estimated 20,000 cases in 1984 to less than 208 in 2008. Of the cases that occurred, almost all were in unvaccinated children. Infection with *H. influenzae* can be treated successfully with antibiotics.

Varicella (Chickenpox)

Varicella (chickenpox) is a common, highly contagious, and potentially serious disease of childhood. The causative organism is varicella-zoster virus, a member of the herpesvirus group. Patients typically develop 250 to 500 maculopapular or vesicular lesions, usually on the face, scalp, or trunk. Other symptoms include fever, malaise, and loss of appetite. Among children, the most common complications are bacterial superinfection and acute cerebellar ataxia. Reye's syndrome and encephalitis develop rarely. Among adults, the most serious common complication is varicella pneumonia. As a rule, symptoms in adults are more severe than in children: Hospitalization is 10 times more likely in adults, and death is 20 times more likely. Although adults account for only 2% of varicella cases, they account for 50% of varicella-related deaths. Before varicella vaccine became available, over 90% of children in the United States got chickenpox by age 11, which corresponds to 4 million cases a year. In addition, about 11,000 victims were hospitalized each year, and about 100 died. Since universal vaccination began in 1995, hospitalizations have dropped dramatically: One study indicates that, between 2000 and 2006, an estimated 50,000 hospitalizations were avoided.

Herpes zoster, also known as *shingles* or simply *zoster*, develops in 15% of patients years after childhood chickenpox has resolved. The cause is reactivation of varicella-zoster viruses that had been dormant within sensory nerve roots. Episodes of zoster begin with neurologic pain in the area of skin supplied by the affected nerve roots. Blister-like lesions develop within 3 to 4 days, and usually disappear 2 to 3 weeks later. However, in about 14% of patients, neurologic pain persists for a month or more—and in a few cases, pain lasts for years.

Hepatitis B

Hepatitis B is a serious liver infection caused by the hepatitis B virus. Acute infection can cause anorexia, malaise, diarrhea, vomiting, jaundice, pain (in muscles, joints, and stomach), and death. Chronic infection can result in cirrhosis, liver cancer, and death. Each year in the United States, hepatitis B infects 50,000 people, puts 11,000 in the hospital, and kills 3000 to 5000. Worldwide, 170 million people have chronic hepatitis B, and 250,000 die from it annually.

Although hepatitis B is found in virtually all body fluids, only blood, serum-derived fluids, saliva, semen, and vaginal

fluids are infectious. The most common modes of transmission are needle-stick accidents, sexual contact with an infected partner, maternal-child transmission during birth, and use of contaminated IV equipment or solutions.

Hepatitis B is discussed further in Chapter 93 (Antiviral Agents I: Drugs for Non-HIV Viral Infections).

Hepatitis A

Hepatitis A is a serious liver infection caused by the hepatitis A virus. In the United States, hepatitis A infects between 125,000 and 200,000 people annually, and causes about 100 deaths (from acute liver failure). Symptoms of hepatitis A include fever, malaise, nausea, jaundice, anorexia, diarrhea, and stomach pain. However, not all infected persons become symptomatic. Among children less than 6 years old, only 30% develop symptoms. In contrast, symptoms are present in most older infected children and adults. When symptoms do occur, they develop rapidly and then usually fade in less than 2 months. However, between 10% and 15% of patients experience prolonged or relapsing disease that persists up to 6 months. During the course of the infection, the virus undergoes replication in the liver, passage into the bile, and then excretion in the feces. As a result, the usual mode of transmission is fecal-oral in the context of close personal contact with an infected person. In addition, hepatitis A can be contracted by ingesting contaminated food or water. Blood-borne transmission is rare. Individuals at risk include household and sexual contacts of infected individuals, international travelers, and people living in areas where hepatitis A is endemic (eg, American Indian reservations, Alaskan Native villages).

Pneumococcal Infection

In the United States, *Streptococcus pneumoniae* (pneumococcus) is the leading bacterial cause of childhood meningitis, sepsis, pneumonia, and otitis media. Among children with pneumococcal meningitis, up to 50% suffer permanent brain damage or hearing loss, and about 10% die. The risk of acquiring pneumococcal infection is highest for children under the age of 2 years. Factors that increase infection risk include sickle cell disease, immunodeficiency, asplenia, chronic diseases, attending a group day care center, and being a Native American, African American, Alaskan Native, or socially disadvantaged person. Worldwide, pneumococcal infection ranks among the leading causes of death from infectious disease. Routine childhood immunization against pneumococcal disease began in 2000. Since then, the incidence of severe pediatric infection has dropped sharply.

Meningococcal Infection

Meningococcal infection is a serious disease caused by *Neisseria meningitidis*, also known as the meningococcus. Invasive meningococcal disease is a leading cause of meningitis in American children. Worldwide, the majority of infections are caused by five *N. meningitidis* serogroups—designated A, B, C, Y, and W-135—identified on the basis of antigenic differences in surface polysaccharides. In the United States, only three serogroups—B, C, and Y—cause most cases. Meningococcal infection is readily transmitted through direct contact with respiratory secretions from patients and from asymptomatic

carriers. Injury results from a meningococcal endotoxin, which is produced so quickly that death can result within hours of infection onset. Although only 1400 to 2800 cases occur here each year, the disease is clearly of great concern, with a fatality rate of 10% to 14% despite antibiotic therapy. Furthermore, of those who survive, 11% to 19% suffer severe and permanent sequelae, including neurologic disability, deafness, mental retardation, and limb amputations. Infection rate is highest during infancy, with a second peak during adolescence and early adulthood. Outbreaks can occur in day care centers, schools, and colleges. Risk factors for acquiring the disease include immunodeficiency, antecedent viral infection, household crowding, chronic underlying disease, active and passive smoking, and anatomic and functional asplenia. A meningococcal vaccine was approved in 1981, but it was not very effective in children. Hence, routine childhood immunization was not recommended until 2005, the year a more effective vaccine was introduced.

Influenza

Influenza is a serious infection of the respiratory tract and a major cause of morbidity and mortality worldwide. Characteristics of the influenza virus and of influenza itself (mode of transmission, symptoms, time course, methods of prevention and treatment) are discussed in Chapter 93.

Rotavirus Gastroenteritis

Rotavirus, which infects the intestinal mucosa, is the most common diarrheal pathogen worldwide. Infection presents initially as upset stomach and vomiting, usually with fever, and then progresses to several days of diarrhea, which can be mild to severe. The combination of vomiting and severe diarrhea can result in life-threatening dehydration. Virtually all children become infected repeatedly within the first 5 years of life. However, the first episode is generally the worst. As a result, severe diarrhea and dehydration are most likely in the very young—children 3 to 35 months old. Before a rotavirus vaccine became available, rotavirus infected 2.7 million American children under the age of 5 each year, resulting in more than 400,000 office visits, 55,000 to 70,000 hospitalizations, and 20 to 60 deaths. Worldwide, annual deaths are estimated in the hundreds of thousands. Infected children shed large amounts of rotavirus in their stool, and hence transmission is usually fecal-oral, resulting from touching the stool or a contaminated object. Rotavirus infection can be prevented with two vaccines: RotaTeq and Rotarix. An older vaccine—RotaShield—was withdrawn owing to a high rate of intussusception, a life-threatening blockage of the intestine.

Genital Human Papillomavirus Infection

Human papillomavirus (HPV) infection is the cause of virtually all anogenital warts and cervical cancers. Transmission occurs most often by direct genital contact during vaginal or anal intercourse. The types of HPV that infect the anogenital region can also cause cancers of the vulva, vagina, urethra, tongue, tonsils, penis, and anus. Cancer of the penis is rare. By contrast, cancer of the anus in men and women who have anal intercourse is now as common as cervical cancer was before the Papanicolaou (Pap) test was introduced. Discus-

sion below focuses on the role of HPV in cervical cancer and genital warts. Treatment of genital warts is discussed in Chapter 105 (Drugs for the Skin).

Genital HPV is the most common sexually transmitted infection. In the United States, about 6.2 million people become infected each year. Among sexually active males and females, about 50% will be infected at some time during their life. Fortunately, although HPV infections are common, most are benign and clear spontaneously, usually within a few months to a year. As a result, most men and women never get genital warts, and most women never get precancerous cervical lesions or cervical cancer.

About 100 types of HPV are known to exist, about 40 of which infect the anogenital region. The types of HPV associated with malignancy are referred to as *oncogenic* or *high-risk*, whereas the types associated with genital warts are called *low-risk*. About 95% of genital warts are caused by just two HPV types, known as HPV-6 and HPV-11. About 70% of cervical cancers are caused by two other types, known as HPV-16 and HPV-18. Fortunately, only 2.2% of women carry high-risk strains.

Worldwide, cervical cancer is the second leading cause of cancer deaths among women. Each year, more than 500,000 cases are diagnosed, and about 280,000 prove fatal. In the United States, cervical cancer is less prevalent: Total new cases for 2006 were estimated at 9700, with about 3700 being fatal. Why so few deaths in the United States? Because American women undergo regular Pap tests, which detect precancerous and cancerous changes, thereby allowing early intervention (excision or ablation of the affected tissue) before advanced cancer can develop.

SPECIFIC VACCINES AND TOXOIDS

The discussion below is limited to the vaccines and toxoids used for routine childhood immunization. The major preparations employed are listed in Table 68-3. Their adverse effects are summarized in Table 68-4. Childhood immunization schedules for the year 2011—as recommended by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP)—are summarized in Figures 68-1 and 68-2 (see pp. 867-868). As noted earlier, catch-up schedules and recent changes are available online at www.cdc.gov/vaccines/.

Measles, Mumps, and Rubella Virus Vaccine (MMR)

Description. Measles, mumps, and rubella vaccine (MMR), marketed under the trade name *M-M-R II*, is a combination product composed of three live virus vaccines. Administration induces synthesis of antibodies directed against measles, mumps, and rubella viruses. Immunization with MMR is preferred to immunization with the three vaccines separately.

Efficacy. Following a single dose of MMR, an effective response develops in 97% of vaccinees within 2 to 6 weeks. A second dose increases protection.

Adverse Effects. *Mild.* Local soreness, erythema, and swelling may develop soon after vaccination. Within 1 to

2 weeks, some children experience glandular swelling in the cheeks and neck and under the jaw. Transient rash develops in 5% to 15% of vaccinees. Fever (103°F or higher) that persists for several days occurs in 5% to 15% of vaccinees 5 to 12 days after vaccination. MMR-induced fever poses a small risk of febrile seizures, but these seizures do *not* increase the risk of developing epilepsy. Within 1 to 3 weeks of the first dose, about 1% of vaccinees experience pain, stiffness, and swelling in one or more joints; these symptoms usually subside in a few days, but occasionally persist for a month or more. Fever, soreness, and pain can be reduced with acetaminophen or a nonaspirin, nonsteroidal anti-inflammatory drug, such as ibuprofen.

Severe. Transient thrombocytopenia occurs very rarely (0.0025% incidence). MMR-induced thrombocytopenia is generally benign, but hemorrhage has developed in a few vaccinees.

MMR can induce anaphylactic reactions. However, the incidence is extremely low: Only 11 certain cases have occurred in over 70 million vaccinations. In the past, MMR-induced anaphylaxis was thought to result from allergy to eggs (the measles component of the vaccine is produced in chick embryo fibroblasts). However, it now appears that egg allergy is not involved. Rather, the leading suspect is a hydrolysis product of gelatin. Until more is known, authorities recommend that MMR be used with extreme caution in children with a known allergy to gelatin. The ACIP is reconsidering whether caution is still required for children with an allergy to eggs.

There is no causal link between MMR and development of autism, Crohn's disease, or any other serious long-term illness. A 1998 paper by Andrew Wakefield,* showing a connection between MMR and "autistic enterocolitis," was an elaborate fraud, perpetrated with the intention of earning millions (in part by selling diagnostic kits and a single-component vaccine against measles). The publisher withdrew Wakefield's paper in 2010.

Precautions and Contraindications. MMR is *contraindicated* during pregnancy and should be used with *caution* in children with a history of (1) thrombocytopenia or thrombocytopenic purpura or (2) anaphylactic-like reactions to gelatin, eggs, or neomycin (MMR contains a small amount of this antibiotic).

MMR can be administered to children with *mild febrile illness* (eg, upper respiratory infection with or without low-grade fever). However, for children with *moderate or severe febrile illness*, vaccination should be postponed until the illness has resolved.

Products that contain *immune globulins* (eg, whole blood, serum, specific immune globulins) contain antibodies against the viruses in MMR, and therefore can inhibit the immune response to the vaccine. Accordingly, in children who have received immune globulins, vaccination with MMR should be postponed for at least 3 to 6 months.

In vaccinees who are *immunocompromised*, replication of the viruses in MMR may be much greater than normal. If the immunodeficiency is severe, death may occur. However, of the more than 200 million people who have received MMR

*Wakefield AJ, et al: Ileal-lymphoid nodular hyperplasia, nonspecific colitis, and pervasive developmental disorder in children. *Lancet* 351:637-641, 1998 [Retraction, *Lancet* 375:445, 2010].

TABLE 68-3 ■ Some Vaccines and Toxoids Available in the United States

Preparation Name (Synonym)	Trade Name	Type of Preparation	Route and Site
Measles, mumps, and rubella virus vaccine (MMR)	M-M-R II	Live virus	subQ, in outer aspect of upper arm
Measles, mumps, and rubella, and varicella virus vaccine (MMRV)	ProQuad*	Live virus	subQ, in anterolateral thigh or outer aspect of upper arm
Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP)	Tripedia, DAPTACEL, Infanrix, Boostrix, [†] Adacel [†]	Toxoids (diphtheria and tetanus) plus inactivated bacteria components (pertussis)	IM, in deltoid or mediolateral thigh
Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and inactivated poliovirus vaccine	PEDIARIX	Toxoids (diphtheria and tetanus) plus inactivated bacteria components (pertussis) plus inactive viral antigen (hepatitis B) plus inactivated viruses (poliovirus)	IM, in deltoid or anterolateral thigh
Tetanus and diphtheria toxoids	Generic only	Toxoids	IM, in deltoid or mediolateral thigh
<i>Haemophilus influenzae</i> type b (Hib) conjugate vaccine	ActHIB, PedvaxHIB, Hiberix, Comvax [‡]	Bacterial polysaccharide conjugated to protein	IM, in midthigh or outer aspect of upper arm
Poliovirus vaccine, inactivated (IPV, Salk vaccine)	IPOL	Inactivated viruses of all three polio serotypes	subQ, in anterolateral thigh
Varicella virus vaccine	Varivax	Live virus	subQ, in deltoid or anterolateral thigh
Hepatitis A vaccine (HepA)	Havrix, VAQTA	Inactive viral antigen	IM, in deltoid
Hepatitis B vaccine (HepB)	Recombivax HB, Engerix-B, Comvax [‡]	Inactive viral antigen	IM, in deltoid or anterolateral thigh
Pneumococcal conjugate vaccine (PCV13)	Prennar 13 [§]	Bacterial polysaccharide conjugated to protein	IM, in deltoid or anterolateral thigh
Pneumococcal polysaccharide vaccine (PPV)	Pneumovax 23	Bacterial polysaccharide (unconjugated)	IM, in deltoid or anterolateral thigh
Influenza vaccine (inactivated)	Fluzone, Fluvirin, others	Inactive viral antigen	IM, in deltoid or anterolateral thigh
Influenza vaccine (live)	FluMist	Live virus	Intranasal
Meningococcal conjugate vaccine (MCV4)	Menactra, Menveo	Bacterial polysaccharide conjugated to protein	IM, in deltoid
Meningococcal polysaccharide vaccine (MPSV4)	Menomune	Bacterial polysaccharide (unconjugated)	subQ
Rotavirus vaccine	Rotarix, RotaTeq	Live virus	Oral
Human papillomavirus vaccine	Cervarix, Gardasil	DNA-free virus-like particles	IM, in deltoid or anterolateral thigh

*ProQuad, approved in 2005, combines two older vaccines: M-M-R II and Varivax.

[†]Boostrix and Adacel are indicated for *booster* immunization, *not* for the *initial* immunization series. Boostrix is for patients 11 to 18 years old. Adacel is for patients 11 to 64 years old.

[‡]Comvax is a combination vaccine for immunization against *H. influenzae* type b and hepatitis B.

[§]Prennar 13, a 13-valent pneumococcal conjugate vaccine approved in 2010, has replaced Prennar, a 7-valent pneumococcal conjugate vaccine approved in 2000.

in the United States, only 5 such deaths have been reported. Nonetheless, *children with severe immunodeficiency should NOT be given MMR*. Severe immunodeficiency may result from immunosuppressive drugs (eg, glucocorticoids, cytotoxic anticancer drugs), certain cancers (eg, leukemia, lymphoma, generalized malignancy), and advanced HIV infection. It is important to note, however, that if HIV infection is *asymptomatic*, MMR should be given. In this situation, there is no risk of serious adverse events from MMR, whereas there *is* a risk of severe complications from measles should

the disease develop. Vaccination with MMR early in the course of HIV infection is preferred. Why? Because the immune response to vaccination diminishes as HIV infection progresses.

Route, Site, and Immunization Schedule. MMR is administered subQ into the outer aspect of the upper arm. Each child should receive two vaccinations, the first between 12 and 15 months of age, and the second between 4 and 6 years. If the scheduled second dose is missed, it can be given between ages 7 and 18 years.

TABLE 68-4 ■ Adverse Effects of Some Vaccines and Toxoids

Preparation	Mild Effects	Serious Effects
Measles, mumps, and rubella virus vaccine	Local reactions; rash; fever; swollen glands in cheeks and neck and under the jaw; pain, stiffness, and swelling in joints	Anaphylaxis, thrombocytopenia (A study showing a connection with autism was a fraud)
Diphtheria and tetanus toxoids and acellular pertussis vaccine	Local reactions, fever, fretfulness, drowsiness, anorexia, persistent crying	Acute encephalopathy, convulsions, shock-like state
<i>Haemophilus influenzae</i> type b conjugate vaccine	Local reactions, fever, crying, diarrhea, vomiting	None
Poliovirus vaccine (IPV and OPV*)	Local reactions (only from IPV)	Vaccine-associated paralytic poliomyelitis (only from OPV*)
Varicella virus vaccine	Local reactions, fever, mild varicella-like rash (local or generalized)	None
Hepatitis A vaccine	Local soreness, headache, anorexia, fatigue	Anaphylaxis
Hepatitis B vaccine	Local discomfort, fever	Anaphylaxis
Pneumococcal conjugate vaccine	Local reactions, fever, irritability	None
Influenza vaccine (inactivated)	Local reactions, fever	Guillain-Barré syndrome (association not proved)
Influenza vaccine (live attenuated)	Runny nose, headache, cough, fever	Guillain-Barré syndrome (association not proved)
Meningococcal conjugate vaccine	Local reactions, headache, fatigue	None
Rotavirus vaccine	Diarrhea, vomiting, ear infection, runny nose, sore throat	Intussusception?
Human papillomavirus vaccine	Local reactions, fainting	Guillain-Barré syndrome (association not proved)

*OPV is no longer used in the United States.

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine

Preparations. Primary vaccination against diphtheria, tetanus, and pertussis is usually done simultaneously using a combination product, composed of diphtheria toxoid, tetanus toxoid, and *acellular* pertussis vaccine (DTaP). This vaccine, which is relatively new, has replaced an older product, composed of diphtheria toxoid, tetanus toxoid, and *whole-cell* pertussis vaccine (DTP). DTaP is more effective than DTP and causes fewer and milder side effects. Vaccination with DTaP produces antibodies against diphtheria toxin, tetanus toxin, and *B. pertussis*. DTaP is available under several trade names, including *Tripedia*, *DAPTACEL*, and *Infanrix*.

After children have received a full series of DTaP shots, they will need subsequent booster shots. Two booster products are available: *Tdap* and *Td*. *Tdap*—sold as *Boostrix* and *Adacel*—is composed of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine—and hence boosts protection against all three diseases. By contrast, *Td* boosts protection against only two diseases: tetanus and diphtheria. *Tdap* was approved in 2005, whereas *Td* has been used for years. Because the incidence of pertussis is on the rise, a booster shot with *Tdap*, rather than *Td*, is now recommended for all children 11 to 18 years old. Boosters with *Td* are given every 10 years thereafter.

Products used for immunization against diphtheria, tetanus, and pertussis are summarized in Table 68-5.

Efficacy. Immunization with DTaP reduces the risk of disease by 80% to 90%. Protection begins after the third dose and persists 4 to 6 years (against pertussis) and 10 years (against diphtheria and tetanus).

Adverse Effects. Mild. Mild reactions are common. The reactions seen most often are low fever (50%), fretfulness (50%), drowsiness (30%), anorexia (20%), and local reactions: pain (50%), swelling (40%), and redness (30%). Mild reactions usually develop a few hours to 48 hours after vaccination and then resolve in 1 to 2 days. Ibuprofen can decrease fever and pain.

Moderate. Moderate reactions occur less often than mild reactions. Persistent, inconsolable crying lasting 3 hours or longer, occurs in 1% of vaccinees. Crying is most likely with the first dose of DTaP and is not associated with long-term sequelae. Fever (105°F or higher) occurs in 0.3% of vaccinees; the pertussis component appears responsible. Approximately 0.06% of vaccinees develop convulsions (with or without fever). These seizures have no permanent sequelae and do not increase the risk of subsequent febrile or afebrile seizures. A shock-like state develops in 0.06% of vaccinees and has no lasting sequelae.

Severe: Encephalopathy. Very rarely, DTaP causes acute encephalopathy. The incidence is between zero and 10.5 episodes per million doses. Most cases occur within 3 days of vaccination. Some of the children who experience acute encephalopathy develop chronic neurologic dysfunction later in life. However, the contribution of acute encephalopathy to long-term neurologic deficits is unclear.

Precautions and Contraindications. DTaP can be administered to children with *mild febrile illness* (eg, upper respiratory infection with or without low-grade fever). However, for children with *moderate or severe febrile illness*, administration should be postponed until the illness has resolved.

TABLE 68-5 ■ Products for Immunization Against Diphtheria, Tetanus, and Pertussis

Symbol	Description	Trade Names	Comments
Vaccines for Children Younger Than 10 Years			
DTaP	Diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine	Tripedia, DAPTACEL, Infanrix	Used for routine vaccination against diphtheria, tetanus, and pertussis
DT	Diphtheria toxoid and tetanus toxoid	Generic only	Used for children under 7 years who should not get pertussis vaccine
Vaccines for Adolescents and Adults			
Tdap	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adolescent preparation	Boostrix, Adacel	Used as a <i>booster</i> in adolescents and adults to protect against all three diseases
Td	Tetanus toxoid and diphtheria toxoid	Generic only	Used as a <i>booster</i> for adolescents and adults to protect against tetanus and diphtheria, but not pertussis

DTaP is *contraindicated* if a prior vaccination with DTaP produced (1) an immediate anaphylactic reaction or (2) encephalopathy within 7 days of vaccination.

DTaP should be administered with *caution* (if at all) if a prior vaccination with DTaP produced any of the following:

- A shock-like state
- Fever (105°F or higher) occurring within 48 hours of vaccination and not attributable to another identifiable cause
- Persistent, inconsolable crying, lasting 3 or more hours and occurring within 48 hours of vaccination
- Convulsions (with or without fever) occurring within 3 days of vaccination.

Route, Site, and Immunization Schedule. DTaP is injected IM into the deltoid muscle or thigh. Routine vaccination consists of five injections, the first at 2 months, the second at 4 months, the third at 6 months, the fourth between 15 and 18 months, and the fifth between 4 and 6 years. Children who began the series with DTP (no longer available) should complete it with DTaP. After the initial series, all children should receive a booster shot of Td every 10 years.

The following recommendations also apply:

- Children 11 to 12 years old who completed the series at least 5 years previously should receive a booster shot of Tdap, followed by Td boosters every 10 years.
- Children 11 to 18 years old who have not received Tdap should receive a single dose, followed by Td boosters every 10 years.
- Children 7 through 10 years old who are not fully immunized against *pertussis* should receive a single dose of Tdap.

Poliovirus Vaccine

Preparations. In the past, two polio vaccines were used in the United States: *oral poliovirus vaccine* (OPV, Sabin vaccine) and *inactivated poliovirus vaccine* (IPV, Salk vaccine). OPV is composed of *live*, attenuated viruses. In contrast, IPV is composed of *inactivated* polioviruses. As discussed below, OPV has *caused* polio in a few children, whereas IPV has not and cannot. Because the benefit/risk ratio of IPV is clearly

superior, OPV has been withdrawn from the U.S. market. The trade name for IPV is *IPOL*.

Efficacy. Between 97.5% and 100% of children receiving IPV or OPV develop antibodies to poliovirus types 1, 2, and 3. Antibodies develop after two or more doses and persist for many years.

Adverse Effects of IPV. IPV is devoid of serious adverse effects. As with other injected drugs, local soreness may occur. IPV contains trace amounts of streptomycin, neomycin, and bacitracin. Children with an allergy to these drugs should be monitored.

Adverse Effects of OPV. Very rarely, OPV has caused *vaccine-associated paralytic poliomyelitis* (VAPP). The severity of VAPP is similar to that of paralytic poliomyelitis caused by the wild-type virus. In immunocompromised children, VAPP can prove fatal. The incidence of VAPP is 1 case for each 2.4 million doses of OPV administered, which corresponds to 1 case for each 750,000 children starting the vaccination series. In the United States, eight to nine cases of VAPP have occurred each year. Because wild-type poliovirus has been eliminated from the Western hemisphere, the risk of Americans acquiring polio from OPV now greatly exceeds the risk of acquiring the disease from the environment. In response to this change in risk/benefit ratio, the ACIP changed its recommendations: Whereas OPV had been the preferred vaccine for many years, the ACIP now recommends exclusive use of IPV.

Route, Site, and Immunization Schedule. IPV is administered subQ in the anterolateral thigh. All children should receive four doses, the first at 2 months of age, the second at 4 months, the third between 6 and 18 months, and the fourth between 4 and 6 years. If four doses were administered before age 4 years, an additional (fifth) dose should be given between ages 4 and 6 years.

Haemophilus influenzae Type b Conjugate Vaccine

Preparations. Vaccines directed against *H. influenzae* type b (Hib) are prepared by conjugating (covalently binding) a purified capsular polysaccharide (PRP) from *H. influenzae* to either (1) tetanus toxoid or (2) an outer membrane protein (OMP) isolated from *Neisseria meningitidis*. The reason for conjugating PRP to these other compounds is to enhance antigenicity. The vaccines made with OMP—marketed as *Peak*

vaxHIB and Comvax* and abbreviated PRP-OMP—elicit a stronger immune response than the vaccines made with tetanus toxoid, marketed as ActHIB and Hiberix.

Efficacy. Immunization with Hib vaccine decreases the risk of disease by 88% to 98%. When PedvaxHIB is used, protection begins 1 week after the first dose. However, when ActHIB is used, protection is delayed, beginning 1 to 2 weeks after the fourth dose. With both vaccines, protection persists for several years.

Adverse Effects. Hib vaccine is among the safest of all vaccines. Serious adverse effects have not been reported. The few adverse effects that do occur are generally transient and mild. Between 2% and 5% of vaccinees develop local reactions (swelling, erythema, warmth, and tenderness). About 1% experience fever (above 101°F), crying, diarrhea, or vomiting.

Route, Site, and Immunization Schedule. Hib vaccines are administered IM into the midhigh or the outer aspect of the upper arm. Most children should receive four doses, the first at 2 months of age, the second at 4 months, the third at 6 months, and the fourth between 12 and 15 months. If PedvaxHIB or Comvax is used for the first two doses, the third dose (6-month dose) can be omitted.

Varicella Virus Vaccine

Description. Varicella virus vaccine is composed of live, attenuated varicella viruses. Two subQ products are available: varicella vaccine by itself, sold as *Varivax*, and varicella vaccine combined with MMR [MMRV], sold as *ProQuad*. Varicella vaccine was developed in Japan in 1973, but was not available in the United States until 1995.

Efficacy. Varicella vaccine, given as a two-dose series, confers full protection in about 99% of vaccinees. Furthermore, among those who get chickenpox despite vaccination, symptoms are always mild: These children develop fewer lesions (less than 50, compared with 250 to 500 for unvaccinated children), experience less fever, and recover more quickly. In Japan, herpes zoster (shingles) has not been observed in any adult who received varicella vaccine as a child, even if breakthrough chickenpox had occurred.

Adverse Effects. Varicella vaccine is very safe; no serious adverse events have been reported. About 25% of vaccinees experience erythema, soreness, and swelling at the injection site; 15% develop fever (above 102°F); and 3% develop a mild, local varicella-like rash, consisting of just a few lesions. About 5% of healthy children develop a sparse, generalized varicella-like rash within a month of the injection. In children with leukemia, the incidence of generalized rash is much higher—about 50%. For all vaccinees, rates of fever and rash are higher when MMRV is used than when MMR and varicella vaccine are given separately.

In theory, children receiving the vaccine can transmit vaccine viruses to others. However, among otherwise healthy vaccinees, such transmission has not been reported. In contrast, among leukemic children who developed a rash after vaccination, a few cases of viral transmission have occurred. To reduce the risk of transmission, vaccinees should temporarily avoid close contact with susceptible, high-risk individu-

als (eg, neonates, pregnant women, immunocompromised people).

Precautions and Contraindications. Varicella vaccine is *contraindicated* for pregnant women, individuals with certain cancers (eg, leukemia, lymphomas), and individuals with hypersensitivity to neomycin or gelatin, both of which are in the vaccine. In addition, the vaccine should generally be avoided by individuals who are immunocompromised, including those with HIV infection or congenital immunodeficiency and those taking immunosuppressive drugs.

Children receiving the vaccine should avoid aspirin and other salicylates for 6 weeks. This precaution is based on the theoretical risk of developing Reye's syndrome: If the child develops chickenpox (albeit a mild case) in response to the vaccine, the very small risk of developing Reye's syndrome is somewhat increased by concurrent use of salicylates.

Route, Site, and Immunization Schedule. Varicella vaccine is administered subQ into the outer aspect of the upper arm or into the anterolateral thigh. All recipients should get *two* doses. Because the vaccine wasn't available in the United States before 1995, many children missed their first shot at the preferred age: 12 to 15 months. Accordingly, the vaccination schedule for older children necessarily differs from that for younger children. Current recommendations are as follows:

- *Children who have never had chickenpox*—Give the first dose between 12 and 15 months of age, and the second dose between 4 and 6 years of age. If needed, the second dose can be given sooner—but no sooner than 3 months after the first dose.
- *Children 13 or more years old who have not been vaccinated yet and have not had chickenpox*—Give two doses at least 28 days apart.
- *Catch-up vaccination*—Anyone who is not fully vaccinated and has never had chickenpox should receive one or two doses. Dosage timing depends on the person's age (see the catch-up immunization schedule at www.cdc.gov/vaccines/).

We Need to Vaccinate More Children. Although rates of varicella vaccination have increased, many eligible children still do not get vaccinated. Several misconceptions are responsible: Some parents believe chickenpox is a mild disease (it's actually the leading cause of vaccine-preventable child death in the United States); some think vaccine is not effective (vaccination prevents severe chickenpox in 100% of vaccinees); and some think the vaccine is not safe (serious reactions are extremely rare, and proof that the vaccine was the cause is lacking).

The major impact of failure to vaccinate will be felt when today's children grow up. Recall that chickenpox in adults is much more severe than in children: Compared with children, adults have a 10- to 20-fold increased risk of serious complications, including death. Because many children are being vaccinated, the overall incidence of chickenpox is on the decline. As a result, children who remain unvaccinated may nonetheless avoid chickenpox, and hence may reach adulthood without developing antibodies to the disease. Therefore, if they acquire the disease as adults, it is likely to be severe. The moral to this story is that vaccinating children now will not only protect them from chickenpox during childhood, it will also protect them from serious harm when they grow up.

*Comvax is a combination vaccine for immunization against *H. influenzae* type b and hepatitis B.

Hepatitis B Vaccine

Preparations. Hepatitis B vaccine (HepB) contains *hepatitis B surface antigen* (HBsAg), the primary antigenic protein in the viral envelope. Administration of HepB promotes synthesis of specific antibodies directed against hepatitis B virus. Because HepB is made from a viral component, rather than from a live virus, it cannot cause disease.

HepB is available in pediatric and adult formulations. The pediatric formulation, marketed as *Recombivax HB*, contains 10 mcg of HBsAg/mL. The adult formulation, marketed as *Energix-B*, contains 20 mcg of HBsAg/mL. A combination vaccine for adults, marketed as *Twinrix*, protects against hepatitis A and hepatitis B. In all three products, the HBsAg is produced in yeast using recombinant DNA technology.

Efficacy. Greater than 85% of vaccinees are protected after the second dose of HepB, and more than 90% are protected after the third dose. Although the duration of protection has not been determined with precision, it appears to be at least 5 to 7 years.

Adverse Effects and Contraindications. HepB is one of our safest vaccines. The most common reactions are soreness at the injection site and mild to moderate fever. Acetaminophen or ibuprofen may be used to relieve discomfort, but aspirin should be avoided. The only contraindication to HepB is a prior anaphylactic reaction either to HepB itself or to baker's yeast.

Route, Site, and Immunization Schedule. HepB is injected IM. In neonates and infants, the injection is made into the anterolateral thigh. In adolescents and adults, the injection is made into the deltoid. All vaccinees should receive three doses.

The immunization protocol for *infants* is based on whether the mother is *HBsAg-positive* or *HBsAg-negative* (ie, on whether the mother has laboratory evidence of hepatitis B infection). All infants should receive monovalent HepB vaccine soon after birth. The following protocols for infants are recommended:

- *Infants born to mothers who are HBsAg-negative*—Give 5 mcg of Recombivax HB within 12 hours of birth.* Give the second dose between 1 and 2 months of age and the third dose no sooner than 6 months of age.
- *Infants born to mothers who are HBsAg-positive*—Give 5 mcg of Recombivax HB within 12 hours of birth, and give 0.5 mL of *hepatitis B immune globulin* (HBIG) at the same time but at a separate site. (The purpose of the HBIG is to provide immediate protection against hepatitis B acquired from the mother.) Give the second dose of HepB between 1 and 2 months of age, and the third dose no sooner than 6 months of age.
- *Infants born to mothers whose HBsAg status is unknown*—Give 5 mcg of Recombivax HB within 12 hours of birth. Subsequent doses are based on the mother's HBsAg status, which is determined by analyzing a maternal blood sample obtained during delivery. If the mother is HBsAg-positive, the infant should be given HBIG as soon as possible—and no later than 1 week after birth.

Infants who did not receive a birth dose should receive a three-dose series. The second dose is given 1 month after the first, and third dose is given 6 months after the first.

*In rare circumstances, the first dose can be delayed—but only if a prescriber's order to withhold the vaccine and a copy of the mother's original HBsAg-negative test result are filed in the infant's medical record.

Children and adolescents who were not vaccinated against hepatitis B during infancy may begin the three-dose series at any time. Once the first dose is given, the second is given 1 month (or more) later, and the third 4 months (or more) after the first dose and no less than 2 months after the second dose. For children 11 years and older, a two-dose schedule can be used; the second dose is given 4 to 6 months after the first.

Hepatitis A Vaccine

Preparations. Hepatitis A vaccine (HepA) is prepared from inactivated hepatitis A virus (HAV). In the United States, two products are available: *Havrix* and *VAQTA*.

Efficacy. Immunization with HepA decreases the risk of clinical disease by 94% to 100%. Protective levels of antibodies are seen in 94% to 100% of adults and children 1 month after the first dose, and in 100% of vaccinees 1 month after the second dose. Protection appears to be long lasting: Among vaccinated children who were followed for 7 years, no cases of hepatitis A were detected.

Who Should Be Vaccinated? Hepatitis A vaccination is recommended for *all* children 12 through 23 months old, and for children older than 23 months who live in areas where vaccination programs target older children (owing to increased risk of infection). In addition, HepA is recommended for

- People at least 1 year old traveling to places with high rates of hepatitis A, including Central or South America, Mexico, the Caribbean islands, Africa, Asia (except Japan), and southern or eastern Europe
- People in communities that have frequent outbreaks of hepatitis A
- Men who have sex with men
- People who use street drugs
- People with chronic liver disease
- People who receive clotting factor concentrates
- People who work with HAV-infected primates or who work with HAV in research labs

Adverse Effects. HepA is extremely safe. By 1999, over 65 million doses had been administered worldwide, causing no serious adverse events that could be definitively linked to the vaccine.

Mild reactions are common. Soreness at the injection site occurs in about 54% of adults and 18% of children. Headache occurs in 14% of adults and 9% of children. Other mild reactions include loss of appetite and malaise. When mild reactions occur, they usually begin 3 to 5 days after vaccination and last only 1 to 2 days.

Route, Site, and Immunization Schedule. Hepatitis A vaccines should be given IM into the deltoid muscle. Two doses are required, given at least 6 months apart. The first can be given at 12 months of age. The second should be given 6 to 12 months after the first (for *Havrix*) or 6 to 18 months after the first (for *VAQTA*).

Pneumococcal Conjugate Vaccine

In 2010, the FDA approved a *13-valent pneumococcal conjugate vaccine* (PCV13), sold as *Prevnar 13*, for prevention of invasive pneumococcal disease in infants and children. This

new vaccine replaces *Prenar*, a 7-valent pneumococcal conjugate vaccine approved in 2000.

An unconjugated vaccine—*pneumococcal polysaccharide vaccine* (PPV), sold as *Pneumovax 23*—is also available. However, PPV is approved only for adults and high-risk children over the age of 2 years. PPV does not work in children younger than 2 years.

Description. PCV13 consists of 13 pneumococcal capsular polysaccharide antigens that have been conjugated to a protein carrier—specifically, CRM197, a nontoxic variant of diphtheria toxin. The protein carrier increases antigenicity, especially in infants. The 13 antigens in the vaccine are from the 13 serotypes of *Streptococcus pneumoniae* that cause the majority of invasive pneumococcal infections in American children under the age of 6 years.

Efficacy. PCV13 is at least as effective as PCV7, as shown in recent comparative trials. The efficacy of PCV7 had been demonstrated previously. In a large trial that enrolled 37,868 healthy infants, half the infants were given PCV7, and half were given a control injection. The results? Vaccination was 100% effective in preventing invasive disease caused by the *S. pneumoniae* serotypes that the vaccine was designed to protect against. Vaccination was also 89% effective at preventing invasive disease caused by all serotypes of *S. pneumoniae*. In addition to preventing invasive pneumococcal disease, vaccination caused a modest reduction in cases of otitis media (see Chapter 106).

Adverse Effects. PCV13 appears very safe. No serious adverse effects have been reported. About 50% of vaccinees get drowsy after the shot, lose their appetite, or develop erythema or tenderness at the injection site. About 33% develop localized swelling. Mild fever develops in 33%, and a higher fever (temperature over 102.2°F) develops in 5%. About 80% become irritable or fussy.

Who Should Be Vaccinated? The ACIP recommends vaccinating children in the following groups:

- All children under 2 years of age
- All healthy children between their second and fifth birthdays who have not completed the PCV series
- All children between their second and fifth birthdays who have conditions that put them at high risk of serious pneumococcal disease. In this group are children with sickle cell anemia, injury to the spleen, cochlear implants, chronic heart or lung disease, or immunosuppression of any cause (eg, diabetes, cancer, liver disease, HIV infection, use of immunosuppressive drugs).

Route, Site, and Immunization Schedule. Vaccination is done by IM injection into the anterolateral aspect of the thigh (in infants) or into the deltoid muscle of the upper arm (in toddlers and young children). The vaccine is a suspension, and hence must be shaken before use. All doses are 0.5 mL.

Children Under 2 Years of Age. The number of doses and their timing depend on the child's age when the first dose is given. Children who began the series with PCV7 should complete it with PCV13 (since PCV7 is no longer available).

- *First dose at age 2 months*—four doses total; one each at ages 2, 4, and 6 months and one between ages 12 and 15 months.
- *First dose between ages 7 and 11 months*—three doses total; the first two doses should be given at least 4 weeks

apart, and the third should be at least 8 weeks after the second, but not before the child's first birthday

- *First dose between ages 12 and 23 months*—two doses total, given at least 8 weeks apart

Children Between Their Second and Fifth Birthdays.

- Healthy children who have not completed the PCV series should get one dose of PCV13.
- Children at high risk who have already received three doses of PCV vaccine should get one additional dose of PCV13.
- Children at high risk who have received no, one, or two doses of PCV vaccine should get two doses of PCV13, given at least 8 weeks apart.

Children Who Have Completed the 4-Dose Series with PCV7. Healthy children who have not yet turned 5, and children at high risk who have not yet turned 6, should get one additional dose of PCV13.

Meningococcal Conjugate Vaccine

In the United States, we have two *meningococcal conjugate polysaccharide vaccines* (MCVs): *Menactra*, approved in 2005, and *Menveo*, approved in 2010. Both vaccines protect against the same four meningococcal serotypes, hence their abbreviation *MCV4*. *Menactra* is indicated for people 9 months to 55 years old, and *Menveo* is indicated for people 2 to 55 years old.

An unconjugated vaccine—*meningococcal polysaccharide vaccine* (MPSV4) [*Menomune*]—has been available since the 1970s, but is not very effective in children. Accordingly, MCV4 is currently preferred. MPSV4 is active against the same meningococcal serotypes as MCV4.

Description. *Menactra* is a tetravalent conjugate vaccine directed against four meningococcal serogroups: A, C, Y, and W-135. Each dose consists of 4 mcg of capsular polysaccharide from each of the four serogroups conjugated with 48 mcg of a protein carrier, specifically, diphtheria toxoid. The carrier protein increases immunogenicity.

Menveo is nearly identical to *Menactra*. However, there are two differences. First, the amount of capsular polysaccharide in each dose of *Menveo* is greater (10 mcg of polysaccharide from serogroup A, and 5 mcg of polysaccharide from serogroups C, Y, and W-135). Second, in *Menveo*, the polysaccharides are conjugated to a different diphtheria protein.

Efficacy. The efficacy of MCV4 at preventing meningococcal disease has not been evaluated in clinical trials. However, we do know the vaccine is highly immunogenic. For example, when 423 adolescents were vaccinated, rates of seroconversion for serogroups A, C, Y, and W-135 were 100%, 99%, 98%, and 99%, respectively, as measured by bactericidal antibody assay. FDA approval of MCV4 was based on its documented immunogenicity and the documented ability of other vaccines to prevent meningococcal infection.

Adverse Effects. The most common reactions are local pain (59% in adolescents and 54% in adults), headache (36% and 41%), and fatigue (30% and 35%). Local redness, swelling, and induration are also common.

Concerns that MCV4 might cause *Guillain-Barré syndrome* (GBS)* appear to be unfounded, as shown by two large studies. In one study, there were 99 confirmed cases of GBS among 12,589,910 vaccinees. In the other study, there were 5 cases among 889,684 vaccinees. In both studies, the incidence of GBS was no higher than would be expected in the absence of vaccination. In light of this information, the CDC and ACIP have removed precautionary language regarding a risk of GBS after meningococcal vaccination.

Who Should Be Vaccinated? The ACIP recommends routine MCV4 vaccination for all children and adolescents 11 through 18 years of age. Children who were not vaccinated at this time should be vaccinated as soon as possible. Vaccination is also recommended for people at increased risk for meningococcal disease, including

- College freshmen living in dormitories
- U.S. military recruits
- Microbiologists who are routinely exposed to meningococcal bacteria
- Anyone traveling to (or living in) a part of the world where meningococcal disease is common
- Anyone who has an injured spleen, or whose spleen has been removed
- Anyone who has an immune disorder known as terminal complement component deficiency
- Anyone who might have been exposed to meningitis during an outbreak
- Persons with persistent complement component deficiency, anatomic or functional asplenia, and certain other risk factors

MCV4 is the preferred vaccine for people 2 to 55 years old in these risk groups, but MPSV4 can be used if MCV4 is not available. Only MPSV4 should be used for adults over 55 (not because MPSV4 is more effective—but because it is approved for use in this age group, whereas MCV4 is not).

How Many Doses? Most children should receive *two* doses: a primary dose and a booster dose. This recommendation is new. In the past, one dose was considered sufficient. However, we now know that protection does not last as long as previously believed, hence the need for a booster.

Specific dosing recommendations, based on age and risk group, are as follows:

- **Healthy Children 11 to 18 Years Old.** Give the initial dose between ages 11 and 12 years, and the booster at age 16 years. If the initial dose is given late (between 13 and 15 years), give the booster between ages 16 and 18 years. If the initial dose was given even later (on or after age 16 years), no booster is needed.
- **Children 11 to 18 Years Old with HIV Infection.** Give a primary two-dose series (2 months apart) between ages 11 and 12 years, and a booster at age 16 years. If the primary series is given late (between 13 and 15 years), give the booster between ages 16 and 18 years. If the primary series was given even later (on or after age 16 years), no booster is needed.

*GBS is a serious neurologic disorder that involves inflammatory demyelination of peripheral nerves. Symptoms include symmetric weakness in the arms and legs, sensory abnormalities, and paralysis of the muscles of respiration. Most patients eventually recover.

- **Persons 2 to 55 Years Old with Persistent Complement Component Deficiency or Functional or Anatomic Asplenia.** Give a two-dose primary series (2 months apart), and then a booster dose every 5 years. If a one-dose primary series had been used, give a booster dose as soon as possible, and then every 5 years.
- **Children with Prolonged Increased Risk for Exposure.** For children 2 to 6 years old, give a single initial dose, followed by a booster 3 years later. For children age 7 years or older, give a single initial dose, followed by a booster 5 years later.
- **Additional Dosing Recommendations.** For more details on dosing, refer to the Meningococcal Vaccine Information Statement and the Adult Immunization Schedule, available online at www.cdc.gov/vaccines, and to Healthcare Personnel Vaccination Recommendations, available online at www.immunize.org/catg.d/p2017.pdf.

Route and Site. Vaccination is done by IM injection, preferably into the deltoid muscle of the upper arm.

Influenza Vaccine

Annual vaccination against influenza, including the H1N1 subtype, is now recommended for all children between 6 months and 18 years of age (as well as all adults). Properties of IM, intradermal, and intranasal influenza vaccines (composition, efficacy, adverse effects, contraindications, preparations, dosage, route), along with information on adult vaccination, are presented in Chapter 93.

Rotavirus Vaccine

Preparations and Efficacy. In the United States, two rotavirus vaccines are available: *RotaTeq*, approved in 2006, and *Rotarix*, approved in 2008. Both contain live, attenuated viruses. To induce a strong immune response, these viruses must replicate within the infant's gut. Accordingly, the vaccine is administered PO. *RotaTeq* and *Rotarix* differ in composition and dosing schedule.

RotaTeq is a *pentavalent* vaccine directed against the five most common serotypes of human rotavirus, termed G1, G2, G3, G4, and P1A. In trials in the United States and Finland, *RotaTeq* prevented 74% of *all* rotavirus gastroenteritis cases, and 98% of *severe* cases. Vaccination also reduced the need for diarrhea-related hospitalization by 96%.

Rotarix is a *monovalent* vaccine developed from a rotavirus with the most common serotype found in humans. However, although *Rotarix* is monovalent, it confers protection against four rotavirus serotypes: G1, G3, G4, and G9. In clinical trials, *Rotarix* prevented 79% of *all* rotavirus gastroenteritis cases, 90% of *severe* cases, and 96% of diarrhea-related hospitalizations.

Safety. Although generally very safe, both *RotaTeq* and *Rotarix* may carry a small risk of *intussusception*, a rare, life-threatening form of bowel obstruction that occurs when the bowel folds in on itself, like a collapsing telescope. Of note, during prelicensure testing in over 130,000 infants, no cases of intussusception were seen. However, with both vaccines, several cases were reported during postmarketing surveillance. Fortunately, the estimated risk is very low: about 1 case for each 50,000 to 70,000 vaccinees. An older

rotavirus vaccine—RotaShield—was withdrawn because of intussusception.

Who Should Be Vaccinated? The ACIP recommends that all infants receive rotavirus vaccine, beginning around 8 weeks of age.

Who Should Not Be Vaccinated? Rotarix, but not RotaTeq, is contraindicated for infants with any uncorrected congenital malformation of the GI tract that could predispose to intussusception. Both vaccines are contraindicated for children with a history of intussusception.

Some vaccinees with *severe combined immunodeficiency (SCID)*, a rare inherited disorder, have developed vaccine-acquired rotavirus infection. Accordingly, these vaccines are contraindicated for infants with SCID. Rotavirus vaccines have not been evaluated in children who are immunocompromised for other reasons. Nonetheless, since these vaccines contain live viruses, it would seem prudent to use them with caution in all immunocompromised infants, regardless of the cause.

Infants with moderate to severe diarrhea or vomiting should probably not be vaccinated until they recover.

Preparations, Route, and Immunization Schedule. *RotaTeq* is supplied in single-dose, 2-mL vials for oral dosing. The vaccination series consists of *three* doses, starting at 6 to 12 weeks of age. The second dose is given 4 to 10 weeks after the first, and the third dose is given 4 to 10 weeks after the second (but no later than 32 weeks of age).

Rotarix is supplied as a powder for suspension in 1 mL of the liquid supplied. Dosing is oral. Effective vaccination requires *two* doses (compared with three for *RotaTeq*). The first dose is given between 6 and 12 weeks of age, and the second is given 4 weeks or more later. The series should be completed by 24 weeks of age.

Human Papillomavirus Vaccine

Two HPV vaccines are available: *Gardasil* and *Cervarix*. These vaccines differ in composition, indications, and immunogenicity. *Gardasil* is a quadrivalent vaccine; *Cervarix* is bivalent. *Gardasil* protects against cervical, vulvar, and vaginal cancer in females, as well as anal cancer and genital warts in females and males. By contrast, *Cervarix* only protects against cervical cancer—but the protection may last longer than with *Gardasil*. *Gardasil* was the first vaccine licensed in the United States for the specific purpose of protecting against cancer of any type.

Quadrivalent HPV Vaccine: Gardasil

Composition. *Gardasil* is a quadrivalent vaccine designed to stimulate production of neutralizing antibodies directed at four types of HPV—specifically, types 16 and 18 (which cause 70% of cervical cancers), and types 6 and 11 (which cause 95% of genital warts). The vaccine consists of *virus-like particles (VLPs)*, which are virus-sized, empty spheres composed of viral capsid proteins. To the immune system, VLPs look like the actual virus, and hence VLPs can evoke an immune response. Because VLPs are empty (and hence don't contain viral DNA), VLPs cannot cause infection. *Gardasil* is available in 0.5-mL, single-use vials.

Indications. *Gardasil* is used to prevent cancers, precancerous lesions, and genital warts in females and males.

Cancers and Precancerous Lesions in Females. *Gardasil* is indicated for girls and women 9 to 26 years old to prevent the following cancers caused by HPV types 16 and 18:

- Cervical cancer
- Vulvar cancer
- Vaginal cancer

In addition, *Gardasil* is indicated for prevention of the following precancerous and dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Cervical adenocarcinoma *in situ*
- Cervical intraepithelial neoplasia grade 2 and grade 3
- Vulvar intraepithelial neoplasia grade 2 and grade 3
- Vaginal intraepithelial neoplasia grade 2 and grade 3
- Cervical intraepithelial neoplasia grade 1

Genital Warts in Females and Males. *Gardasil* is indicated for females and males 9 to 26 years old to prevent genital warts caused by HPV types 6 and 11.

Anal Cancer in Females and Males. *Gardasil* is indicated for females and males 9 to 26 years old to prevent anal cancer and precancerous lesions caused by HPV types 6, 11, 16, and 18.

Efficacy. *Gardasil* is highly effective, as demonstrated in *FUTURE II*, a Phase III, randomized, double-blind, placebo-controlled trial. Researchers enrolled 12,167 healthy women, ages 16 to 23, and gave them three IM injections of *Gardasil* or placebo over a 6-month interval. The result? During 2 years of follow-up, *Gardasil* was nearly 100% effective at preventing precancerous cervical lesions, precancerous vaginal and vulvar lesions, and genital warts caused by HPV types 6, 11, 16, and 18. However, although *Gardasil* protected against new HPV infection, it didn't eliminate infection that was already present. Furthermore, although *Gardasil* prevented precancerous cervical lesions, the study period was too short to tell if vaccination prevents cervical cancer. Nonetheless, given that HPV infection causes more than 99% of cervical cancers, it seems highly likely that protection against this cancer will be conferred. At this time, the estimated duration of protection against HPV is 5 to 10 years. Studies are underway to determine if and when booster vaccination may be needed.

Is a Pap Test Still Needed? For two reasons, the answer is a resounding *YES!* First, *Gardasil* only protects against four types of HPV, leaving vaccinees at risk of cervical cancer caused by other types of HPV. Second, since *Gardasil* does not eliminate pre-existing HPV infection, vaccinees remain at risk of cancer from infection that was present before the vaccine was given. Therefore, vaccinated women should still undergo routine Pap screening to detect precancerous cervical changes, thereby permitting timely treatment before cancer develops.

Safety. *Gardasil* appears to be very safe. Injection-site reactions—pain (84%), erythema (25%), swelling (25%), and itching (3%)—although common, are mild and short lived. Fainting has occurred in teenage girls, sometimes resulting in hospitalization. However, the incidence of fainting is no greater than with other vaccines. Vaccinees who feel faint should sit or lie down to prevent falling.

What about severe side effects? Millions of girls and women have been vaccinated, and only a few severe events had been reported, including 27 deaths and 10 confirmed

cases of Guillain-Barré syndrome. However, a causal relationship between HPV vaccination and either of these severe effects has not been established.

Who Should Be Vaccinated? Given that HPV infection is sexually transmitted, and that HPV infects males and females, universal vaccination would be required to achieve maximal protection in the community. Accordingly, ACIP now recommends *routine* vaccination for males and females with quadrivalent HPV vaccine.

Females: Routine Vaccination. The ACIP recommends routine vaccination for all girls 11 to 12 years old. Why girls this young? Because the vaccine only protects against *acquiring* HPV infection. It can't clear infection that already exists. Therefore, vaccination is most beneficial when done before vaccinees become sexually active, which is the case for most girls in this age group.

Vaccination with the HPV vaccine remains voluntary, not compulsory, throughout most of the United States. Shortly after Gardasil was approved, bills to make vaccination mandatory were introduced in 24 states. However, as of January 2011, only Virginia and the District of Columbia required the vaccine for school attendance. Furthermore, parents in Virginia who object can easily have their girls opt out. Reasons for objection include expense (about \$360 for the three-dose series), concerns about safety and efficacy (because HPV vaccine is relatively new), and concerns that conferring protection against a sexually transmitted infection might encourage promiscuity (a concern that has no basis in fact). Parents who are considering withholding vaccination would do well to ask this question: Does protecting my daughter against developing cervical cancer later in life outweigh my concerns about vaccination? If the answer is yes—as I hope it would be—then vaccination should not be withheld.

Males: Routine Vaccination. ACIP recommends the quadrivalent HPV vaccine for all males 11 to 12 years old. Vaccination of males can help protect them from genital warts and HPV-related cancers, and may help prevent spread of HPV to females.

Females and Males: Catch-up Vaccination. ACIP recommends the quadrivalent HPV vaccine for females and males 13 to 21 years old who did not receive the vaccine when they were younger.

Who Should Not Be Vaccinated? HPV vaccine is not recommended for women who are pregnant. However, receiving the vaccine during pregnancy is not a reason to consider pregnancy termination. Women who are breast-feeding may receive the vaccine.

Route, Site, and Immunization Schedule. The HPV vaccine is injected IM into the deltoid region of the upper arm or the high anterolateral thigh. Three doses are given over a 6-month interval. The first is given at a time selected by the vaccinee and her/his provider. The second is given 2 months after the first, and the third is given 6 months after the first.

Bivalent HPV Vaccine: Cervarix

Composition and Indications. Cervarix is a bivalent vaccine designed to stimulate production of neutralizing antibodies against two types of HPV—specifically, types 16 and 18, which cause 70% of cervical cancers. In contrast to Gardasil, Cervarix does not confer immunity against HPV types 6 and 11, which cause most cases of genital warts. Accordingly, Cervarix is indicated only for prevention of cervical cancers and precancerous lesions caused by HPV types 16 and 18. Unlike Gardasil, Cervarix is not indicated to prevent vaginal or vulvar cancer in females, or anal cancer or genital warts in females or males.

Efficacy. The efficacy of Cervarix was evaluated in a trial that enrolled about 18,000 girls and women ages 15 through 25 years. Half received Cervarix and half received a control vaccine (Havrix, a vaccine against hepatitis A). The result? Among subjects who did not have HPV infection when the study began, Cervarix was 93% effective at preventing precancerous lesions caused by HPV types 16 and 18. In addition, the vaccine provided cross-protection against HPV types 31, 33, and 45, the next most common causes of cervical cancer after HPV types 16 and 18. By contrast, Gardasil only confers cross-protection against HPV 31.

Like Gardasil, Cervarix does not confer 100% protection against cervical cancer, and is not active against cancer that began before the vaccine was given. Accordingly, vaccinated women should still undergo routine Pap screens to permit early detection and treatment of precancerous lesions.

Duration of Protection. Protection with Cervarix may last longer than with Gardasil. Why? Because Cervarix is made with a unique adjuvant, a combination of aluminum hydroxide and monophosphoryl lipid A (derived from the bacterial cell wall). This adjuvant induces a stronger immune response than does the adjuvant in Gardasil (aluminum hydroxyphosphate sulfate).

Safety. Like Gardasil, Cervarix appears very safe. Both vaccines often cause mild reactions, although Cervarix causes more of them. The most common *local* reactions with Cervarix are pain (92%), redness (48%), and swelling (44%). The most common *systemic* reactions are fatigue (55%), headache (53%), myalgia (49%), GI symptoms (28%), arthralgia (21%), fever (13%), and rash (10%). Like Gardasil, Cervarix has been associated with fainting, primarily in teenage girls. Vaccinees who feel faint should sit or lie down to prevent falling.

Who Should Be Vaccinated? And How? The ACIP recommends routine vaccination for all girls 11 to 12 years old. In addition, vaccination is recommended for all girls and women 13 to 26 years old who were not vaccinated when they were younger. The route, site, and immunization schedule are the same as for Gardasil (see above).

Who Should Not Be Vaccinated? Like Gardasil, Cervarix is not recommended for women who are pregnant, but may be used by women who are breast-feeding. Receipt of the vaccine during pregnancy is not a reason to consider pregnancy termination.

Vaccine	Age	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19-23 months	2-3 years	4-6 years
Hepatitis B ¹		HepB	HepB			HepB						
Rotavirus ²			RV	RV	RV	RV ²						
Diphtheria, Tetanus, Pertussis ³			DTaP	DTaP	DTaP	DTaP	see footnote ³	DTaP				DTaP
Haemophilus influenzae type b ⁴			Hib	Hib	Hib ⁴	Hib						
Pneumococcal ⁵			PCV	PCV	PCV	PCV					PPSV	
Inactivated Poliovirus ⁶			IPV	IPV		IPV						IPV
Influenza ⁷						Influenza (Yearly)						
Measles, Mumps, Rubella ⁸						MMR				see footnote ⁸		MMR
Varicella ⁹						Varicella				see footnote ⁹		Varicella
Hepatitis A ¹⁰						HepA (2 doses)					HepA Series	
Meningococcal ¹¹												MCV4

Range of recommended ages for all children

Range of recommended ages for certain high-risk groups

1. Hepatitis B vaccine (HepB). (Minimum age: birth)

- At birth:**
- Administer monovalent HepB to all newborns before hospital discharge.
 - If mother is hepatitis B surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
 - If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG (no later than age 1 week).
- Doses following the birth dose:**
- The second dose should be administered at age 1 or 2 months. Monovalent HepB should be used for doses administered before age 6 weeks.
 - Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg 1 to 2 months after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).
 - Administration of 4 doses of HepB to infants is permissible when a combination vaccine containing HepB is administered after the birth dose.
 - Infants who did not receive a birth dose should receive 3 doses of HepB on a schedule of 0, 1, and 6 months.
 - The final (3rd or 4th) dose in the HepB series should be administered no earlier than age 24 weeks.

2. Rotavirus vaccine (RV). (Minimum age: 6 weeks)

- Administer the first dose at age 6 through 14 weeks (maximum age: 14 weeks 6 days). Vaccination should not be initiated for infants aged 15 weeks 0 days or older.
- The maximum age for the final dose in the series is 8 months 0 days
- If Rotarix is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). (Minimum age: 6 weeks)

- The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

4. Haemophilus influenzae type b conjugate vaccine (Hib). (Minimum age: 6 weeks)

- If PRP-OMP (PedvaxHIB or Comvax [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
- Hiberix should not be used for doses at ages 2, 4, or 6 months for the primary series but can be used as the final dose in children aged 12 months through 4 years.

5. Pneumococcal vaccine. (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])

- PCV is recommended for all children aged younger than 5 years. Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- A PCV series begun with 7-valent PCV (PCV7) should be completed with 13-valent PCV (PCV13).
- A single supplemental dose of PCV13 is recommended for all children aged 14 through 59 months who have received an age-appropriate series of PCV7.
- A single supplemental dose of PCV13 is recommended for all children aged 60 through 71 months with underlying medical conditions who have received an age-appropriate series of PCV7.

- The supplemental dose of PCV13 should be administered at least 8 weeks after the previous dose of PCV7. See *MMWR* 2010;59(No. RR-11).
 - Administer PPSV at least 8 weeks after last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant.
- 6. Inactivated poliovirus vaccine (IPV).** (Minimum age: 6 weeks)
- If 4 or more doses are administered prior to age 4 years an additional dose should be administered at age 4 through 6 years.
 - The final dose in the series should be administered on or after the fourth birthday and at least 6 months following the previous dose.
- 7. Influenza vaccine (seasonal).** (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])
- For healthy children aged 2 years and older (i.e., those who do not have underlying medical conditions that predispose them to influenza complications), either LAIV or TIV may be used, except LAIV should not be given to children aged 2 through 4 years who have had wheezing in the past 12 months.
 - Administer 2 doses (separated by at least 4 weeks) to children aged 6 months through 8 years who are receiving seasonal influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.
 - Children aged 6 months through 8 years who received no doses of monovalent 2009 H1N1 vaccine should receive 2 doses of 2010-2011 seasonal influenza vaccine. See *MMWR* 2010;59(No. RR-8):33-34.
- 8. Measles, mumps, and rubella vaccine (MMR).** (Minimum age: 12 months)
- The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- 9. Varicella vaccine.** (Minimum age: 12 months)
- The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose.
 - For children aged 12 months through 12 years the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
- 10. Hepatitis A vaccine (HepA).** (Minimum age: 12 months)
- Administer 2 doses at least 6 months apart.
 - HepA is recommended for children aged older than 23 months who live in areas where vaccination programs target older children, who are at increased risk for infection, or for whom immunity against hepatitis A is desired.
- 11. Meningococcal conjugate vaccine, quadrivalent (MCV4).** (Minimum age: 2 years)
- Administer 2 doses of MCV4 at least 8 weeks apart to children aged 2 through 10 years with persistent complement component deficiency and anatomic or functional asplenia, and 1 dose every 5 years thereafter.
 - Persons with human immunodeficiency virus (HIV) infection who are vaccinated with MCV4 should receive 2 doses at least 8 weeks apart.
 - Administer 1 dose of MCV4 to children aged 2 through 10 years who travel to countries with highly endemic or epidemic disease and during outbreaks caused by a vaccine serogroup.
 - Administer MCV4 to children at continued risk for meningococcal disease who were previously vaccinated with MCV4 or meningococcal polysaccharide vaccine after 3 years if the first dose was administered at age 2 through 6 years.

Figure 68-1 • Recommended Immunization Schedule for Children from Birth Through 6 Years—United States, 2011. This schedule indicates the recommended ages for routine administration of currently licensed vaccines, as of December 21, 2010, for children from birth through age 6 years. These recommendations are approved by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). *Gold-colored bars* indicate recommended ages for each dose; a bar that spans more than one age bracket indicates an acceptable range of ages for that dose. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and approved by the FDA for that dose of the series, provided other components of the combination are not contraindicated. *Purple bars* indicate certain high-risk groups.

Vaccine	Age	Age Group		
		7-10 years	11-12 years	13-18 years
Tetanus, Diphtheria, Pertussis ¹			Tdap	Tdap
Human Papillomavirus ²		see footnote ²	HPV (3 doses)	HPV Series
Meningococcal ³		MCV4	MCV4	MCV4
Influenza ⁴			Influenza (Yearly)	
Pneumococcal ⁵			Pneumococcal	
Hepatitis A ⁶			HepA Series	
Hepatitis B ⁷			Hep B Series	
Inactivated Poliovirus ⁸			IPV Series	
Measles, Mumps, Rubella ⁹			MMR Series	
Varicella ¹⁰			Varicella Series	

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

- Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).** (Minimum age: 10 years for Boostrix and 11 years for Adacel)
 - Persons aged 11 through 18 years who have not received Tdap should receive a dose followed by Td booster doses every 10 years thereafter.
 - Persons aged 7 through 10 years who are not fully immunized against pertussis (including those never vaccinated or with unknown pertussis vaccination status) should receive a single dose of Tdap. Refer to the catch-up schedule if additional doses of tetanus and diphtheria toxoid-containing vaccine are needed.
 - Tdap can be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
- Human papillomavirus vaccine (HPV).** (Minimum age: 9 years)
 - Quadrivalent HPV vaccine (HPV4) or bivalent HPV vaccine (HPV2) is recommended for the prevention of cervical precancers and cancers in females.
 - HPV4 is recommended for prevention of cervical precancers, cancers, and genital warts in females.
 - HPV4 is recommended in a 3-dose series to males aged 11 through 18 years to reduce their likelihood of genital warts, and to reduce transmission of HPV to females.
 - Administer the second dose 1 to 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).
- Meningococcal conjugate vaccine, quadrivalent (MCV4).** (Minimum age: 2 years)
 - Administer MCV4 at age 11 through 12 years with a booster dose at age 16 years.
 - Administer 1 dose at age 13 through 18 years if not previously vaccinated.
 - Persons who received their first dose at age 13 through 15 years should receive a booster dose at age 16 through 18 years.
 - Administer 1 dose to previously unvaccinated college freshmen living in a dormitory.
 - Administer 2 doses at least 8 weeks apart to children aged 2 through 10 years with persistent complement component deficiency and anatomic or functional asplenia, and 1 dose every 5 years thereafter.
 - Persons with HIV infection who are vaccinated with MCV4 should receive 2 doses at least 8 weeks apart.
 - Administer 1 dose of MCV4 to children aged 2 through 10 years who travel to countries with highly endemic or epidemic disease and during outbreaks caused by a vaccine serogroup.
 - Administer MCV4 to children at continued risk for meningococcal disease who were previously vaccinated with MCV4 or meningococcal polysaccharide vaccine after 3 years (if first dose administered at age 2 through 6 years) or after 5 years (if first dose administered at age 7 years or older).
- Influenza vaccine (seasonal).**
 - For healthy nonpregnant persons aged 7 through 18 years (i.e., those who do not have underlying medical conditions that predispose them to influenza complications), either LAIV or TIV may be used.
 - Administer 2 doses (separated by at least 4 weeks) to children aged 6 months

- through 8 years who are receiving seasonal influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.
 - Children 6 months through 8 years of age who received no doses of monovalent 2009 H1N1 vaccine should receive 2 doses of 2010-2011 seasonal influenza vaccine. See *MMWR* 2010;59(No. RR-8):33-34.
- Pneumococcal vaccines.**
 - A single dose of 13-valent pneumococcal conjugate vaccine (PCV13) may be administered to children aged 6 through 18 years who have functional or anatomic asplenia, HIV infection or other immunocompromising condition, cochlear implant or CSF leak. See *MMWR* 2010;59(No. RR-11).
 - The dose of PCV13 should be administered at least 8 weeks after the previous dose of PCV7.
 - Administer pneumococcal polysaccharide vaccine at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. A single revaccination should be administered after 5 years to children with functional or anatomic asplenia or an immunocompromising condition.
 - Hepatitis A vaccine (HepA).**
 - Administer 2 doses at least 6 months apart.
 - HepA is recommended for children aged older than 23 months who live in areas where vaccination programs target older children, or who are at increased risk for infection, or for whom immunity against hepatitis A is desired.
 - Hepatitis B vaccine (HepB).**
 - Administer the 3-dose series to those not previously vaccinated. For those with incomplete vaccination, follow the catch-up schedule.
 - A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB is licensed for children aged 11 through 15 years.
 - Inactivated poliovirus vaccine (IPV).**
 - The final dose in the series should be administered on or after the fourth birthday and at least 6 months following the previous dose.
 - If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.
 - Measles, mumps, and rubella vaccine (MMR).**
 - The minimum interval between the 2 doses of MMR is 4 weeks.
 - Varicella vaccine.**
 - For persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007;56[No. RR-4]), administer 2 doses if not previously vaccinated or the second dose if only 1 dose has been administered.
 - For persons aged 7 through 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
 - For persons aged 13 years and older, the minimum interval between doses is 4 weeks.

Figure 68-2 Recommended Immunization Schedule for Children 7 Through 18 Years of Age—United States, 2011.

This schedule indicates the recommended ages for routine administration of currently licensed vaccines, as of December 21, 2010, for children from 7 through 18 years of age. These recommendations are approved by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). Gold-colored bars indicate recommended ages for each dose; a bar that spans more than one age bracket indicates an acceptable range of ages for that dose. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Licensed combination vaccines may be used whenever any components of the combination are both indicated and approved by the FDA for that dose of the series, provided other components of the combination are not contraindicated. Purple bars indicate certain high-risk groups. Green bars indicate times for catch-up immunization.

KEY POINTS

- Vaccines promote synthesis of antibodies directed against bacteria and viruses, whereas toxoids promote synthesis of antibodies directed against toxins that bacteria produce, but not against the bacteria themselves.
- Killed vaccines are composed of whole, killed microbes or isolated microbial components, whereas live vaccines are composed of live microbes that have been weakened or rendered completely avirulent.
- Vaccination is defined as the administration of any vaccine or toxoid.
- Vaccination produces active immunity. Antibodies develop over weeks to months and then persist for years.
- Passive immunity is conferred by administering preformed antibodies (immune globulins). Protection is immediate but lasts only as long as the antibodies remain in the body.
- Thanks to widespread vaccination, five VPDs are virtually gone from the United States, measles and wild-type polio are gone from the Western hemisphere, and smallpox is gone from the planet. Also, the incidence of several other VPDs has been greatly reduced.
- Although vaccines are very safe, mild reactions are common, and serious reactions can occur rarely.
- Several large, high-quality studies have failed to find a causal link between thimerosal-containing vaccines and autism.
- Acetaminophen, ibuprofen, and other analgesic/antipyretics can reduce the immune response to vaccines, and hence should generally be avoided before vaccination and immediately after.
- Immunocompromised children are at special risk from live vaccines and should not receive them.
- Measles, mumps, and rubella virus vaccine (MMR) is a combination product composed of three live virus vaccines.
- Rarely, MMR causes thrombocytopenia and anaphylactic reactions. Until recently, anaphylactic reactions were thought to result from allergy to eggs, but now we think they result from allergy to gelatin.
- MMR is contraindicated during pregnancy and should be used with caution in children with a history of either thrombocytopenia or anaphylactic reactions to gelatin, eggs, or neomycin.
- Until recently, we had two vaccines for protection against diphtheria, tetanus, and pertussis. One (DTP) contains whole-cell pertussis and the other (DTaP) contains acellular pertussis. DTaP is more effective than DTP and causes fewer and milder side effects. Accordingly, DTaP is recommended for all children. DTP is no longer available.
- Rarely, DTaP causes acute encephalopathy.
- There are two vaccines against polioviruses: oral poliovirus vaccine (OPV, Sabin vaccine) and inactivated poliovirus vaccine (IPV, Salk vaccine). OPV contains live, attenuated viruses, whereas IPV contains inactivated polioviruses.
- OPV can cause vaccine-associated paralytic poliomyelitis (VAPP); IPV does not. Because IPV is safer, it has replaced OPV for routine vaccination against polio in the United States.
- *Haemophilus influenzae* type b vaccine is one of our safest vaccines. No serious adverse events have been reported.
- Varicella virus vaccine is composed of live, attenuated varicella viruses.
- All children receiving varicella vaccine are fully protected against severe varicella (chickenpox), although some get mild disease. The children who get mild chickenpox despite vaccination develop far fewer lesions than unvaccinated children, experience less fever, and recover more quickly.
- Varicella vaccine is very safe; no serious adverse events have been reported.
- Varicella vaccine is contraindicated for pregnant women, individuals hypersensitive to neomycin or gelatin, and immunocompromised people.
- Hepatitis B vaccine (HepB) contains hepatitis B surface antigen (HBsAg), the primary antigenic protein in the viral envelope. Administration of HepB promotes synthesis of specific antibodies directed against hepatitis B virus.
- HepB is one of our safest vaccines. The only contraindication is a prior anaphylactic reaction either to HepB itself or to baker's yeast.
- All infants should receive monovalent HepB within 12 hours of birth (except in rare circumstances). Infants whose mothers are HBsAg-positive should also receive hepatitis B immune globulin (HBIG).
- Hepatitis A vaccine is composed of inactivated hepatitis A viruses.
- Pneumococcal conjugate vaccine is the first vaccine for preventing invasive pneumococcal disease in infants and toddlers.
- Meningococcal conjugate vaccine (MCV4), approved in 2005, is more effective in children than meningococcal polysaccharide vaccine (MPSV4), approved in the 1970s.
- Annual influenza vaccination is recommended for all children 6 months to 18 years of age.
- Two rotavirus vaccines are available: RotaTaq and Rotarix. Both may carry a small risk of intussusception, a life-threatening complication that led to withdrawal of RotaShield, an earlier rotavirus vaccine.
- We have two HPV vaccines: a quadrivalent vaccine sold as Gardasil, and a bivalent vaccine sold as Cervarix.
- Gardasil can prevent cancers unique to females (cervical, vaginal, and vulvar), as well as anal cancer and genital warts in females and males.
- Cervarix has only one indication: prevention of cervical cancer.
- Gardasil and Cervarix do not protect against all the types of HPV that can cause cervical cancer, and they do not protect against HPV infection that was present prior to vaccination. Accordingly, vaccinated women should still undergo routine Pap screens to detect precancerous cervical lesions, thereby permitting timely treatment before cancer develops.

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Calcineurin Inhibitors

Cyclosporine

Tacrolimus

mTOR Inhibitors

Sirolimus

Everolimus

Glucocorticoids

Cytotoxic Drugs

Antibodies

Immunosuppressive drugs inhibit immune responses. They have two principal applications: (1) prevention of organ rejection in transplant recipients, and (2) treatment of autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus). At the doses required to suppress allograft rejection, almost all of these drugs are toxic. Two toxicities are of particular concern: (1) increased risk of infection and (2) increased risk of neoplasms. Furthermore, because allograft recipients must take immunosuppressants for life, the risk of toxicity continues lifelong. Sites of action of immunosuppressants are summarized in Figure 69-1.

CALCINEURIN INHIBITORS

Cyclosporine and tacrolimus are the most effective immunosuppressants available. Although cyclosporine and tacrolimus differ in structure, they share the same mechanism: Both drugs inhibit calcineurin, and thereby suppress production of interleukin-2 (IL-2), a compound needed for T-cell proliferation. Their principal use is prevention of organ rejection in transplant recipients. Cyclosporine was developed before tacrolimus and is used more often.

Cyclosporine

Cyclosporine [Sandimmune, Gengraf, Neoral] is a powerful immunosuppressant and the drug of choice for preventing organ rejection in recipients of an allogenic transplant.* Major adverse effects are nephrotoxicity and increased risk of infection.

Mechanism of Action

Cyclosporine acts on helper T lymphocytes to suppress production of IL-2, interferon gamma, and other cytokines. The drug's primary molecular target is a protein known as *cyclophilin*. After binding to cyclophilin, cyclosporine

*An *allogenic transplant* is defined as donor tissue that is genetically distinct from tissues of the recipient, and hence subject to attack by the recipient's immune system.

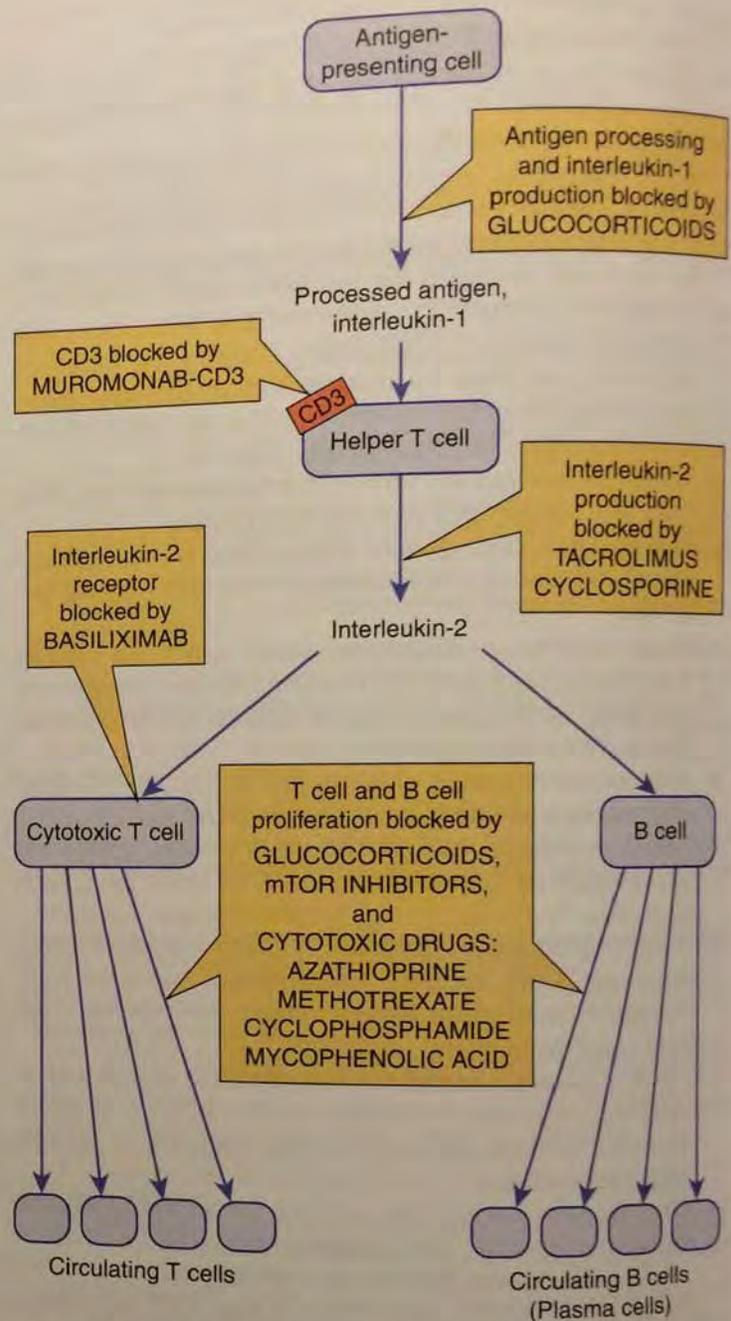


Figure 69-1 ■ Sites of action of immunosuppressant drugs.

inhibits *calcineurin*, a key enzyme in the pathway that promotes synthesis of IL-2 and other cytokines. In the absence of these cytokines, proliferation of B cells and cytolytic T cells is suppressed. In contrast to methotrexate and other cytotoxic immunosuppressants, cyclosporine does not cause bone marrow suppression.

Therapeutic Uses

Cyclosporine is used primarily to prevent rejection of allogenic kidney, liver, and heart transplants. A glucocorticoid (prednisone) is usually given concurrently. Azathioprine,

tacrolimus, or sirolimus may be given as well. Additional indications are psoriasis (see Chapter 105) and rheumatoid arthritis (see Chapter 73).

Pharmacokinetics

Cyclosporine may be administered orally or IV. Oral administration is preferred; IV therapy is reserved for patients who cannot take the drug orally. Absorption from the GI tract is incomplete (about 30%) and erratic. Accordingly, to avoid toxicity (from high drug levels) and organ rejection (from low drug levels), blood levels of cyclosporine should be measured periodically.

Most cyclosporine in the body is bound. In the blood, the drug is bound to red cells (60% to 70%), white cells (10% to 20%), and plasma lipoproteins. Outside the vascular system, the drug is bound to tissues.

Cyclosporine undergoes extensive metabolism by hepatic microsomal enzymes. Therefore, drugs that increase or decrease the activity of these enzymes can have a significant impact on cyclosporine levels. Excretion of both cyclosporine and its metabolites is via the bile. Practically none of the drug appears in the urine.

Adverse Effects

The most common adverse effects are nephrotoxicity, infection, hypertension, tremor, and hirsutism. Of these, nephrotoxicity and infection are the most serious.

Nephrotoxicity. Renal damage occurs in up to 75% of patients. Injury manifests as reduced renal blood flow and reduced glomerular filtration rate. These effects are dose dependent and usually reverse following a dosage reduction.

Nephrotoxicity is evaluated by monitoring for elevated blood urea nitrogen (BUN) and serum creatinine. However, be aware that a rise in these values could also indicate rejection of a kidney transplant. Patients should be informed about the possibility of kidney damage and the importance of periodic tests for BUN and creatinine.

Infection. Cyclosporine increases the risk of infections, which develop in 74% of those treated. Activation of latent infection with the BK virus can result in kidney damage, primarily in kidney recipients. Patients should be warned about early signs of infection (fever, sore throat) and instructed to report them immediately.

Hepatotoxicity. Liver damage occurs in 4% to 7% of patients. Injury is evaluated by monitoring for serum bilirubin and liver transaminases. Signs of liver injury reverse rapidly with a reduction in dosage. Inform the patient about the need for periodic tests of liver function.

Lymphomas. Cyclosporine and other immunosuppressants can cause lymphoproliferative diseases. The incidence with cyclosporine alone is low. However, when cyclosporine is combined with other immunosuppressants, the risk of malignant lymphomas increases.

Other Common Adverse Effects. Hypertension, indicated by a 10% to 15% increase in blood pressure, develops in about 50% of patients; standard antihypertensive drugs are used for treatment. Tremor (21% to 55%) and hirsutism (21% to 45%) are also common. Less frequently, patients experience leukopenia (6%), gingival hyperplasia (4%), gynecostasia (4%), sinusitis (3% to 7%), and hyperkalemia.

Anaphylactic Reactions. Anaphylactic reactions are rare, occurring in 1 of every 1000 patients. Signs include flushing, respiratory distress, hypotension, and tachycardia. Anaphylaxis occurs only with IV therapy, not with oral therapy. Patients should be monitored for 30 minutes after infusion onset. If anaphylaxis develops, discontinue the infusion and treat with epinephrine and oxygen.

Use in Pregnancy and Lactation. At doses 2 to 5 times those used clinically, cyclosporine is embryotoxic and fetotoxic in rats and rabbits. However, experience to date shows minimal fetal risk in humans. Nonetheless,

prudence dictates avoiding the drug during pregnancy, if possible. Patients taking cyclosporine should be advised to use a mechanical form of contraception (condom, diaphragm) rather than oral contraceptives. Cyclosporine is classified in Food and Drug Administration (FDA) Pregnancy Risk Category C. The drug is excreted in breast milk, and nursing should be avoided.

Drug and Food Interactions

Many interactions have been reported. However, only a few appear to have clinical significance. These are considered below.

Drugs That Can Decrease Cyclosporine Levels. Drugs that induce hepatic microsomal enzymes can accelerate metabolism of cyclosporine, causing cyclosporine levels to fall. Organ rejection can result. Drugs known to lower cyclosporine levels include *phenytoin*, *phenobarbital*, *carbamazepine*, *rifampin*, *terbinafine*, and *trimethoprim/sulfamethoxazole*. Cyclosporine levels should be monitored and the dosage adjusted accordingly.

Drugs That Can Increase Cyclosporine Levels. A variety of drugs can raise cyclosporine levels, thereby increasing the risk of toxicity. Drugs known to increase cyclosporine levels include *azole antifungal drugs* (eg, ketoconazole), *macrolide antibiotics* (eg, erythromycin), and *amphotericin B*. The mechanism is inhibition of cyclosporine metabolism. When any of these drugs is combined with cyclosporine, the dosage of cyclosporine must be reduced.

Some physicians administer ketoconazole concurrently with cyclosporine for the express purpose of permitting a reduction in cyclosporine dosage. By slowing metabolism of cyclosporine, ketoconazole permits cyclosporine dosage to be reduced by up to 88%, while continuing to maintain cyclosporine levels within the therapeutic range. The lowered dosage greatly reduces the cost of treatment—from about \$7000 per year to about \$3000 per year.

Nephrotoxic Drugs. Renal damage may be intensified by concurrent use of other nephrotoxic drugs. These include *amphotericin B*, *aminoglycosides*, and *nonsteroidal anti-inflammatory drugs* (NSAIDs).

Grapefruit Juice. A compound present in grapefruit juice inhibits metabolism of cyclosporine. As a result, consuming grapefruit juice can raise cyclosporine levels by 50% to 200%, thereby greatly increasing the risk of toxicity.

Repaglinide. Cyclosporine can increase levels of repaglinide [Prandin], a drug for diabetes, and can thereby cause hypoglycemia. Blood glucose should be monitored closely.

Preparations, Dosage, and Administration

Preparations. Cyclosporine is available under three trade names: *Sandimmune*, *Neoral*, and *Gengraf*. These preparations are NOT bioequivalent and cannot be used interchangeably. In *Neoral* and *Gengraf*, cyclosporine is present as a microemulsion. As a result, absorption is greater than from the *Sandimmune* formulation. As *Sandimmune*, cyclosporine is available in capsules (25 and 100 mg), an oral solution (100 mg/mL), and an IV solution (50 mg/mL). As *Neoral* or *Gengraf*, cyclosporine is available in capsules (25 and 100 mg) and an oral solution (100 mg/mL). To improve palatability, oral solutions can be mixed with plain milk, chocolate milk, or orange juice just before dosing.

Dosage and Monitoring for Allograft Recipients. Dosing is complex and depends on the organ transplanted, the formulation employed (*Neoral* or *Gengraf* vs. *Sandimmune*), and other immunosuppressants taken concurrently. The dosages below are representative.

Sandimmune. Oral therapy is preferred to IV therapy. The initial oral dose is 15 mg/kg given 4 to 24 hours prior to surgery. This dose is continued once daily for 1 to 2 weeks. Dosage is then gradually reduced to a maintenance level of 3 to 10 mg/kg/day.

For intravenous therapy, 1 mL of concentrate is diluted in 20 to 100 mL of 0.9% sodium chloride or 5% dextrose. The initial dose is 5 to 6 mg/kg

(one-third the oral dose) infused over 2 to 6 hours. The solution should be protected from light. Because of the risk of anaphylaxis, epinephrine and oxygen must be immediately available. The patient should be switched to oral therapy as soon as possible.

Neoral and Gengraf. Dosage depends on the transplanted organ and other immunosuppressive drugs taken concurrently. Typical dosages are 9 mg/kg/day for a kidney transplant, 8 mg/kg/day for a liver transplant, and 7 mg/kg/day for a heart transplant.

Monitoring. Dosage is adjusted on the basis of nephrotoxicity and cyclosporine trough levels. Blood for drug levels is drawn just prior to the next dose. For patients receiving a kidney transplant, the target level in whole blood is 100 to 200 ng/mL.

Dosage for Rheumatoid Arthritis. Rheumatoid arthritis is treated with Neoral or Gengraf. The initial dosage is 1.25 mg/kg twice daily. Dosage may be gradually increased to a maximum of 2 mg/kg twice daily. If there is no response by 16 weeks, cyclosporine should be discontinued.

Dosage for Psoriasis. Psoriasis is treated with Neoral or Gengraf. The initial dosage is 1.25 mg/kg twice daily. This may be gradually increased to a maximum of 4 mg/kg twice daily. If the maximum dosage is not effective within 6 weeks, cyclosporine should be discontinued. If a response does occur, the dosage should be reduced to the lowest effective amount for maintenance. Continuous therapy for more than 1 year is not recommended.

Tacrolimus

Tacrolimus [Prograf, Advagraf[®]], also known as FK506, is an alternative to cyclosporine for preventing allograft rejection. The drug is somewhat more effective than cyclosporine, but also more toxic.

Therapeutic Use. Systemic tacrolimus is approved for prophylaxis of organ rejection in patients receiving liver, kidney, or heart transplants. Concurrent use of glucocorticoids is recommended (along with azathioprine or mycophenolate mofetil for heart or kidney recipients). Compared with patients receiving cyclosporine, those receiving tacrolimus experience fewer episodes of acute transplant rejection, but twice as many patients discontinue the drug because of toxicity. Tacrolimus is under investigation for use in patients receiving bone marrow, pancreas, and small bowel transplants. As discussed in Chapter 105, tacrolimus is also used for topical therapy of atopic dermatitis.

Mechanism of Action. Tacrolimus acts much like cyclosporine, although the two drugs are structurally dissimilar. Like cyclosporine, tacrolimus inhibits calcineurin, and thereby prevents helper T cells from producing IL-2, interferon gamma, and other cytokines. The end result is decreased proliferation of B cells and cytotoxic T cells. Tacrolimus and cyclosporine differ only in that cyclosporine must first bind to cyclophilin in order to act, whereas tacrolimus must first bind to an intracellular protein named FKBP-12.

Pharmacokinetics. Tacrolimus may be administered orally or IV. Following oral administration, absorption is slow and incomplete; bioavailability is less than 25%. The drug is metabolized in the liver by an isozyme of cytochrome P450. Excretion is via the bile. Less than 1% is excreted unchanged in the urine. The mean plasma half-life is 8 to 9 hours.

Adverse Effects. Adverse effects are much like those of cyclosporine. As with cyclosporine, nephrotoxicity is the major concern; the incidence is 33% to 40%. Other common reactions include neurotoxicity (headache, tremor, insomnia), GI effects (diarrhea, nausea, vomiting), hypertension, hyperkalemia, hyperglycemia, hirsutism, and gum hyperplasia. Anaphylaxis can occur with IV administration. Like other immunosuppressants, tacrolimus increases the risk of infection and lymphomas.

Drug and Food Interactions. Because tacrolimus is metabolized by CYP3A (an isozyme of cytochrome P450), agents that inhibit CYP3A—erythromycin, ketoconazole, fluconazole, chloramphenicol, and grapefruit juice—can increase tacrolimus levels. Like tacrolimus, NSAIDs can injure the kidneys. Accordingly, NSAIDs should be avoided.

Preparations, Dosage, and Administration. Tacrolimus [Prograf, Advagraf[®]] is supplied in capsules (0.5, 1, and 5 mg) for oral use and in solution (5 mg/mL) for IV use. Oral therapy is preferred. However, initial IV therapy may be needed when initial oral therapy is not tolerated. Oral dosages for adults are as follows:

- **Liver transplants**—The initial dosage is 50 to 75 mcg/kg every 12 hours, beginning no sooner than 6 hours after surgery. If treatment is initiated with IV therapy, oral dosing should begin 8 to 12 hours after stopping the infusion. To monitor therapy, trough levels in whole blood should be measured; the desired range is 5 to 20 ng/mL.
- **Kidney transplants**—The initial dosage is 100 mcg/kg every 12 hours. Oral therapy can start within 24 hours after surgery, but not until renal function has recovered. To monitor maintenance therapy, trough levels in whole blood should be measured; the desired ranges are 7 to 20 ng/mL for months 1 through 3, and 5 to 15 ng/mL thereafter.
- **Heart transplants**—The initial dosage is 37.5 mcg/kg every 12 hours, beginning no sooner than 6 hours after surgery. If IV therapy is used initially, oral therapy should begin 8 to 12 hours after the last IV dose. To monitor maintenance therapy, trough levels in whole blood should be measured; the desired ranges are 10 to 20 ng/mL for months 1 through 3, and 5 to 15 ng/mL thereafter.

mTOR INHIBITORS

The mTOR inhibitors are so named because they inhibit an enzyme known as *mammalian target of rapamycin*, or simply mTOR, a protein kinase that helps regulate cell growth, proliferation, and survival. The ultimate result is suppression of B-cell and T-cell proliferation. Although the mTOR inhibitors—sirolimus and everolimus—are structurally similar to tacrolimus, they work by a somewhat different mechanism, one that does not involve inhibition of calcineurin.

Sirolimus

Actions and Therapeutic Use. Sirolimus [Rapamune] is an immunosuppressant approved only for preventing rejection of renal transplants. The drug should be used in conjunction with cyclosporine and glucocorticoids. Owing to severe adverse effects, and no proof of efficacy in patients receiving heart, liver, or lung transplants, sirolimus should not be used by these patients.

How does sirolimus work? It binds with a cytoplasmic protein known as FKBP-12 to form a complex that then inhibits mTOR, an enzyme that helps regulate immune responses. As a result of mTOR inhibition, IL-2 is unable to cause B-cell and T-cell activation. Although sirolimus and tacrolimus both bind with FKBP-12, the consequences differ: Binding by tacrolimus causes inhibition of calcineurin, whereas binding by sirolimus causes inhibition of mTOR.

Pharmacokinetics. Sirolimus is rapidly but incompletely absorbed. Food reduces the rate of absorption but increases the extent. In the blood, most of the drug is sequestered in erythrocytes. As a result, concentrations in plasma are considerably lower than in whole blood. Sirolimus undergoes extensive metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450). Excretion is via the bile. The half-life is prolonged—2.5 days.

Adverse Effects. Like all other immunosuppressants, sirolimus increases the risk of infection, including BK virus-associated nephropathy in kidney recipients. Owing to the risk of infection, patients should avoid sources of contagion. In addition, for 12 months after transplant surgery, patients should take medicine to prevent *Pneumocystis pneumonia* (PCP), an infection caused by *Pneumocystis jirovecii* (formerly thought to be *Pneumocystis carinii*). Also, for 3 months after transplant surgery, patients should take medicine to prevent infection with cytomegalovirus.

Sirolimus raises levels of cholesterol and triglycerides. In clinical trials, about 50% of patients required treatment with lipid-lowering drugs. Exercise caution in patients with pre-existing hyperlipidemias.

Sirolimus, combined with cyclosporine, poses a significant risk of renal injury. Renal function should be monitored.

Severe complications have developed in liver and lung recipients. Liver recipients treated with sirolimus plus cyclosporine or tacrolimus have developed hepatic artery thrombosis, resulting in graft rejection or death. Lung recipients have developed bronchial anastomotic dehiscence; some cases were fatal. Sirolimus is not approved for liver or lung recipients, and should not be given to these patients.

Other side effects include rash, acne, anemia, thrombocytopenia, joint pain, diarrhea, and hypokalemia. In addition, sirolimus increases the risk of

lymphocele (a complication of renal transplant surgery). In contrast to cyclosporine, sirolimus is not neurotoxic, and, in contrast to everolimus, it is not diabetogenic.

Use in Pregnancy and Lactation. In rats, sirolimus can cause fetal death and reduced birth weight, but does not cause fetal malformations. Effects in pregnant women have not been studied systematically. At this time, sirolimus is categorized in FDA Pregnancy Risk Category C, and hence should be avoided during pregnancy. Women should initiate effective contraception before starting sirolimus, and continue it for at least 12 weeks after stopping sirolimus. Sirolimus is excreted into breast milk, and hence breastfeeding should be avoided.

Drug and Food Interactions. Levels of sirolimus can be raised or lowered by drugs that inhibit or induce CYP3A4, thereby posing a risk of toxicity or treatment failure. Drugs that induce CYP3A4, and thereby decrease sirolimus levels, include carbamazepine, phenytoin, phenobarbital, rifabutin, and rifampine. Drugs that inhibit CYP3A4, and thereby increase sirolimus levels, include verapamil, nicardipine, azole antifungal agents (eg, ketoconazole), macrolide antibiotics (eg, erythromycin), and HIV-protease inhibitors (eg, saquinavir). Because cyclosporine, tacrolimus, and sirolimus are metabolized by CYP3A4, they can compete with each other for metabolism, and can thereby raise each other's levels.

Sirolimus can reduce the immune response to all vaccines. In addition, the drug can render patients vulnerable to infection from live virus vaccines, which must be avoided.

High-fat foods can increase sirolimus absorption by about 35%. To minimize variability, patients should take all doses consistently (ie, all with food or all without food).

Grapefruit juice can inhibit the metabolism of sirolimus, causing its level to rise. Accordingly, taking sirolimus with grapefruit juice should be avoided.

Monitoring. Monitoring of sirolimus trough levels is recommended for all patients, and especially for pediatric patients, patients with liver disease, and patients taking strong inducers or inhibitors of CYP3A4. Monitoring is also recommended whenever the dosage of cyclosporine (taken concurrently with sirolimus) is raised or lowered substantially.

Preparations, Dosage, and Administration. Sirolimus is available in tablets (1 and 2 mg) and solution (1 mg/mL) for oral dosing. The treatment program should include cyclosporine and glucocorticoids. Sirolimus dosing should begin as soon as possible after transplant surgery. The recommended regimen consists of a 6-mg loading dose followed by 2-mg daily maintenance doses. For patients who weigh less than 40 kg (but are at least 13 years old), the loading dose is 3 mg/m² and the maintenance dosage is 1 mg/m² once a day. For all patients, maintenance doses should be taken 4 hours after taking cyclosporine, should be taken consistently with respect to food intake (ie, either with food or without food), and should not be taken with grapefruit juice. In patients with liver impairment, maintenance doses (but not the loading dose) should be reduced by 33%.

Everolimus

Therapeutic Use. Everolimus [Zortress, Afinitor] was approved in 2010 to prevent organ rejection in adults following an allogeneic kidney transplant. The drug is not approved in the United States for use in children or for use in adults who have received a heart, lung, or liver transplant. Everolimus should be used in conjunction with basiliximab, along with reduced doses of cyclosporine and glucocorticoids. In over 70 countries outside the United States, everolimus is used for heart transplants as well as for kidney transplants. As discussed in Chapter 103, everolimus, sold under the trade name *Afinitor*, is used in high doses to treat advanced renal cancer.

Mechanism of Action. Everolimus works by the same mechanism as sirolimus; it forms a complex with FKBP-12, which then inhibits mTOR, and thereby prevents activation of B cells and T cells by IL-2. Like sirolimus, everolimus does not cause inhibition of calcineurin.

Pharmacokinetics. Administration is oral, and plasma levels peak 1 to 2 hours after dosing. Food decreases both the peak plasma level and the total amount absorbed. Everolimus undergoes metabolic inactivation by CYP3A4 followed by excretion in the feces. The drug's half-life is about 30 hours.

Adverse Effects. At the dosage used for immunosuppression, the most common adverse effects are peripheral edema (45%), constipation (38%), hypertension (30%), nausea (29%), anemia (26%), urinary tract infections (22%), and hyperlipidemia (21%). Like all other immunosuppressants, everolimus can increase the risk of malignancy (especially lymphomas) and serious infection, including BK virus-associated nephropathy. Other serious effects include delayed wound healing, noninfectious pneumonitis, new-onset diabetes, male infertility, arterial and venous thrombosis in the kidney allograft, and direct kidney damage, which can be exacerbated by cyclosporine, and which patients using everolimus are required to take.

Effects in Pregnancy and Lactation. Although everolimus has not been studied in pregnant women, animal studies indicate the drug is toxic to the developing fetus. Accordingly, everolimus should be used during pregnancy only if the benefits to the mother are deemed to outweigh the risks to the fetus. Women of child-bearing age should use effective contraception while taking everolimus and for 8 weeks after stopping.

Although studies in lactating women have not been conducted, we know that everolimus readily enters the milk of lactating rats, and hence probably enters the milk of lactating women. Accordingly, women taking everolimus should avoid breast-feeding.

Drug and Food Interactions. Everolimus is subject to the same drug and food interactions as sirolimus. Hence, as with sirolimus, levels of everolimus can be raised or lowered by drugs that inhibit or induce CYP3A4, thereby posing a risk of toxicity or treatment failure. Drugs that induce CYP3A4, and can thereby decrease everolimus levels, include carbamazepine, phenytoin, phenobarbital, rifabutin, and rifampine. Drugs that inhibit CYP3A4, and can thereby increase everolimus levels, include verapamil, nicardipine, azole antifungal agents (eg, ketoconazole), macrolide antibiotics (eg, erythromycin), and HIV-protease inhibitors (eg, saquinavir). Because cyclosporine and everolimus are metabolized by CYP3A4, they can compete with each other for metabolism, and can thereby raise each other's levels.

Like sirolimus, everolimus can reduce the immune response to all vaccines. In addition, everolimus can render patients vulnerable to infection from live virus vaccines, which must be avoided.

As with sirolimus, high-fat foods can increase absorption of everolimus. To minimize variability, patients should take all doses consistently, either with food or without food.

Grapefruit juice can inhibit the metabolism of everolimus, causing its level to rise. Accordingly, taking everolimus with grapefruit juice should be avoided.

Preparations, Dosage, and Administration. The Zortress* brand of everolimus is supplied in tablets (0.25, 0.5, and 0.75 mg) for oral dosing, which should start as soon as possible after transplant surgery. The tablets should be swallowed whole with a glass of water, and should be taken consistently either with food or without food (to minimize variability in absorption). In patients with normal liver function, the initial dosage is 0.5 mg twice daily. In patients with moderate liver impairment, the initial dosage should be cut in half (ie, to 0.25 mg twice daily). For all patients, maintenance doses should be adjusted to yield a trough level of 3 to 8 ng/mL.

GLUCOCORTICOIDS

Glucocorticoids (eg, prednisone) are used widely to suppress immune responses. Applications range from suppression of allograft rejection to treatment of asthma to therapy of autoimmune disorders, such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

Glucocorticoids have multiple effects on elements of the immune system. They cause lysis of antigen-activated lymphocytes, suppression of lymphocyte proliferation, and sequestration of lymphocytes at extravascular locations. In addition, they reduce production of IL-2 by monocytes and lymphocytes, and they reduce the responsiveness of T lymphocytes to interleukin-1.

Immunosuppressive doses are large. For example, to prevent organ rejection, an initial dose of 0.5 to 2 mg/kg of prednisone is employed. To treat episodes of acute organ rejection, 500 to 1500 mg of IV methylprednisolone is given.

Because large doses are employed, the full range of glucocorticoid adverse effects can be expected. These include increased risk of infection, thinning of the skin, bone dissolution with resultant fractures, impaired growth in children, and suppression of the hypothalamic-pituitary-adrenal axis.

The pharmacology of glucocorticoids is discussed at length in Chapter 72 (Glucocorticoids in Nonendocrine Diseases).

*As noted in Chapter 103, the *Afinitor* brand of everolimus, used for advanced renal cancer, is supplied in 5- and 10-mg tablets.

CYTOTOXIC DRUGS

Cytotoxic drugs suppress immune responses by killing B and T lymphocytes that are undergoing proliferation. With the exception of mycophenolate mofetil, these drugs are nonspecific. That is, they are toxic to all proliferating cells. As a result, they can cause bone marrow suppression, GI disturbances, reduced fertility, and alopecia (hair loss). Neutropenia and thrombocytopenia from bone marrow suppression are of particular concern. Because of their serious adverse effects, the cytotoxic drugs are usually reserved for patients who have not responded to safer immunosuppressants (ie, cyclosporine, tacrolimus, and glucocorticoids).

Azathioprine

Immunosuppressant effects result from suppression of B and T lymphocytes secondary to interference with folate metabolism.

Mechanism of Action. Azathioprine [Imuran] suppresses cell-mediated and humoral immune responses by inhibiting the proliferation of B and T lymphocytes. The underlying mechanism is inhibition of DNA synthesis by the drug's active form: mercaptopurine. Because of its mechanism, azathioprine acts selectively during the S phase of the cell cycle. As discussed in Chapter 102, mercaptopurine is used to treat cancer.

Therapeutic Uses. Prior to the advent of cyclosporine, azathioprine (combined with prednisone) was the principal drug employed to suppress rejection of renal transplants. Today, azathioprine is generally used as an adjunct to cyclosporine and glucocorticoids to help suppress transplant rejection. In addition, the drug is approved for severe refractory rheumatoid arthritis in nonpregnant adults (see Chapter 73). Azathioprine has been used investigatively to treat various autoimmune diseases, including myasthenia gravis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis.

Adverse Effects and Drug Interactions. Although uncommon at usual therapeutic doses, *neutropenia* and *thrombocytopenia* from bone marrow suppression can be serious concerns. Accordingly, complete blood counts should be performed at baseline and periodically thereafter. Azathioprine is *mutagenic* and *teratogenic* in animals, and hence should be avoided during pregnancy. Long-term therapy is associated with an increased incidence of *neoplasms*.

Allopurinol delays conversion of mercaptopurine to inactive products, and thereby increases the risk of toxicity. If allopurinol and azathioprine are used concurrently, the dose of azathioprine must be reduced by about 70%.

Preparations, Dosage, and Administration. Azathioprine [Imuran] is available in 50-mg tablets for oral dosing, and as a powder to be reconstituted with sterile water for IV use. For patients receiving a kidney transplant, therapy is initiated with a single daily dose of 3 to 5 mg/kg, usually beginning on the day of surgery. Daily maintenance doses range from 1 to 3 mg/kg. Oral administration is preferred to IV.

Cyclophosphamide

Cyclophosphamide, an anticancer drug, is discussed at length in Chapter 102. Discussion here is limited to its immunosuppressant use. Cyclophosphamide is a prodrug that is converted to its active form by the liver. The active form is an alkylating agent that cross-links DNA, leading to cell injury and death. Immunosuppressant effects result from a decrease in the number and activity of B and T lymphocytes. Toxicity to other cells produces adverse effects, including neutropenia (from bone marrow suppression), hemorrhagic cystitis, and sterility in males and females. Cyclophosphamide has been used for its immunosuppressant actions to treat rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. The drug is as effective as azathioprine for suppressing rejection of kidney transplants.

Methotrexate

Methotrexate [Rheumatrex, Trexall], developed as an anticancer agent (see Chapter 102), was later found to be effective in psoriasis (see Chapter 105), and arthritis (see Chapter 73) and other autoimmune disorders. Immunosuppressant effects result from suppression of B and T lymphocytes secondary to interference with folate metabolism. The doses employed for immunosuppression are lower than those employed to treat cancer. As a result, toxicities differ with the two applications: In cancer chemotherapy, bone marrow suppression, ulcerative stomatitis, and renal damage are primary concerns, whereas in immunosuppressive therapy, hepatic fibrosis and cirrhosis are primary concerns.

Mitoxantrone

Like methotrexate, mitoxantrone [Novantrone] was developed to treat cancer (see Chapter 102), and then used later for immunosuppression, owing to its toxic effects on macrophages and B and T lymphocytes. As an immunosuppressant, mitoxantrone has only one indication; reduction of neurologic disability and clinical relapse in patients with multiple sclerosis. Mitoxantrone is a dangerous drug reserved for patients unresponsive to safer agents. The basic pharmacology of the drug and its use in multiple sclerosis are discussed in Chapter 23.

Mycophenolate Mofetil

Therapeutic Use. Mycophenolate mofetil is approved for prophylaxis of organ rejection in patients receiving allogenic heart, liver, or kidney transplants. The drug should be combined with cyclosporine and glucocorticoids.

Mechanism of Action. Following oral administration, mycophenolate mofetil is rapidly converted to mycophenolic acid (MPA), its active form. MPA then acts on B and T lymphocytes to inhibit inosine monophosphate dehydrogenase, an enzyme required for *de novo* synthesis of purines. Since these cells are uniquely dependent on *de novo* synthesis for proliferation (other cells acquire needed purines via salvage pathways), MPA causes selective inhibition of B- and T-lymphocyte proliferation.

Pharmacokinetics. With oral administration, mycophenolate mofetil undergoes nearly complete absorption, followed by rapid and nearly complete hydrolysis to MPA. MPA is converted in the liver to an inactive metabolite, which is then excreted in the urine. The half-life of MPA is about 18 hours.

Adverse Effects. Major adverse effects include diarrhea, vomiting, severe neutropenia, sepsis (primarily cytomegalovirus viremia), and pure red-cell aplasia (a form of anemia characterized by selective reductions in red blood cell precursors in bone marrow). As with other immunosuppressive drugs, there is an increased risk of malignancies (especially lymphomas) and infection (including BK virus-associated nephropathy). Very rarely, patients have developed progressive multifocal leukoencephalopathy, a severe infection of the brain. However, a causal relationship has not been established.

Drug Interactions. Absorption of mycophenolate can be decreased by antacids that contain magnesium and aluminum hydroxides and by cholestyramine, a drug that lowers blood cholesterol. Accordingly, mycophenolate should not be given simultaneously with these drugs.

Use in Pregnancy. When given to pregnant rats in doses at or below those used clinically, mycophenolate causes fetal malformations and fetal resorption. Controlled studies in women have not been performed. Because of the serious risk of fetal toxicity, the drug should be avoided during pregnancy. Before initiating treatment, pregnancy should be ruled out. During therapy, women of child-bearing age should use two reliable forms of contraception.

Preparations, Dosage, and Administration. Administration is PO or IV. For oral dosing, mycophenolate mofetil is available in 250-mg capsules, 250- and 500-mg immediate-release tablets, and a 200-mg/mL suspension. For IV dosing, the drug is available as a lyophilized powder for reconstitution to a 6-mg/mL solution. Intravenous administration is reserved for patients who cannot take the drug orally, and should be done by *slow infusion* (over 2 hours or longer). Adult dosages are as follows:

- *Kidney transplant*—1 gm twice daily, IV or PO
- *Heart transplant*—1.5 gm twice daily, IV or PO
- *Liver transplant*—1 gm twice daily IV or 1.5 gm twice daily PO

Dosing should begin within 24 hours of transplant surgery. All patients who receive IV therapy initially should switch to oral therapy within 14 days. As a rule, oral dosing should be done on an empty stomach to increase absorption.

ANTIBODIES

Antibodies directed against components of the immune system can suppress immune responses. The preparations discussed below are used to suppress allograft rejection in transplant recipients.

Muromonab-CD3

Actions and Uses. Muromonab-CD3 [Orthoclone OKT3] is a monoclonal antibody, developed in mice, that binds to the CD3 site on human T lymphocytes. Upon binding, the antibody blocks T-cell function. All T cells—both those in the circulation and those in tissues—are affected.

Muromonab-CD3 is used to prevent acute rejection of kidney, heart, and liver transplants. In addition, the drug is given to deplete T cells from bone marrow prior to bone marrow transplantation.

Adverse Effects. Relatively mild reactions are common. Among these are fever (73%), chills (59%), dyspnea (21%), chest pain (14%), and nausea and vomiting (12%). These effects are most intense on the first day and then rapidly subside.

In some patients, potentially fatal *anaphylactoid reactions* have occurred. Manifestations include pulmonary edema, cardiovascular collapse, and cardiac or respiratory arrest. Accordingly, patients should be monitored closely. Also, the drug should be used only in facilities with equipment and staffing for cardiopulmonary resuscitation.

Preparations, Dosage, and Administration. Muromonab-CD3 is supplied in solution (1 mg/mL) for IV administration. The usual dosage is 5 mg/day for 10 to 14 days. Administration is by IV bolus. The preparation should be drawn through a filter before injection. Treatment is begun following diagnosis of acute transplant rejection. To minimize first-dose adverse reactions, the patient should be pretreated with an IV glucocorticoid. The wholesale cost for a course of treatment averages \$7000.

Basiliximab

Actions and Uses. Basiliximab [Simulect] is a monoclonal antibody, developed in mice, that binds to the receptor for IL-2 on T lymphocytes. By doing so, it blocks activation of T cells by IL-2.

Basiliximab has only one indication: prophylaxis of *acute* organ rejection following renal transplantation. The regimen should also include cyclosporine and a glucocorticoid. In clinical trials, basiliximab helped reduce the incidence of acute organ rejection during the first 6 months after transplant surgery, but had little or no impact on graft survival after 1 year.

Adverse Effects. Basiliximab is generally well tolerated. The incidence and severity of adverse effects is much lower than with muromonab-CD3. In contrast to other immunosuppressants, basiliximab does not increase the risk of opportunistic infections. Furthermore, no cancers have been observed 1 year after treatment.

Rarely, basiliximab causes severe, acute *hypersensitivity reactions*, including anaphylaxis. Accordingly, medications for managing hypersensitivity

should be immediately available. If a severe hypersensitivity reaction occurs, the drug should be permanently discontinued.

Preparations, Dosage, and Administration. Basiliximab is available as a powder to be reconstituted for IV administration. Treatment consists of two 20-mg doses, given by either (1) IV bolus or (2) IV infusion over 20 to 30 minutes. The first dose is given within 2 hours prior to transplant surgery. The second is given 4 days later.

Lymphocyte Immune Globulin, Antithymocyte Globulin (Equine)

Basic Pharmacology. Lymphocyte immune globulin [Atgam] is prepared by extraction from the serum of horses that have been inoculated with human T lymphocytes. Therapeutic effects result from a decrease in the number and activity of thymus-derived lymphocytes. Lymphocyte immune globulin has two approved uses: (1) preventing rejection of renal transplants and (2) treating aplastic anemia. Investigational uses include treatment of multiple sclerosis and myasthenia gravis, and suppressing rejection of liver, bone marrow, and heart transplants. Lymphocyte immune globulin is usually employed in combination with glucocorticoids and azathioprine. Because these other immunosuppressants are present, immune reactions to this horse-derived drug are generally mild (chills, fever, leukopenia, skin reactions). However, anaphylactic reactions can occur. Accordingly, epinephrine and facilities for respiratory support should be immediately available.

Preparations, Dosage, and Administration. Lymphocyte immune globulin is supplied in solution (50 mg/mL) for IV dosing. The concentrate should be diluted in saline solution as per the manufacturer's instructions, and the infusion apparatus should have an in-line filter. To minimize phlebitis, a vein with high flow should be employed. Monitor the patient for anaphylaxis. Each dose should be infused over 4 or more hours. Dosages for adults are as follows:

- *Prevention of renal allograft rejection*—15 mg/kg/day for 14 days, followed by alternate-day dosing for 14 more days, to make a total of 21 doses over 28 days.
- *Treatment of aplastic anemia*—10 to 20 mg/kg/day for 8 to 14 days followed, if needed, by alternate-day dosing for up to a total of 21 doses.

KEY POINTS

- Immunosuppressants are used to prevent organ rejection in allograft recipients and to treat autoimmune disorders (eg, rheumatoid arthritis).
- Allograft recipients must take immunosuppressants for life.
- Immunosuppressants increase the risk of infection and lymphomas.
- Cyclosporine and tacrolimus are the most effective immunosuppressants available.
- Cyclosporine and tacrolimus are used primarily in allograft recipients.
- Cyclosporine causes kidney injury in up to 75% of patients.
- Kidney damage from cyclosporine can be intensified by other nephrotoxic drugs, including amphotericin B, aminoglycosides, and NSAIDs.
- Drugs that inhibit hepatic microsomal enzymes can increase cyclosporine levels, and drugs that induce these enzymes can decrease cyclosporine levels.
- Grapefruit juice inhibits cyclosporine metabolism, and can thereby greatly increase cyclosporine levels.
- Like cyclosporine, tacrolimus causes renal damage, and hence should not be combined with other nephrotoxic drugs.
- Immunosuppressant applications of glucocorticoids include suppression of transplant rejection and treatment of rheumatoid arthritis and other autoimmune disorders.
- Prolonged use of glucocorticoids can cause osteoporosis, thinning of the skin, increased risk of infection, impaired growth in children, and adrenal insufficiency (secondary to suppression of the hypothalamic-pituitary-adrenal axis).
- Cytotoxic immunosuppressants (eg, azathioprine) decrease immune responses by killing B and T lymphocytes.
- Cytotoxic immunosuppressants (except mycophenolate mofetil) injure all proliferating cells. As a result, these drugs can cause bone marrow suppression (neutropenia, thrombocytopenia), GI disturbances, reduced fertility, and alopecia.
- Immune responses can be suppressed with muromonab-CD3, basiliximab, and other antibodies directed against components of the immune system.

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Summary of Major Nursing Implications*

CYCLOSPORINE

Preadministration Assessment

Therapeutic Goal

Prevention of allograft rejection

Baseline Data

Obtain baseline data on kidney function (serum creatinine, BUN), liver function (aspartate aminotransferase, alanine aminotransferase, serum amylase, bilirubin, alkaline phosphatase), and serum potassium levels.

Identifying High-Risk Patients

Cyclosporine has the following *contraindications*: hypersensitivity to cyclosporine or its intravenous vehicle (polyoxyethylated castor oil), pregnancy, recent inoculation with a live virus vaccine, and chickenpox or herpes zoster (or recent contact with a person with either infection).

Use with *caution* in patients taking potassium-sparing diuretics and in those with intestinal malabsorption, hypertension, hyperkalemia, active infection, and renal or hepatic dysfunction.

Implementation: Administration

Routes

Oral, intravenous.

Preparations

Cyclosporine is available under three trade names: Sandimmune, Neoral, and Gengraf. Sandimmune has lower bioavailability than Neoral or Gengraf, and hence is not interchangeable with them.

Patient Education for Oral Administration

Dispense the oral liquid into a glass container using the specially calibrated pipette. Mix well with diluent and drink immediately. Rinse the container with diluent and drink to ensure ingestion of the complete dose. Dry the outside of the pipette and return to its cover for storage.

To improve palatability, mix the concentrated drug solution with plain milk, chocolate milk, or orange juice just before dosing.

Intravenous Dosage and Administration

Dilute 1 mL of concentrate in 20 to 100 mL of 0.9% sodium chloride or 5% dextrose. Protect from light. Administer the initial dose (5 to 6 mg/kg) slowly—over 2 to 6 hours. Because of the risk of anaphylactic reactions, monitor the patient closely for 30 minutes after starting administration. Have epinephrine and oxygen available. Switch to oral therapy as soon as possible.

Dosage Adjustment

Adjust dosage on the basis of nephrotoxicity and cyclosporine trough levels. Draw blood for drug levels just prior to the next dose. The target trough level is 100 to 200 ng/mL in whole blood.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Graft tenderness or fever may indicate rejection. In renal transplant recipients, elevated BUN and elevated serum creatinine in conjunction with low cyclosporine may indicate rejection. Therapeutic failure can be confirmed with ultrasound, a biopsy, or renal flow scan.

Minimizing Adverse Effects

Nephrotoxicity. Cyclosporine can cause a dose-dependent reduction in kidney function. Monitor for elevation of serum creatinine and BUN. **Inform outpatients about the importance of undergoing periodic tests of kidney function.**

Infection. Cyclosporine increases the risk of infection, including BK virus-associated nephropathy. **Inform patients about early signs of infection (fever, sore throat), and instruct them to report these immediately.**

Hepatotoxicity. Cyclosporine causes reversible liver damage. Monitor for elevation of serum bilirubin and liver transaminases. **Inform patients about the need for periodic tests of liver function.**

Hirsutism. Cyclosporine promotes hair growth. **Assure the patient that the effect is reversible.**

Use in Pregnancy and Lactation. Cyclosporine is embryotoxic. **Advise women of child-bearing age to use a mechanical form of contraception (diaphragm, condom) and to avoid oral contraceptives. Cyclosporine is excreted in breast milk; warn patients against breast-feeding.**

Anaphylactic Reactions. See *Intravenous Dosage and Administration*.

Minimizing Adverse Interactions

Drugs That Can Decrease Cyclosporine Levels. Phenytoin, phenobarbital, carbamazepine, rifampin, terbinafine, and trimethoprim-sulfamethoxazole can reduce cyclosporine levels, leading to organ rejection. Monitor cyclosporine levels and increase the dosage as needed.

Drugs That Can Increase Cyclosporine Levels. Azole antifungal drugs (eg, ketoconazole), macrolide antibiotics (eg, erythromycin), and amphotericin B can elevate cyclosporine levels, thereby increasing the risk of toxicity. Monitor cyclosporine levels and reduce the dosage as needed.

Nephrotoxic Drugs. Amphotericin B, aminoglycosides, and NSAIDs increase the risk of cyclosporine-induced kidney damage. Monitor renal function.

Grapefruit Juice. Grapefruit juice inhibits cyclosporine metabolism, and can thereby increase cyclosporine levels. Toxicity may result.

Repaglinide. Cyclosporine can increase levels of repaglinide, a drug for diabetes, and can thereby cause hypoglycemia. **Advise diabetic patients to monitor blood glucose closely.**

*Patient education information is highlighted as blue text.

Histamine**Distribution, Synthesis, Storage, and Release****Physiologic and Pharmacologic Effects****Role of Histamine in Allergic Responses****The Two Types of Antihistamines: H₁ Antagonists and H₂ Antagonists****H₁ Antagonists I: Basic Pharmacology****H₁ Antagonists II: Preparations****First-Generation H₁ Antagonists****Second-Generation (Nonsedating) H₁ Antagonists**

Histamine is a small molecule produced in specialized cells throughout the body. The compound plays an important role in allergic reactions and regulation of gastric acid secretion. The antihistamines, a widely used family of drugs, block histamine actions.

In order to understand the antihistamines, we must first understand histamine itself. Accordingly, the chapter begins with a discussion of histamine, emphasizing its contribution to allergic responses. Discussion of the antihistamines follows.

HISTAMINE

Histamine is a locally acting compound with prominent and varied effects. In the vascular system, histamine dilates small blood vessels and increases capillary permeability. In the bronchi, histamine produces constriction of smooth muscle. In the stomach, histamine stimulates secretion of acid. In the central nervous system (CNS), histamine acts as a neurotransmitter. Despite this impressive spectrum of actions, clinical use of histamine is limited to diagnostic procedures. However, although its clinical utility is minimal, histamine is still of great interest owing to its involvement in two common pathologic states: allergic disorders and peptic ulcer disease.

Distribution, Synthesis, Storage, and Release

Distribution. Histamine is present in practically all tissues. Levels are especially high in the skin, lungs, and GI tract. The histamine content of plasma is low.

Synthesis and Storage. In the periphery, histamine is synthesized and stored in two types of cells: *mast cells* and *basophils*. Mast cells are present in the skin and other soft tissues. Basophils are present in blood. In both mast cells and basophils, histamine is stored in secretory granules. (In addi-

tion to histamine, secretory granules contain other substances that, like histamine, are mediators of allergic reactions.)

In the CNS, histamine is produced by neurons with cell bodies in the posterior hypothalamus and with axonal projections to the frontal and temporal cortices and other brain regions.

Release. Release of histamine from mast cells and basophils is produced by allergic and nonallergic mechanisms.

Allergic Release. The initial requirement for allergic release is production of antibodies of the immunoglobulin E class. These antibodies are generated following exposure to specific allergens (eg, pollens, insect venoms, certain drugs). Once made, the antibodies become attached to the outer surface of mast cells and basophils (Fig. 70-1). When the individual is re-exposed to the allergen, the allergen becomes bound by the antibodies. As indicated in Figure 70-1, binding of allergen to adjacent antibodies creates a bridge between those antibodies. By a mechanism that is not fully understood, this bridging process mobilizes intracellular calcium. The calcium, in turn, causes the histamine-containing storage granules to fuse with the cell membrane and discharge their contents into the extracellular space. Note that allergic release of histamine requires *prior exposure* to the allergen; an allergic reaction cannot occur during initial allergen exposure.

Nonallergic Release. Several agents (certain drugs, radiocontrast media, plasma expanders) can act directly on mast cells to trigger histamine release. With these agents, no prior sensitization is needed. Cell injury can also cause direct release.

Physiologic and Pharmacologic Effects

Histamine acts primarily through two types of receptors, named H₁ and H₂. The response produced depends on which of these receptors is involved.

Effects of H₁ Stimulation

Vasodilation. Activation of H₁ receptors causes dilation of small blood vessels (arterioles and venules). Vasodilation is prominent in the skin of the face and upper body, causing the area to become warm and flushed. If extensive vasodilation occurs, total peripheral resistance declines and blood pressure falls.

Increased Capillary Permeability. Activation of H₁ receptors increases capillary permeability. How? Receptor activation causes capillary endothelial cells to contract, creating openings between these cells through which fluid, protein, and platelets can escape. Escape of fluid and protein into the interstitial space produces edema. If loss of intravascular fluid is substantial, blood pressure may fall.

Bronchoconstriction. Histamine₁ activation causes constriction of the bronchi. If histamine is administered to an

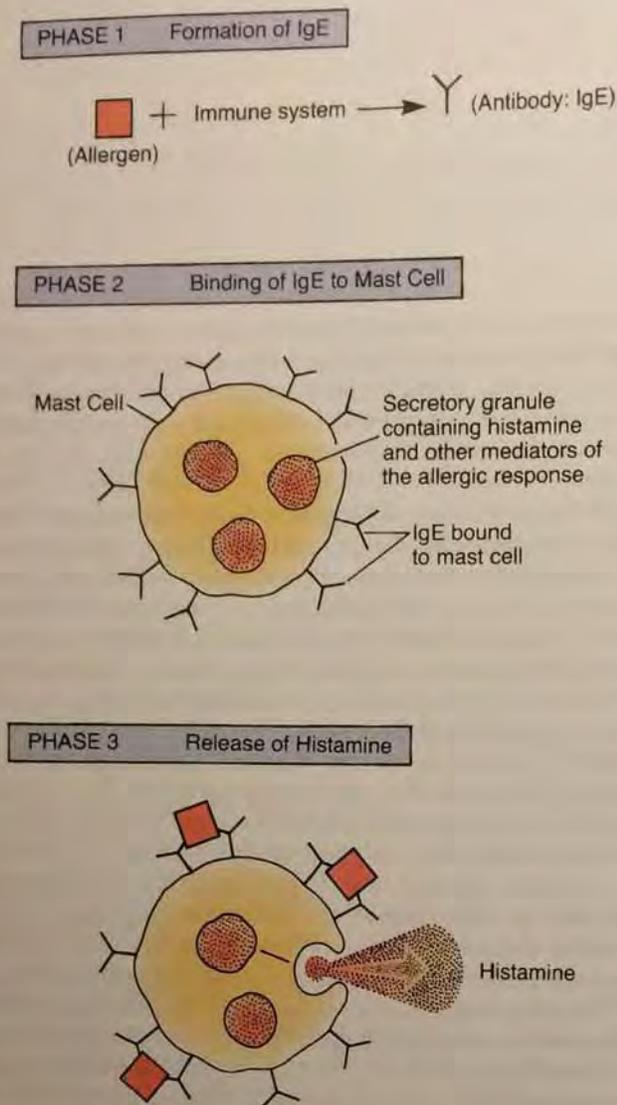


Figure 70-1 • Release of histamine by allergen-antibody interaction.

(IgE = immunoglobulin E.)

individual with asthma, severe bronchoconstriction will follow. However, although *exogenous* histamine can induce bronchial constriction, histamine is not the cause of bronchoconstriction that occurs during a spontaneous asthma attack. Consequently, antihistamines are of no use for treating asthma.

CNS Effects. In the CNS, H_1 receptors have a role in cognition, memory, and the cycle of sleeping and waking. In addition, H_1 receptors appear to have a role in seizure suppression, modulation of neurotransmitter release, and regulation of energy and endocrine homeostasis.

Other Effects. Activation of H_1 receptors on sensory nerves produces *itching* and *pain*. Histamine₁ activation also promotes *secretion of mucus*.

Effects of H_2 Stimulation

The major response to activation of H_2 receptors is *secretion of gastric acid*. Histamine acts directly on parietal cells of the stomach to promote acid release. Although acetylcholine and gastrin also help regulate acid release, histamine has a dominant role. We know this because, in the presence of H_2

blockade, acetylcholine and gastrin are unable to elicit acid secretion.

Role of Histamine in Allergic Responses

Allergic reactions are mediated by histamine and other compounds (eg, prostaglandins, leukotrienes, tryptase). The intensity of an allergic reaction is determined by which mediator is involved.

Mild Allergy. The symptoms of mild allergy (eg, rhinitis, itching, localized edema) are caused largely by histamine, acting at H_1 receptors. As a result, mild allergic conditions (eg, hay fever, acute urticaria, mild transfusion reactions) are generally responsive to antihistamine therapy.

Severe Allergic Reactions (Anaphylaxis). Severe allergic reactions manifest as *anaphylactic shock*, a syndrome characterized by bronchoconstriction, hypotension, and edema of the glottis. Although histamine is involved in anaphylaxis, it plays a minor role; other substances (eg, leukotrienes) are the principal mediators. Since histamine has little to do with producing anaphylaxis, it follows that antihistamines are of little help as treatment. The drug of choice for anaphylaxis is *epinephrine*. The rationale for using epinephrine is discussed in Chapter 17.

THE TWO TYPES OF ANTIHISTAMINES: H_1 ANTAGONISTS AND H_2 ANTAGONISTS

Antihistamines fall into two basic categories: H_1 receptor antagonists and H_2 receptor antagonists. The H_1 antagonists produce selective blockade of H_1 receptors. The H_2 antagonists produce selective blockade of H_2 receptors. The principal use of H_1 blockers is treatment of mild allergic disorders. The principal use of H_2 blockers is treatment of gastric and duodenal ulcers. Because H_2 antagonists do not block H_1 receptors, these drugs are of no use for treating allergies. In this chapter, we focus on H_1 antagonists. The H_2 blockers, which are important and widely used, are discussed in Chapter 78 (Drugs for Peptic Ulcer Disease).

H_1 ANTAGONISTS I: BASIC PHARMACOLOGY

The H_1 antagonists are the classic antihistamines. These agents were in use long before H_2 blockers came along. In fact, before H_2 blockers became available, the term *H_1 antagonist* did not exist; the drugs that we now call H_1 antagonists or H_1 blockers were simply referred to as *antihistamines*. Because of its historic use, the term *antihistamines* is still employed as a synonym for the subgroup of histamine antagonists that produce selective H_1 blockade. In this chapter, we respect tradition and continue to use the term *antihistamine* interchangeably with H_1 blocker and H_1 antagonist.

Although all H_1 antagonists available have similar antihistaminic actions, these drugs differ significantly in side effects. Because of these differences, selection of a prototype to represent the group is not feasible. Hence, rather than structuring discussion around one prototypic drug, we discuss the H_1 antagonists collectively. Differences among individual antihistamines are addressed as appropriate.

Classification of H₁ Antagonists

The H₁ antagonists fall into two major groups; *first-generation H₁ antagonists* and *second-generation H₁ antagonists*. The principal difference between the groups is that first-generation antihistamines are highly sedating, whereas second-generation antihistamines are not.

Mechanism of Action

Histamine₁ blockers bind selectively to H₁-histaminic receptors, thereby blocking the actions of histamine at these sites. H₁ antagonists do not block H₂ receptors. Also, they do not block release of histamine from mast cells or basophils.

It should be noted that, although interaction of the classic antihistamines with *histaminic* receptors is limited to the H₁ receptor subtype, these drugs can also bind to *nonhistaminic* receptors. Most notably, certain antihistamines can bind to and block *muscarinic* receptors. This action underlies several important side effects.

Pharmacologic Effects

Peripheral Effects. The major therapeutic effects of the H₁ antagonists can be attributed to preventing the actions of histamine at H₁ receptors. In arterioles and venules of the skin, H₁ blockers inhibit the dilator actions of histamine, and thereby reduce localized flushing. In capillary beds, the antihistamines prevent histamine-induced increases in permeability, and thereby reduce edema. By blocking histamine at sensory nerves, H₁ antagonists reduce itching and pain. Blockade of H₁ receptors in mucous membranes suppresses secretion of mucus.

Effects on the CNS. Antihistamines can cause both excitation and depression of the CNS. At *therapeutic doses*, antihistamines produce CNS *depression*: reaction time is slowed, alertness is diminished, and drowsiness is likely. These effects are more pronounced with some antihistamines than with others. With most second-generation antihistamines (eg, fexofenadine), CNS depression is negligible.

Overdose with antihistamines can produce *CNS stimulation*. Convulsions frequently result. Very young children are especially sensitive to CNS stimulation by these drugs.

Other Pharmacologic Effects. Blockade of muscarinic cholinergic receptors by antihistamines can produce typical *anticholinergic* responses. These are discussed below under *Adverse Effects*. Several antihistamines can suppress nausea and vomiting, as discussed below under *Motion Sickness*.

Therapeutic Uses

All of the H₁ antagonists are useful in treating allergic disorders. Some are also indicated for other conditions (eg, motion sickness, insomnia).

Mild Allergy. Antihistamines can reduce symptoms of mild allergies. In people with *seasonal allergic rhinitis* (also known as hay fever or rose fever), H₁ blockers can reduce sneezing, rhinorrhea, and itching of the eyes, nose, and throat (although they can't reduce nasal congestion). In patients with *acute urticaria*, these drugs can reduce redness, itching, and edema. The antihistamines can also reduce symptoms of *allergic conjunctivitis* and urticaria associated with *mild transfusion reactions*. In all of these conditions, benefits result from H₁ receptor blockade—not from preventing allergen-induced release of histamine from mast cells and basophils. Because mild allergic reactions may be mediated by sub-

stances in addition to histamine, antihistamines often fail to produce complete relief.

Severe Allergy. As noted, the major symptoms of anaphylaxis (hypotension, laryngeal edema, bronchospasm) are caused by mediators other than histamine. Hence, although antihistamines may be employed as adjuncts in patients with anaphylaxis, their benefits are limited.

Motion Sickness. Some antihistamines, such as promethazine [Phenergan] and dimenhydrinate [Dramamine], are labeled for use in motion sickness. Benefits derive from blocking H₁ receptors and muscarinic receptors in the neuronal pathway leading from the vestibular apparatus of the inner ear to the vomiting center of the medulla. Motion sickness and its treatment are discussed in Chapter 80. The antihistamines employed for motion sickness, along with their dosages, are listed in Table 80-1.

Insomnia. The ability of antihistamines to cause drowsiness has been exploited in the treatment of insomnia. Practically every over-the-counter (OTC) sleep aid contains an H₁ antagonist—diphenhydramine or pyrilamine—as its active ingredient. However, although antihistamines can induce sleep when used in sufficient dosage, the doses recommended for OTC preparations are usually too low to be effective.

Common Cold. Despite their widespread presence in cold remedies, antihistamines are of practically no value against the common cold. These drugs neither prevent colds nor shorten their duration. Moreover, since histamine does not mediate symptoms of colds, H₁ blockade cannot even provide symptomatic relief. The only benefit these drugs may offer is a moderate reduction in rhinorrhea, an effect that derives from their *anticholinergic* properties, not from H₁ blockade.

Adverse Effects

All of the H₁ blockers can produce undesired effects. As a rule, these responses are more of a nuisance than a source of serious discomfort or danger. Frequently, side effects subside with continued drug use. Because individual antihistamines differ in their abilities to produce particular side effects (Table 70-1), adverse responses can be minimized by judicious drug selection.

Sedation. Sedation is the most common side effect of the antihistamines, and can lead to serious consequences. For students, sedation can impair learning and memory. For drivers, sedation greatly increases the risk of an accident. In fact, the degree of impairment seen with antihistamines equals that seen when blood levels of alcohol exceed the legal limit. Worse yet, impairment can occur without feeling tired. Accordingly, patients should exercise extreme caution when driving or performing other hazardous activities. They should also avoid alcohol and other CNS depressants. Why? Because these agents will intensify the depressant effects of the H₁ antagonist. Fortunately, tolerance to sedation often develops within a few days or weeks. If a preparation with a long half-life is being used, daytime sedation can be minimized by administering the entire daily dose at night.

The second-generation antihistamines exert little or no sedative effect. Why? First, these drugs are relatively large molecules with low lipid solubility, and hence they can't cross the blood-brain barrier. Second, these drugs have low affinity to the type of H₁ receptor found in the brain. In contrast, the first-generation antihistamines are relatively small molecules with high lipid solubility, and hence can readily cross the

TABLE 70-1 ■ Pharmacologic Effects of H₁ Antagonists Used for Parenteral Therapy

Drug	H ₁ -Blocking Activity*	Sedative Effects*	Anticholinergic Effects*
First-Generation Agents			
Alkylamines			
Brompheniramine	+++	+	++
Chlorpheniramine	++	+	++
Dexchlorpheniramine	+++	+	++
Ethanolamines			
Clemastine	+ to +++	++	+++
Diphenhydramine	+ to +++	+++	+++
Phenothiazines			
Promethazine [†]	+++	+++	+++
Piperazines			
Hydroxyzine	++ to +++	+++	++
Piperidines			
Cyproheptadine	++	+	++
Second-Generation (Nonsedating) Agents			
Cetirizine [‡]	+++	+	±
Levocetirizine [‡]	+++	+	±
Fexofenadine	+++	±	±
Loratadine	++ to +++	±	±
Desloratadine	++ to +++	±	±

*± = low to none, + = low, ++ = moderate, +++ = high.

[†]Promethazine is contraindicated in children under 2 years old owing to a risk of fatal respiratory depression. Parenteral promethazine can cause severe local tissue injury.

[‡]Cetirizine and levocetirizine have mild sedative effects.

blood-brain barrier. In addition, these drugs have a high affinity for H₁ receptors of the CNS.

For patients who experience disabling sedation with a first-generation H₁ antagonist, therapy with a second-generation (nonsedating) antihistamine is likely to help. Unfortunately, the nonsedating agents are more expensive than the first-generation agents. The sedative properties of individual antihistamines are indicated in Table 70-1.

Nonsedative CNS Effects. In addition to sedation, antihistamines can cause dizziness, incoordination, confusional states, and fatigue. Older patients are especially sensitive to these actions. In some patients, paradoxical excitation occurs, resulting in insomnia, nervousness, tremors, and even convulsions. CNS stimulation is most common in children and following overdose.

Gastrointestinal Effects. Gastrointestinal disturbances are common. Responses include nausea, vomiting, loss of appetite, and diarrhea or constipation. These reactions can be minimized by administering antihistamines with food.

Anticholinergic Effects. The H₁ antagonists possess weak atropine-like properties. These antimuscarinic actions can produce drying of mucous membranes in the mouth, nasal passages, and throat. Cholinergic blockade may also result in urinary hesitancy, constipation, and palpitations. If dry mouth becomes distressing, discomfort can be minimized by sucking on hard (sugarless) candy and by taking frequent sips of fluid. Antihistamines should be used with caution in patients with asthma, because thickening of bronchial secretions may impair breathing. Care is also needed in patients with other

conditions that can be made worse by muscarinic blockade (eg, urinary retention, prostatic hypertrophy, hypertension). The antimuscarinic efficacy of individual H₁ blockers is indicated in Table 70-1. As you can see, the second-generation antihistamines are the least anticholinergic.

Severe Respiratory Depression. One antihistamine—*promethazine* [Phenergan, Phenadoz]—can cause severe respiratory depression, especially in very young patients. Deaths have occurred. Accordingly, the drug is now contraindicated for use in children under the age of 2 years, and should be used with caution in children older than 2 years.

Severe Local Tissue Injury. Extravasation of IV *promethazine* can cause severe local tissue injury, including gangrene that requires amputation. Severe injury can also occur with inadvertent perivascular or intra-arterial administration, or with administration into or near a nerve. Accordingly, when parenteral dosing is needed, the preferred route is IM; subQ *promethazine* is contraindicated. If IV administration *must* be done, *promethazine* should be given through a large-bore, freely flowing line, in a concentration of 25 mg/mL or less at a rate of 25 mg/min or less. Patients should be advised to report local burning or pain immediately.

Cardiac Dysrhythmias. Potentially fatal cardiac dysrhythmias (torsades de pointes, ventricular fibrillation, and others) have occurred rarely in patients taking *astemizole* [Hismanal] or *terfenadine* [Seldane], two second-generation antihistamines. These drugs promote dysrhythmias by prolonging the QT interval, but only when their levels are excessive. Because of their potential for serious harm, *terfenadine* and *astemizole* were withdrawn from the market.

TABLE 70-2 ■ Some H₁ Antagonists Used for Systemic Therapy: Trade Names, Routes, and Dosage

Generic Name	Trade Names	Routes	Usual Adult Oral Dosage
First-Generation Agents			
Alkylamines			
Brompheniramine	BroveX, others	PO	4 mg q 4–6 h
Chlorpheniramine	Chlor-Trimeton, others	PO	4 mg q 4–6 h
Dexchlorpheniramine	Generic only	PO	2 mg q 4–6 h
Ethanolamines			
Clemastine	Tavist Allergy, Dayhist-1	PO	1.34 mg q 12 h
Diphenhydramine	Benadryl	PO, IV, IM	25–50 mg q 6–8 h
Phenothiazines			
Promethazine*	Phenadoz, Phenergan, others	PO, IV, IM, R [†]	12.5–25 mg q 6–24 h
Piperazines			
Hydroxyzine	Vistaril	PO	25–100 mg q 4–8 h
Piperidines			
Cyproheptadine	Generic only	PO	4 mg q 6–8 h
Second-Generation (Nonsedating) Agents			
Cetirizine [‡]	Zyrtec, Reactine [♣]	PO	See text
Levocetirizine [‡]	Xyzal	PO	See text
Fexofenadine	Allegra, Allegra ODT	PO	See text
Loratadine	Alavert, Claritin, Tavist ND	PO	See text
Desloratadine	Clarinex, Clarinex RediTabs, Aerius [♣]	PO	See text

*Promethazine is contraindicated in children under 2 years old owing to a risk of fatal respiratory depression.

[†]R = rectal suppository.

[‡]Cetirizine and levocetirizine have mild sedative effects.

Drug Interactions: CNS Depressants

Alcohol and other CNS depressants (eg, barbiturates, benzodiazepines, opioids) can intensify the depressant effects of H₁ antagonists. Patients should be advised against drinking alcoholic beverages. If medications with CNS-depressant properties are combined with H₁ blockers, dosage of the depressant may need to be lowered.

Use in Pregnancy and Lactation

Pregnancy. The margin of safety of antihistamines in pregnancy is unknown. There have been reports of fetal malformation, but direct involvement of H₁ antagonists has not been proved. Given the uncertainty over the safety of these drugs, it is recommended that antihistamines be used only when clearly necessary, and only when the benefits of treatment outweigh the potential risks to the fetus. Antihistamines should be avoided late in the third trimester, because newborns are particularly sensitive to the adverse actions of these drugs.

Lactation. The H₁ antagonists can be excreted in breast milk, thereby posing a risk to the nursing infant. Since infants, and especially newborns, are unusually sensitive to antihistamines, these drugs should be avoided by women who are breast-feeding.

Acute Toxicity

Although the antihistamines have a large margin of safety, acute poisoning is nonetheless common, owing to the widespread availability of these drugs. CNS effects are prominent, especially anticholinergic reactions. Specific symptoms and treatment are described below.

Symptoms. The anticholinergic actions of H₁ blockers produce symptoms resembling those of atropine poisoning (dilated pupils, flushed face, hyperpyrexia, tachycardia, dry mouth, urinary retention). In children, CNS excitation is prominent, manifesting as hallucinations, incoordination, ataxia, and convulsions. In extreme cases, intoxication progresses to coma, cardiovascular collapse, and death.

Treatment. There is no specific antidote to antihistamine poisoning. Hence, treatment is directed at drug removal and managing symptoms. Absorption can be minimized by giving activated charcoal (to adsorb the drug), followed by a cathartic (to hasten its export from the GI tract). Convulsions can be treated with IV phenytoin. Anticonvulsants with CNS-depressant actions must be avoided. Hyperthermia can be reduced by applying ice packs or by giving sponge baths.

H₁ ANTAGONISTS II: PREPARATIONS

As noted above, the H₁ antagonists can be divided into two major groups: first-generation H₁ antagonists and second-generation H₁ antagonists. The first-generation agents can cause significant sedation. In contrast, the second-generation agents cause little or no sedation. All of the H₁ blockers can be administered by mouth. In addition, some can be given parenterally, by nasal spray, or by rectal suppository. Routes and dosages for individual H₁ antagonists are summarized in Table 70-2.

First-Generation H₁ Antagonists

The first-generation antihistamines can be grouped into five major categories (see Table 70-1). As indicated in the table, these groups differ in antihistaminic efficacy and the ability to

cause sedation and muscarinic blockade. Given these differences, it may be possible, through judicious drug selection, to produce effective H₁ blockade while minimizing undesired effects.

Sedation can be a significant problem. Among the first-generation agents, CNS depression is most prominent with the ethanolamines (eg, diphenhydramine) and phenothiazines (eg, promethazine), and least prominent with the alkylamines (eg, chlorpheniramine). For many patients, the alkylamines can provide effective H₁ blockade while causing only a modest reduction in alertness. If sedation remains excessive with an alkylamine, a second-generation agent should be tried.

As indicated in Table 70-1, most first-generation agents have significant anticholinergic properties. As a result, they can cause dry mouth, urinary hesitancy, and other typical anticholinergic side effects.

Second-Generation (Nonsedating) H₁ Antagonists

The second-generation antihistamines produce much less sedation than the first-generation agents. Why? Because (1) the second-generation agents cross the blood-brain barrier poorly and (2) they have a low affinity for H₁ receptors of the CNS. Synergism with alcohol and other CNS depressants is low. Nonetheless, combined use of CNS depressants and the second-generation agents should be avoided. In addition to lacking sedative effects, the second-generation agents are largely devoid of anticholinergic actions. When these drugs were introduced, they all required a prescription and their prices were very high. Today, two agents—cetirizine and loratadine—are available over the counter, and prices are falling. Since all of these drugs are very similar, initial selection can usually be based on price. If a cheaper agent proves ineffective, a more expensive agent can be tried.

Descriptions below are limited to the five second-generation agents that are used for systemic (oral) therapy. Two other second-generation agents—azelastine [Astelin, Astepro] and olopatadine [Patanase]—which are used for local effects in the nose, are discussed in Chapter 77 (Drugs for Allergic Rhinitis, Cough, and Colds).

Fexofenadine. Fexofenadine [Allegra, Allegra ODT] is approved for oral therapy of seasonal allergic rhinitis and for chronic idiopathic urticaria. Of the second-generation antihistamines now available, fexofenadine appears to offer the best combination of efficacy and safety. In clinical trials, the incidence of drowsiness and other side effects was nearly the same as with placebo. Fexofenadine has a half-life of 14.4 hours and is excreted unchanged in the urine. The drug is available in standard tablets (30, 60, and 180 mg) and a suspension (6 mg/mL), both marketed as *Allegra*, and in orally disintegrating tablets (30 mg), marketed as *Allegra ODT*. Dosages depend on the drug formulation and patient age as follows:

- *Standard tablets*—patients 12 years and older, 60 mg twice daily or 180 mg once daily; children 6 to 11 years, 30 mg twice daily
- *ODT tablets*—children 6 to 11 years, 30 mg twice daily
- *Suspension*—children 2 to 11 years, 30 mg twice daily; children 6 months to 2 years, 15 mg twice daily

For all formulations, dosage should be reduced in patients with renal impairment.

Certain fruit juices (eg, apple juice, orange juice, grapefruit juice) can reduce fexofenadine absorption, possibly reducing therapeutic effects. The mechanisms is inhibition of *organic anion transporting polypeptides* (OATP), which contribute to absorption of fexofenadine from the GI tract. (This mechanism differs from the grapefruit juice effect discussed in Chapter 6.) To ensure fexofenadine absorption, patients should not drink fruit juices within 4 hours before dosing or 1 to 2 hours after dosing.

Cetirizine. Cetirizine [Zyrtec, Zyrtec ODT, Reactine[®]] is indicated for allergic rhinitis and chronic idiopathic urticaria. Administration is oral, and food delays absorption. Cetirizine is eliminated by a combination of hepatic metabolism and renal excretion. Its half-life is 8.3 hours. Although cetirizine is generally well tolerated, it can cause drowsiness (14%), fatigue (6%), and dryness of the mouth, nose, and throat (5%). Cetirizine—and levocetirizine, its active isomer—cause more sedation than the other second-generation antihistamines, but less sedation than the first-generation drugs. Cetirizine is available in standard tablets (5 and 10 mg), chewable tablets (5 and 10 mg), and a syrup (1 mg/mL). The recommended dosage for adults and for children age 6 years and older is 5 or 10 mg once a day. The dosage for children ages 2 to 5 years is 2.5 mg once a day initially, and may be increased to either 5 mg once a day or 2.5 mg twice a day. Dosage should be reduced in patients with significant hepatic or renal impairment.

Levocetirizine. Levocetirizine [Xyzal] is the levo (active) isomer of cetirizine, and shares that drug's indications: allergic rhinitis and chronic idiopathic urticaria. Like cetirizine, levocetirizine is more sedating than the other second-generation antihistamines, but less sedating than the first-generation agents. The most common side effects are drowsiness, fatigue, muscle weakness, and dry mouth. Alcohol and other CNS depressants can intensify sedation, and hence should be avoided. Although levocetirizine is classified in Food and Drug Administration Pregnancy Risk Category B (it has no teratogenic effects in animals), use in pregnancy should probably be avoided, as should use during breast-feeding. Levocetirizine is eliminated primarily by renal excretion, and hence must not be given to patients with severe renal impairment (creatinine clearance less than 10 mL/min). Levocetirizine is supplied in scored 5-mg tablets that can be administered without regard to meals. To minimize sedation, dosing should be done in the evening. The dosage for patients age 12 years and older is 5 mg once daily; dosage should be reduced for those with *mild to moderate* renal impairment. The dosage for children ages 6 to 11 years is 2.5 mg daily; children with *any degree* of renal impairment should not use the drug.

Loratadine. Loratadine [Claritin, Tavist ND, Alavert, others] is approved only for seasonal allergic rhinitis. Like other second-generation antihistamines, the drug is generally well tolerated. However, in clinical trials, 8% of patients experienced drowsiness, and 12% experienced headache. Loratadine is administered orally, and food delays absorption. The drug undergoes extensive hepatic metabolism and has a half-life of 8 to 28 hours. Loratadine is available in four formulations: a syrup (1 mg/mL), 10-mg standard tablets, 10-mg orally disintegrating tablets [Alavert, others], and 10-mg rapidly disintegrating tablets [Claritin RediTabs] designed to dissolve on the tongue. The recommended dosage for adults and for children age 6 years and older is 10 mg once a day. The dosage for children ages 2 to 5 years is 5 mg (of the syrup) once a day. For patients with significant hepatic or renal impairment, dosing should be done every other day.

Desloratadine. Desloratadine [Clarinex, Clarinex RediTabs, Aerus[®]] is the major active metabolite of loratadine. The two drugs differ primarily in that desloratadine has a longer half-life (27 hours vs. 8.4 hours). However, although desloratadine has a longer half-life, there is no proof that its effects persist longer. Approved indications are seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria. Desloratadine has no significant drug interactions and, at the recommended dosage, the incidence of adverse effects is similar to that of placebo. There is no indication that desloratadine prolongs the QT interval or poses a risk of dysrhythmias. About 7% of patients metabolize desloratadine very slowly, causing its effects to be more intense. Desloratadine is available in 5-mg standard tablets, 5-mg rapidly disintegrating tablets [Clarinex RediTabs], and a syrup (2.5 mg/5 mL). The recommended dosage for adults and children over 12 years is 5 mg once a day. Taking higher doses offers no increase in benefits, but does increase the risk of drowsiness. For patients with liver or renal impairment, the manufacturer recommends reducing the initial dosage to 5 mg every other day.

KEY POINTS

- Histamine is synthesized and stored in mast cells and basophils.
- Histamine release may be triggered by allergic and nonallergic mechanisms.
- There are two major classes of histamine receptors, called H₁ receptors and H₂ receptors.
- Activation of H₁ receptors causes vasodilation, increased capillary permeability, pain, itching, bronchoconstriction, and CNS effects.
- Activation of H₂ receptors causes release of gastric acid from parietal cells of the stomach.
- Histamine is an important mediator of mild allergic reactions, but is only a minor contributor to severe (anaphylactic) reactions.
- There are two major classes of histamine receptor antagonists: H₁ receptor antagonists, which are used to treat mild allergic reactions, and H₂ receptor antagonists, which are used to treat gastric and duodenal ulcers (see Chapter 78).
- Histamine₁ receptor antagonists relieve allergic symptoms by blocking histamine receptors on small blood vessels, capillaries, and sensory nerves. These drugs do not block release of histamine from mast cells and basophils.
- There are two major classes of H₁ receptor antagonists, known as first-generation H₁ receptor antagonists and second-generation H₁ receptor antagonists.
- First-generation H₁ receptor antagonists frequently cause sedation and anticholinergic effects; second-generation agents rarely cause either.
- CNS depression from first-generation H₁ receptor antagonists can be intensified by alcohol and other drugs with CNS-depressant actions.

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Summary of Major Nursing Implications*

H₁ RECEPTOR ANTAGONISTS

First-Generation Antihistamines

Brompheniramine
Chlorpheniramine
Clemastine
Ciproheptadine
Dexchlorpheniramine
Diphenhydramine
Hydroxyzine
Promethazine

Second-Generation Antihistamines

Cetirizine
Desloratadine
Fexofenadine
Levocetirizine
Loratadine

Preadministration Assessment

Therapeutic Goal

Oral Therapy. Relief of symptoms of mild to moderate allergic disorders (eg, allergic rhinitis, allergic conjunctivitis, uncomplicated urticaria and angioedema).

Parenteral Therapy. Treatment of allergic reactions to blood or plasma; adjunctive therapy of anaphylaxis.

Identifying High-Risk Patients

Antihistamines are *contraindicated* during the third trimester of pregnancy and for nursing mothers and newborn infants.

Exercise *caution* when treating young children, the elderly, and patients with conditions that may be aggravated by muscarinic blockade, including asthma, urinary retention, open-angle glaucoma, hypertension, and prostatic hypertrophy.

Implementation: Administration

Routes

All H₁ blockers used for systemic therapy can be given PO. Some can also be administered IM, IV, or by rectal suppository (see Table 70-2).

Administration

Advise patients to take oral antihistamines with food if GI upset occurs.

Warn patients not to crush or chew enteric-coated preparations.

Teach patients how to administer orally disintegrating tablets.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Sedation. For most patients, a first-generation antihistamine in the alkylamine group (see Table 70-1) can provide effective H₁ blockade with only modest sedation. If sedation is excessive with an alkylamine, a second-generation antihistamine (eg, fexofenadine) can be used. With long-acting antihistamines, daytime sedation can be minimized by administering the entire daily dose in the evening. **Caution the**

*Patient education information is highlighted as **blue text**.

Summary of Major Nursing Implications*—cont'd

patient to exercise extreme caution when driving or doing other hazardous activities.

Anticholinergic Effects. Advise patients that dryness of the mouth and throat can be reduced by sucking on hard (sugarless) candy and by taking frequent sips of liquids. Other atropine-like responses (urinary hesitancy, tachycardia, constipation) are not usually problems. Second-generation antihistamines have minimal anticholinergic effects.

Gastrointestinal Distress. Advise the patient that GI disturbances (nausea, vomiting) can be minimized by taking antihistamines with meals.

Effects in the Elderly. Older patients are especially sensitive to CNS and anticholinergic effects. Be alert for CNS effects (eg, dizziness, incoordination, confusion, fatigue) and exaggerated anticholinergic effects (eg, dry mouth, urinary hesitancy, constipation).

Severe Respiratory Depression. *Promethazine* can cause fatal respiratory depression, especially in the very young. Do not give *promethazine* to children under 2 years of age, and use it with caution in children older than 2 years.

Severe Tissue Injury. Parenteral *promethazine* can cause severe local tissue injury if an IV line becomes extravasated, or following inadvertent perivascular, intra-arterial, or intraneuronal dosing. Gangrene requiring amputation has developed. Accordingly, when parenteral dosing is needed, the preferred route is IM. If IV dosing cannot be

avoided, *promethazine* should be administered through a large-bore, freely flowing line, in a concentration of 25 mg/mL or less at a rate of 25 mg/min or less. Advise patients to immediately report local burning or pain.

Minimizing Adverse Interactions

CNS Depressants. Alcohol and other CNS depressants can intensify the depressant actions of the H₁ antagonists. Warn the patient against drinking alcohol. Dosages of CNS depressants (eg, barbiturates, benzodiazepines, opioids) may need to be reduced. Second-generation antihistamines have minimal CNS-depressant effects and hence are less likely to potentiate the actions of CNS depressants.

Fruit Juice. Certain fruit juices (eg, apple juice, orange juice, grapefruit juice) can decrease intestinal absorption of *fexofenadine*, possibly reducing effectiveness. Advise patients to avoid fruit juice in the interval between 4 hours before dosing and 1 to 2 hours after dosing.

Managing Toxicity

There is no specific antidote to antihistamine overdose, and hence treatment is directed at minimizing absorption and managing symptoms. To reduce absorption, give activated charcoal. Treat hyperthermia with ice packs or cooling sponge baths. Control convulsions with IV phenytoin.

*Patient education information is highlighted as blue text.

Cyclooxygenase Inhibitors: Nonsteroidal Anti-inflammatory Drugs and Acetaminophen

Mechanism of Action

Classification of Cyclooxygenase Inhibitors

First-Generation NSAIDs

Aspirin

Nonaspirin First-Generation NSAIDs

Second-Generation NSAIDs (COX-2 Inhibitors, Coxibs)

Celecoxib

Rofecoxib and Valdecoxib

Acetaminophen

AHA Statement on COX Inhibitors in Chronic Pain

The family of cyclooxygenase inhibitors consists of aspirin and related drugs. Most of these agents have three useful effects: they can suppress inflammation, relieve pain, and reduce fever. In addition, aspirin—and only aspirin—can protect against myocardial infarction (MI) and stroke. All of these effects are produced through one central mechanism: inhibition of cyclooxygenase, the enzyme responsible for synthesis of prostanoids (prostaglandins and related compounds). This same mechanism underlies their principal adverse effects: gastric ulceration, bleeding, and renal impairment. Cyclooxygenase inhibition also underlies MI and stroke, which can occur with most of these drugs, but *not* with aspirin.

MECHANISM OF ACTION

All of the drugs discussed in this chapter work by inhibiting *cyclooxygenase* (COX), the enzyme that converts arachidonic acid into *prostanoids*: *prostaglandins* and related compounds (prostacyclin, thromboxane A₂ [TXA₂]). To understand the drugs that inhibit COX, we must first understand COX itself.

Cyclooxygenase is found in all tissues and helps regulate multiple processes. At sites of tissue injury, COX catalyzes the synthesis of prostaglandin E₂ (PGE₂) and prostaglandin I₂ (PGI₂, aka prostacyclin), which promote inflammation and sensitize receptors to painful stimuli. In the stomach, COX promotes synthesis of PGE₂ and PGI₂, which help protect the gastric mucosa. Three mechanisms are involved: reduced secretion of gastric acid, increased secretion of bicarbonate and cytoprotective mucus, and maintenance of submucosal blood flow. In platelets, COX promotes synthesis of TXA₂, which stimulates platelet aggregation. In blood vessels, COX promotes synthesis of prostacyclin, which causes vasodilation. In

the kidney, COX catalyzes synthesis of PGE₂ and PGI₂, which promote vasodilation and thereby maintain renal blood flow. In the brain, COX-derived prostaglandins mediate fever and contribute to perception of pain. In the uterus, COX-derived prostaglandins help promote contractions at term. It is important to appreciate that prostaglandins, prostacyclin, and TXA₂ act *locally*; these compounds do not affect sites distant from where they were made.

Cyclooxygenase has two forms, named cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Cyclooxygenase-1 is found in practically all tissues, where it mediates “housekeeping” chores. Important among these are protecting the gastric mucosa, supporting renal function, and promoting platelet aggregation. In contrast, COX-2 is produced mainly at sites of *tissue injury*, where it mediates inflammation and sensitizes receptors to painful stimuli. Cyclooxygenase-2 is also present in the *brain* (where it mediates fever and contributes to perception of pain), the *kidney* (where it supports renal function), *blood vessels* (where it promotes vasodilation), and the *colon* (where it can contribute to colon cancer). Because COX-1 primarily mediates beneficial processes, whereas COX-2 primarily mediates harmful processes, COX-1 has been dubbed the “good COX” and COX-2 the “bad COX.” Some important functions of COX-1 and COX-2 are summarized in Table 71-1.

Having established the roles of COX-1 and COX-2, we can now predict the effects of drugs that inhibit these enzymes. Inhibition of COX-1 (good COX) results largely in harmful effects:

- Gastric erosion and ulceration
- Bleeding tendencies
- Renal impairment

Inhibition of COX-1 also has one very beneficial effect:

- Protection against MI and stroke (secondary to reduced platelet aggregation)

Inhibition of COX-2 (bad COX) results largely in beneficial effects:

- Suppression of inflammation
- Alleviation of pain
- Reduction of fever
- Protection against colorectal cancer

Inhibition of COX-2 also has two adverse effects:

- Renal impairment
- Promotion of MI and stroke (secondary to suppressing vasodilation)

TABLE 71-1 Cyclooxygenase-1 and Cyclooxygenase-2: Functions and Effect of Inhibition

Location	COX Isoform	COX Reaction Product	Response to COX Reaction Product	Effect of COX Inhibition
Stomach	COX-1	PGE ₂ , PGI ₂	Gastric protection: Increased bicarbonate secretion Increased mucus production Decreased acid secretion Maintenance of submucosal blood flow	Gastric ulceration
Platelets	COX-1	TXA ₂	Platelet aggregation	Bleeding tendencies Protection against MI
Blood vessels	COX-2	Prostacyclin	Vasodilation	Vasoconstriction (which can promote MI)
Kidney	COX-1, COX-2	PGE ₂ , PGI ₂	Maintenance of renal function: Renal vasodilation Maintenance of renal perfusion	Renal impairment
Injured tissue	COX-2	PGE ₂	Inflammation Pain	Reduced inflammation Analgesia
Brain	COX-2	??	Fever Pain	Reduced fever Analgesia
Colon/rectum	COX-2	??	Colorectal cancer promotion	Colorectal cancer protection

COX-1 = cyclooxygenase-1, COX-2 = cyclooxygenase-2, MI = myocardial infarction, PGE₂ = prostaglandin E₂, PGI₂ = prostaglandin I₂ (prostacyclin), TXA₂ = thromboxane A₂.

CLASSIFICATION OF CYCLOOXYGENASE INHIBITORS

The cyclooxygenase inhibitors fall into two major categories: (1) drugs that have anti-inflammatory properties and (2) drugs that lack anti-inflammatory properties. Agents in the first group are referred to as *nonsteroidal anti-inflammatory drugs* (NSAIDs). Representative members include aspirin, ibuprofen [Advil, Motrin, others], naproxen [Aleve, others], and celecoxib [Celebrex]. The second class consists of just one drug: *acetaminophen* [Tylenol, others]. Acetaminophen can reduce pain and fever but cannot suppress inflammation.

The NSAIDs can be subdivided into two groups: (1) *first-generation NSAIDs* (conventional NSAIDs, traditional NSAIDs) and (2) *second-generation NSAIDs* (selective COX-2 inhibitors, coxibs). The first-generation agents inhibit COX-1 and COX-2. The second-generation agents inhibit COX-2 only. Because the first-generation agents inhibit both COX isoforms, they are unable to suppress pain and inflammation without posing a risk of serious side effects (gastric ulceration, bleeding, renal impairment). In contrast, because of their selectivity for COX-2, the second-generation NSAIDs, *in theory*, can suppress pain and inflammation while (possibly) causing fewer adverse effects than the first-generation NSAIDs. However, *in reality*, COX-2 inhibitors appear even less safe than the first-generation agents, owing to an increased risk of MI and stroke.

Table 71-2 summarizes the principal indications and adverse effects of the first-generation NSAIDs, second-generation NSAIDs, and acetaminophen.

FIRST-GENERATION NSAIDs

The first-generation NSAIDs—a large and widely used group of drugs—inhibit COX-1 and COX-2. In the United States, more than 70 million prescriptions are written annu-

ally and more than 30 billion tablets are sold over the counter. The traditional NSAIDs are used to treat inflammatory disorders (eg, rheumatoid arthritis, osteoarthritis, bursitis), alleviate mild to moderate pain, suppress fever, and relieve dysmenorrhea. Because they cannot inhibit COX-2 without inhibiting COX-1, first-generation NSAIDs cannot suppress inflammation without posing a risk of serious harm: NSAID-induced ulcers are responsible for more than 100,000 hospitalizations and at least 16,500 deaths each year. Aspirin is the oldest member of the family and prototype for the group.

Aspirin

Aspirin is an important drug whose effectiveness is frequently underappreciated. Given that aspirin is available without prescription, widely advertised in the media, and used somewhat casually by the general public, you may be surprised to hear that aspirin is a highly valuable and effective medication. The drug provides excellent relief of mild to moderate pain, reduces fever, protects against thrombotic disorders, and remains a drug of choice for rheumatoid arthritis and other inflammatory conditions. You may also be surprised to hear that aspirin can cause serious toxicity, especially gastric ulceration. Despite the introduction of many new NSAIDs, aspirin remains one of the most widely used members of the group, and is the standard against which the others must be compared.

Chemistry

Aspirin belongs to a chemical family known as *salicylates*. All members of this group are derivatives of salicylic acid (Fig. 71-1). Aspirin is produced by substituting an acetyl group onto salicylic acid. Because of this acetyl group, aspirin is commonly known as *acetylsalicylic acid*, or simply ASA.

TABLE 71-2 ■ Principal Indications and Adverse Effects of the Four Major Types of Cyclooxygenase Inhibitors

	First-Generation NSAIDs: Aspirin	First-Generation NSAIDs: All Others	Second-Generation NSAIDs (Coxibs)	Acetaminophen
Indications				
Inflammation	Yes	Yes	Yes	No
Pain	Yes	Yes	Yes	Yes
Fever	Yes	Yes	No	Yes
Prevention of MI and stroke	Yes	No	No	No
Adverse Effects				
Gastric ulceration	Yes	Yes	Yes*	No
Renal impairment	Yes	Yes	Yes	No
Bleeding	Yes	Yes	No	No
MI and stroke	No	Yes	Yes	No
Liver damage with overdose	No	No	No	Yes

*Despite their selectivity for cyclooxygenase-2, coxibs can still cause gastric ulceration, although it may be less than with other NSAIDs.

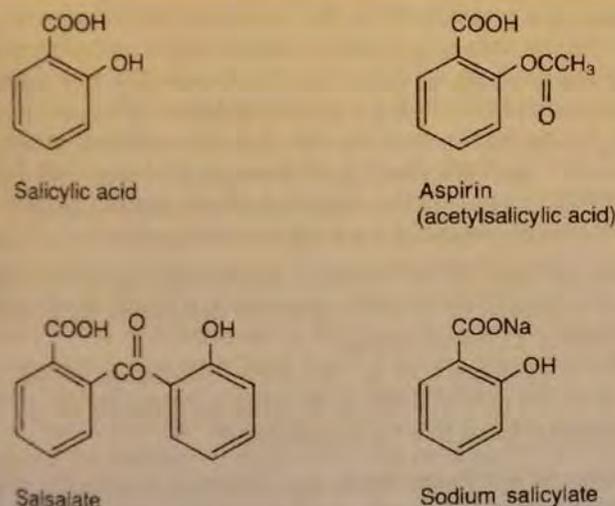


Figure 71-1 ■ Structural formulas of aspirin and related salicylates.

Mechanism of Action

Aspirin is a nonselective inhibitor of cyclooxygenase. Most beneficial effects—reductions of inflammation, pain, and fever—result from inhibiting COX-2. One beneficial effect—protection against MI and ischemic stroke—results from inhibiting COX-1. Major adverse effects—gastric ulceration, bleeding, and renal impairment—result from inhibiting COX-1.

It is important to note that aspirin is an *irreversible* inhibitor of cyclooxygenase. In contrast, all other NSAIDs are *reversible* (competitive) inhibitors. Because inhibition of cyclooxygenase by aspirin is irreversible, duration of action depends on how quickly specific tissues can synthesize new molecules of COX-1 and COX-2. With other NSAIDs, effects decline as soon as drug levels fall.

Pharmacokinetics

Absorption. Aspirin is absorbed rapidly and completely after oral dosing. The principal site of absorption is the small intestine. When administered by rectal suppository, aspirin is absorbed slowly and blood levels are lower than with oral dosing.

Metabolism. Aspirin has a very short half-life (15 to 20 minutes) owing to rapid conversion to *salicylic acid*, an *active* metabolite. The rate of inactivation of salicylic acid depends on the amount present: At low therapeutic levels, salicylic acid has a half-life of approximately 2 hours, but at high therapeutic levels, the half-life may exceed 20 hours.

Distribution. Salicylic acid is extensively bound to plasma albumin. At therapeutic levels, binding is between 80% and 90%. Aspirin undergoes distribution to all body tissues and fluids, including breast milk, fetal tissues, and the central nervous system (CNS).

Excretion. Salicylic acid and its metabolites are excreted by the kidneys. Excretion of salicylic acid is highly dependent on urinary pH. Accordingly, by raising the pH of urine from 6 to 8, we can increase the rate of excretion fourfold.

Plasma Drug Levels. Low therapeutic doses of aspirin produce plasma salicylate levels in the range of 100 mcg/mL. Anti-inflammatory doses produce salicylate levels of about 400 mcg/mL. Signs of salicylism (toxicity) begin when plasma salicylate levels exceed 200 mcg/mL. Severe toxicity occurs at levels above 400 mcg/mL.

Therapeutic Uses

Suppression of Inflammation. Aspirin is an initial drug of choice for rheumatoid arthritis, osteoarthritis, and juvenile arthritis. Aspirin is also indicated for other inflammatory disorders, including rheumatic fever, tendinitis, and bursitis. The dosages employed to suppress inflammation are considerably larger than dosages used for analgesia or reduction of fever. The use of aspirin and other NSAIDs to treat arthritis is discussed further in Chapter 73.

The precise mechanisms by which aspirin decreases inflammation have not been established. We do know that prostanoids contribute to several, but not all, components of the inflammatory process. Hence, inhibition of COX-2 provides a partial explanation of anti-inflammatory effects. Other possible mechanisms include modulation of T-cell function, suppression of inflammatory cell infiltration, and stabilization of lysosomes.

Analgesia. Aspirin is used widely to relieve mild to moderate pain. The degree of analgesia produced depends on the type of pain. Aspirin is most active against joint pain, muscle pain, and headache. For some forms of postoperative pain, aspirin can be more effective than opioids. However, aspirin is relatively ineffective against severe pain of visceral origin. In contrast to opioid analgesics, aspirin produces neither tolerance nor physical dependence. In addition, aspirin is safer than opioids.

Aspirin relieves pain primarily through actions in the periphery. At sites of injury, prostanoids sensitize pain receptors to mechanical and chemical stimulation. Aspirin reduces pain by inhibiting COX-2, thereby suppressing prostanoid production. In addition to this peripheral mechanism, aspirin works in the CNS to help relieve pain.

Reduction of Fever. Aspirin is a drug of choice for reducing temperature in febrile adults. However, because of the risk of Reye's syndrome (see below), aspirin should not be used to treat fever in children. Although aspirin readily reduces fever, it will not lower normal body temperature, nor will it lower temperature that has become elevated in response to physical activity or to a rise in environmental temperature.

How does aspirin reduce fever? Body temperature is regulated by the hypothalamus, which maintains a balance between heat production and heat loss. Fever occurs when the set point of the hypothalamus becomes elevated, causing the hypothalamus to increase heat production and decrease heat loss. Set-point elevation is triggered by local synthesis of prostaglandins in response to endogenous pyrogens (fever-promoting substances). Aspirin lowers the set point by inhibiting COX-2, and thereby inhibits pyrogen-induced synthesis of prostaglandins.

Dysmenorrhea. Aspirin can provide relief from primary dysmenorrhea. Benefits derive from inhibiting prostaglandin synthesis in uterine smooth muscle. (Prostaglandins promote uterine contraction, and hence suppression of prostaglandin synthesis relieves cramping.) Some of the newer aspirin-like drugs (eg, ibuprofen, naproxen) are superior to aspirin for dysmenorrhea. The efficacy of the newer drugs is attributed to a greater ability to inhibit COX in the uterus.

Suppression of Platelet Aggregation. Synthesis of TXA₂ in platelets promotes aggregation. Aspirin suppresses platelet aggregation by causing irreversible inhibition of COX-1, the enzyme that makes TXA₂. Because platelets lack the machinery to synthesize new COX-1, the effects of a single dose persist for the life of the platelet (about 8 days).

There is a large body of evidence demonstrating that aspirin, through its antiplatelet actions, can benefit a variety of patients. Accordingly, in 1999, the Food and Drug Administration (FDA) recommended wider use of aspirin for antiplatelet effects. Professional labeling now recommends daily aspirin for men and women with the following:

- *Ischemic stroke* (to reduce the risk of death and nonfatal stroke)
- *Transient ischemic attacks* (to reduce the risk of death and nonfatal stroke)

- *Acute MI* (to reduce the risk of vascular mortality)
- *Previous MI* (to reduce the combined risk of death and nonfatal MI)
- *Chronic stable angina* (to reduce the risk of MI and sudden death)
- *Unstable angina* (to reduce the combined risk of death and nonfatal MI)
- *Angioplasty and other revascularization procedures* (in patients who have a pre-existing condition for which aspirin is already indicated)

According to a 2007 review published in JAMA—*Aspirin Dose for the Prevention of Cardiovascular Disease*—a dose of 75 to 81 mg/day for these indications is adequate. Higher doses, which are commonly prescribed in these circumstances, offer no greater protection, but will increase the risk of GI bleeding.

In addition to these applications, aspirin can be taken by healthy people for *primary prevention* of MI and stroke. However, benefits differ for men and women. In men, daily aspirin reduces the risk of a first MI, but not the risk of a first ischemic stroke. In women, the opposite applies: daily aspirin reduces the risk of a first ischemic stroke, but not the risk of a first MI. In both sexes, these potential benefits must be weighed against the major risk of aspirin, namely, GI hemorrhage. Hence, to determine the *net* benefit of primary prevention for any man or woman, we need to determine his or her individual risk for a GI bleed, and compare that risk with his or her individual risk for a cardiovascular (CV) event (ie, the risk for an MI in men, or the risk for ischemic stroke in women).^{*} In 2009, the U.S. Preventive Services Task Force (USPSTF) employed this approach when making the following recommendations for primary prevention:

- For men ages 45 to 79 years—Encourage aspirin use when the potential for preventing an MI outweighs the potential harm of a GI hemorrhage.
- For women ages 55 to 79 years—Encourage aspirin use when the potential for preventing a stroke outweighs the potential harm of a GI hemorrhage.

How do we know when the potential to prevent a CV event outweighs the risk of GI hemorrhage? By using the data in Table 71-3. For example, if the patient is a 65-year-old woman, and her 10-year risk for stroke is 8% or higher, then the benefits of primary prevention are considered to outweigh the risks of a GI bleed. Conversely, if this patient's 10-year stroke risk were below 8%, then the risks of a GI bleed would outweigh the benefits. How do we calculate 10-year risk for a CV event? Risk for ischemic stroke can be assessed using the online calculator at <http://www.western-stroke.org/PersonalStrokeRisk1.xls>. Risk for an MI can be assessed using the online calculator at www.mcm.edu/calculators/CoronaryHeartDiseaseRisk.htm.

Cancer Prevention. Colorectal Cancer. There is good evidence that regular use of aspirin decreases the risk of

^{*}Major factors that increase the risk of a GI bleed are use of NSAIDs and a history of ulcers. Major risk factors for an MI are advancing age, diabetes, high total cholesterol, low HDL cholesterol, and smoking. Major risk factors for an ischemic stroke are advancing age, hypertension, diabetes, smoking, atrial fibrillation, left ventricular hypertrophy, and a history of cardiovascular disease.

TABLE 71-3 ■ Risk Level at Which CVD Events Prevented Exceed GI Harms

Age (years)	Men	Women	
	10-yr CHD Risk	Age (years)	10-yr Stroke Risk
45-59	4% or higher	55-59	3% or higher
60-69	9% or higher	60-69	8% or higher
70-79	12% or higher	70-79	11% or higher

CHD = coronary heart disease, CVD = cardiovascular disease. Data are from U.S. Preventive Services Task Force: Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 150:396, 2009.

colorectal cancer, even when the dosage is low. Results from the Nurses' Health Study, reported in 2005, showed that regular use of *high-dose* aspirin (650 mg/day or more) reduces the risk of colorectal cancer. This dosage is much greater than that used to prevent cardiovascular disease, and hence poses a significant risk of bleeding. In fact, for every one or two cancers prevented, high-dose aspirin would cause eight additional serious bleeds. Fortunately, more recent studies indicate that *low-dose* aspirin is effective too. For example, results of a study reported in *The Lancet* (2010; 376:1741), indicate that taking low-dose aspirin (75 to 300 mg/day) for more than 5 years reduces the incidence of colorectal cancer (by 24%) as well as mortality from colon cancer (by 35%). At these low doses, the benefits of cancer protection may well outweigh the risk of possible bleeding and other adverse events.

How does aspirin protect against colorectal cancer? Probably by inhibiting COX-2. In animal models, COX-2 promotes tumor growth and metastases, and inhibition of COX-2 slows tumor growth. In humans, most colorectal cancers express COX-2. Furthermore, protection by aspirin is limited to colon cancers that have high COX-2 levels. Aspirin does not protect against colon cancers with little or no COX-2.

Other Cancers. Available data suggest that protection may not be limited to colorectal cancer. Results of a meta-analysis reported in *The Lancet* (2011; 377:31) show that daily low-dose aspirin reduces the risk of death from *all* solid tumors (by 34%), but does not reduce the risk of death from hematologic cancers. Earlier studies have shown protection against specific cancers. In a study involving men over the age of 60, daily use of aspirin and other NSAIDs was associated with a 50% decrease in the incidence of prostate cancer. In a study involving 2884 women, aspirin appeared to reduce the risk of breast cancer, especially among women with hormone receptor-positive tumors, and among those who took 7 or more aspirin tablets a week. In another study, taking aspirin at least 3 times a week for at least 6 months was associated with a 40% reduction in the incidence of ovarian cancer. In contrast to these positive results, results from the Women's Health Study, released in 2005, found no protection with low-dose aspirin against cancer of the breast, colon, or any other tissue. The reasons for this discrepancy are not clear.

Adverse Effects

When administered short term in analgesic or antipyretic (fever-reducing) doses, aspirin rarely causes serious adverse effects. However, toxicity is common when treating

inflammatory disorders, which require long-term high-dose treatment.

Gastrointestinal Effects. The most common side effects are *gastric distress*, *heartburn*, and *nausea*. These can be reduced by taking aspirin with food or a full glass of water.

Occult GI bleeding occurs often. In most cases, the amount of blood lost each day is insignificant. However, with chronic aspirin use, cumulative blood loss can produce anemia.

Long-term aspirin—even in *low doses*—can cause life-threatening *gastric ulceration*, *perforation*, and *bleeding*. Ulcers result from four causes:

- Increased secretion of acid and pepsin
- Decreased production of cytoprotective mucus and bicarbonate
- Decreased submucosal blood flow
- The direct irritant action of aspirin on the gastric mucosa

The first three occur secondary to inhibition of COX-1. Direct injury to the stomach is most likely with aspirin preparations that dissolve slowly: Owing to slow dissolution, particulate aspirin becomes entrapped in folds of the stomach wall, causing prolonged exposure to high concentrations of the drug. Because aspirin-induced ulcers are often asymptomatic, perforation and upper GI hemorrhage can occur without premonitory signs. (Hemorrhage is due in part to erosion of the stomach wall and in part to suppression of platelet aggregation.) Factors that increase the risk of ulceration include:

- Advanced age
- A history of peptic ulcer disease
- Previous intolerance to aspirin or other NSAIDs
- Cigarette smoking
- History of alcohol abuse (Alcohol intensifies the irritant effects of aspirin and should not be consumed.)

What can we do to *prevent* ulcers? According to an expert panel—convened in 2008 by the American College of Gastroenterology, the American Heart Association, and the American College of Cardiology—prophylaxis with a *proton pump inhibitor* (PPI) is recommended for patients at risk, including those with a history of peptic ulcers, the elderly, and those taking glucocorticoids. Proton pump inhibitors (eg, omeprazole, lansoprazole) reduce ulcer generation by suppressing production of gastric acid. Since many ulcers are caused by infection with *Helicobacter pylori* (see Chapter 78), the panel recommends that patients with ulcer histories undergo testing and treatment for *H. pylori* before starting long-term aspirin use. *Treatment* of NSAID-induced ulcers is discussed in Chapter 78.

Bleeding. Aspirin promotes bleeding by inhibiting platelet aggregation. Taking just two 325-mg aspirin tablets can double bleeding time for about 1 week. (Recall that platelets are unable to replace aspirin-inactivated cyclooxygenase, and hence bleeding time is prolonged for the life of the platelet.) Because of its effects on platelets, *aspirin is contraindicated for patients with bleeding disorders* (eg, hemophilia, vitamin K deficiency, hypoprothrombinemia). In order to minimize blood loss during parturition and elective surgery, *high-dose* aspirin should be discontinued at least 1 week before these procedures. There is no need to stop aspirin prior to procedures with a low risk of bleeding (eg, dental, dermatologic, or cataract surgery). In most cases, use of *low-dose* aspirin to protect against thrombosis should *not* be interrupted for elec-

tive surgery and dental procedures. Caution is needed when aspirin is used in conjunction with anticoagulants.

In patients taking daily aspirin, high blood pressure increases the risk of a brain bleed (ie, hemorrhagic stroke), even though aspirin protects against ischemic stroke. To reduce risk of hemorrhagic stroke, blood pressure should be 150/90 mm Hg (and preferably lower) before starting daily aspirin.

Renal Impairment. Aspirin can cause acute, reversible impairment of renal function, resulting in salt and water retention and edema. Clinically significant effects are most likely in patients with additional risk factors: advanced age, existing renal impairment, hypovolemia, hepatic cirrhosis, or heart failure. Aspirin impairs renal function by inhibiting COX-1, thereby depriving the kidney of prostaglandins needed for normal function.

Development of renal impairment is signaled by reduced urine output, weight gain despite use of diuretics, and a rapid rise in serum creatinine and blood urea nitrogen. If any of these occurs, aspirin should be withdrawn immediately. In most cases, kidney function then returns to baseline level.

The risk of acute renal impairment can be reduced by identifying high-risk patients and treating them with the smallest dosages possible.

In addition to its acute effects on renal function, aspirin may pose a risk of renal papillary necrosis and other types of renal injury when used long term.

Salicylism. Salicylism is a syndrome that begins to develop when aspirin levels climb just slightly above therapeutic. Overt signs include *tinnitus* (ringing in the ears), *sweating*, *headache*, and *dizziness*. Acid-base disturbance may also occur (see below). If salicylism develops, aspirin should be withheld until symptoms subside. Aspirin should then resume, but with a small reduction in dosage. In some cases, development of tinnitus can be used to adjust aspirin dosage: When tinnitus occurs, the maximum acceptable dose has been achieved. However, this guideline may be inappropriate for older patients, because they may fail to develop tinnitus even when aspirin levels become toxic.

Acid-base disturbance results from the effects of aspirin on respiration. When administered in high therapeutic doses, aspirin acts on the CNS to stimulate breathing. The resultant increase in CO₂ loss produces *respiratory alkalosis*. In response, the kidneys excrete more bicarbonate. As a result, plasma pH returns to normal and a state of *compensated respiratory alkalosis* is produced.

Reye's Syndrome. This syndrome is a rare but serious illness of childhood that has a mortality rate of 20% to 30%. Characteristic symptoms are encephalopathy and fatty liver degeneration. Epidemiologic data published in 1980 suggested a relationship between Reye's syndrome and use of aspirin by children who have influenza or chickenpox. Although a direct causal link between aspirin and Reye's syndrome was never established, the Centers for Disease Control and Prevention recommended that *aspirin (and other NSAIDs) be avoided by children and teenagers suspected of having influenza or chickenpox*. In response to this recommendation, aspirin was removed from most products intended for children, and aspirin use by children declined sharply. As a result, Reye's syndrome essentially vanished: The incidence declined from a high of 555 cases in 1980 to no more than 2 cases per

year between 1994 and 1997. If a child with chickenpox or influenza needs an analgesic/antipyretic, acetaminophen can be used safely.

Adverse Effects Associated with Use During Pregnancy. Aspirin poses risks to the pregnant patient and her fetus. Accordingly, the drug is classified in *FDA Pregnancy Risk Category D: There is evidence of human fetal risk, but the potential benefits from use of the drug during pregnancy may outweigh the potential for harm*. The principal risks to pregnant women are (1) anemia (from GI blood loss), and (2) postpartum hemorrhage. In addition, by inhibiting prostaglandin synthesis, aspirin may suppress spontaneous uterine contractions, and may thereby prolong labor.

Aspirin crosses the placenta and may adversely affect the fetus. Since prostaglandins help keep the ductus arteriosus patent, inhibition of prostaglandin synthesis by aspirin may induce premature closure of the ductus arteriosus. Aspirin use has also been associated with low birth weight, stillbirth, renal toxicity, intracranial hemorrhage in preterm infants, and neonatal death.

Hypersensitivity Reactions. Hypersensitivity develops in about 0.3% of aspirin users. Reactions are most likely in adults with a history of asthma, rhinitis, and nasal polyps. Hypersensitivity reactions are uncommon in children. The aspirin hypersensitivity reaction begins with profuse, watery rhinorrhea and may progress to generalized urticaria, bronchospasm, laryngeal edema, and shock. Despite its resemblance to severe anaphylaxis, this reaction is not allergic and is not mediated by the immune system. What *does* cause these reactions? Because individuals who react to aspirin are also sensitive to most other NSAIDs, we believe that the reactions are due to inhibition of COX-1, which triggers production of leukotrienes, which in turn causes bronchospasm, hives, and other signs of hypersensitivity. However, if *this is* the mechanism, it remains unclear why hypersensitivity is limited mainly to adults with the predisposing conditions noted above. As with severe anaphylactic reactions, *epinephrine* is the treatment of choice.

Hypersensitivity to aspirin is considered a contraindication to using other drugs with aspirin-like properties. Nonetheless, if an aspirin-like drug must be taken, four such drugs are probably safe. One of these—celecoxib—is selective for COX-2. Another—meloxicam—is somewhat selective for COX-2, but only at low doses. The other two—acetaminophen and salsalate—are only weak inhibitors of COX-1.

Cardiovascular Events. In contrast to all other NSAIDs, aspirin does *NOT* increase the risk of thrombotic events, including MI and ischemic stroke. In fact, when taken in low doses, aspirin *protects* against these events.

Erectile Dysfunction. Daily use of aspirin and other NSAIDs is associated with a 22% increase in the risk of erectile dysfunction (ED), as shown in a 2011 study of 80,966 men in California. However, a causal relationship has not been established.

Summary of Precautions and Contraindications

Aspirin is contraindicated in patients with *peptic ulcer disease*, *bleeding disorders* (eg, hemophilia, vitamin K deficiency, hypoprothrombinemia), and *hypersensitivity to aspirin itself or other NSAIDs*. In addition, the drug should be used with extreme caution by *pregnant women and by chil-*

When who have chickenpox or influenza. Caution should also be exercised when treating elderly patients, patients who smoke cigarettes, and patients with H. pylori infection, heart failure, hepatic cirrhosis, hypovolemia, renal dysfunction, asthma, hay fever, chronic urticaria, nasal polyps, or a history of allergic surgery or the anticipated date of parturition.

Drug Interactions

Because of its widespread use, aspirin has been reported to interact with many other medications. However, most of these interactions have little clinical significance. Significant interactions are discussed below.

Anticoagulants: Warfarin, Heparin, and Others. Aspirin's most important interactions are with anticoagulants. Because aspirin suppresses platelet function and can decrease prothrombin production, aspirin can intensify the effects of warfarin, heparin, and other anticoagulants. Furthermore, since aspirin can initiate gastric bleeding, augmenting antithrombotic effects can increase the risk of gastric hemorrhage. Accordingly, the combination of aspirin with anticoagulants must be used with care—even when aspirin is taken in low doses to reduce the risk of thrombotic events.

Glucocorticoids. Like aspirin, glucocorticoids promote gastric ulceration. As a result, the risk of ulcers is greatly increased when these drugs are combined—as may happen when treating arthritis. To reduce the risk of gastric ulceration, patients can be given a proton pump inhibitor for prophylaxis.

Alcohol. Combining alcohol with aspirin and other NSAIDs increases the risk of gastric bleeding. To alert the public to this risk, the FDA now requires that labels for aspirin include the following statement: *Alcohol Warning: If you consume three or more alcoholic drinks every day, ask your doctor whether you should take aspirin or other pain relievers/fever reducers. Aspirin [and related drugs] may cause stomach bleeding.* A similar label is required for all other NSAIDs and acetaminophen.

Nonaspirin NSAIDs. Ibuprofen, naproxen, and other nonaspirin NSAIDs can reduce the antiplatelet effects of aspirin. How? By blocking access of aspirin to COX-1 in platelets. This interaction is important: In patients taking low-dose aspirin to prevent MI or ischemic stroke, other NSAIDs could negate aspirin's benefits. Since immediate-release aspirin produces complete platelet inhibition about 1 hour after dosing, we can prevent interference by giving aspirin about 2 hours before giving other NSAIDs. Of course, we could eliminate interference entirely by using high-dose aspirin, rather than another NSAID, when conditions call for NSAID therapy.

ACE inhibitors and ARBs. Like aspirin, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can impair renal function. In susceptible patients, combining aspirin with drugs in either class can increase the risk of acute renal failure. High-dose aspirin should be avoided in patients taking these drugs. However, low-dose aspirin taken for antiplatelet effects should be continued. **Vaccines.** Aspirin and other NSAIDs may blunt the immune response to vaccines. Accordingly, these drugs should not be used routinely to prevent vaccination-associated fever and pain.

Acute Poisoning

Aspirin overdose is a common cause of poisoning. Although rarely fatal in adults, aspirin poisoning may be lethal in children. The lethal dose for adults is 20 to 25 gm. In contrast, as little as 400 mg (4 gm) can kill a child.

Signs and Symptoms. Initially, aspirin overdose produces a state of compensated respiratory alkalosis—the same state seen in mild salicylism. As poisoning progresses, respiratory excitation is replaced with respiratory depression. Acidosis, hyperthermia, sweating, and dehydration are prominent, and electrolyte imbalance is likely. Stupor and coma result from effects in the CNS. Death usually results from respiratory failure. The mechanisms that underlie these clinical manifestations are described below.

Many symptoms of aspirin overdose occur secondary to uncoupling of oxidative phosphorylation, the process by which the energy released during the oxidation of carbohydrates, fats, and proteins is used to form ATP from ADP. When oxidative phosphorylation becomes uncoupled, energy from metabolism of carbohydrates and other nutrients can no longer be transferred to ATP and stored. The consequences of this uncoupling are threefold: (1) Production of CO₂ is increased (secondary to the increased rates of metabolism that take place in futile attempts to form needed ATP). (2) There is increased production of lactic and pyruvic acids (as by-products of increased metabolism). (3) Production of heat is increased because the energy that would normally be used to make ATP is released in the form of heat. Increased heat production is responsible for hyperthermia and dehydration, two of the more serious consequences of aspirin overdose.

Acidosis results from multiple causes. Respiratory acidosis occurs because CO₂ production is increased and because toxic levels of salicylate act on the CNS to decrease respiration, thereby allowing even more CO₂ to accumulate. Respiratory acidosis remains uncompensated because bicarbonate stores become depleted during the initial phase of poisoning. Superimposed on respiratory acidosis is true metabolic acidosis. Metabolic acidosis results from (1) the acidity of aspirin and its metabolites, (2) increased production of lactic and pyruvic acids, and (3) accumulation of acidic products of metabolism (eg, sulfinate and phosphoric acids) owing to aspirin-induced impairment of renal excretion. Acidosis is intensified by the following cycle: (1) Because of the pH-partitioning effect, acidosis promotes penetration of salicylate into the CNS. (2) Increased entry of salicylate deepens respiratory depression. (3) Deepening of respiratory depression increases accumulation of CO₂, thereby increasing acidosis. (4) Increasing acidosis causes even more salicylate to enter the CNS, producing even further deepening of respiratory depression. This cycle continues until respiration stops.

Treatment. Aspirin poisoning is an acute medical emergency that requires hospitalization. The immediate threats to life are respiratory depression, hyperthermia, dehydration, and acidosis. Treatment is largely supportive. If respiration is inadequate, mechanical ventilation should be instituted. External cooling (eg, sponging with tepid water) can help reduce hyperthermia. Intravenous fluids are given to correct dehydration; the composition of these fluids is determined by electrolyte and acid-base status. Slow infusion of bicarbonate is given to reverse acidosis. Several measures (eg, gastric lavage, giving activated charcoal) can reduce further GI absorption of aspirin. Alkalinization of the urine with bicarbonate accelerates excretion of aspirin and salicylate. If necessary, hemodialysis or peritoneal dialysis can be used to remove salicylates.

Formulations

Aspirin is available in multiple formulations, including plain and buffered tablets, enteric-coated preparations, and tablets used to produce a buffered solution. These different formulations reflect efforts to increase rates of absorption and decrease gastric irritation. For the most part, the clinical utility of the more complex formulations is no greater than that of plain aspirin tablets. **Aspirin Tablets, Plain.** All brands are essentially the same with respect to analgesic efficacy, onset, and duration. Some less expensive tablets have greater particle size, which results in slower dissolution and prolonged contact with the gastric mucosa, which increases gastric irritation. When aspirin tablets decompose, they smell like vinegar (acetic acid), and should be discarded. **Aspirin Tablets, Buffered.** The amount of buffer in buffered aspirin tablets is too small to produce significant elevation of gastric pH. An equivalent

TABLE 71-4 • Aspirin Dosage

Indication	Adult Dosage	Pediatric Dosage*
Aches and pains; fever	325–650 mg every 4 hr	2–3 yr old: 160 mg 4–5 yr old: 240 mg 6–8 yr old: 325 mg 9–10 yr old: 405 mg 11 yr old: 485 mg Over 11 yr old: 650 mg All of the above doses are administered every 4 hr
Acute rheumatic fever	5–8 gm/day in divided doses	100 mg/kg/day (initially), then 75 mg/kg/day for 4–6 wk
Rheumatoid arthritis	3.6–5.4 gm/day in divided doses	90–130 mg/kg/day in divided doses every 4–6 hr
Suppression of platelet aggregation		
Initial therapy	325 mg once a day	
Chronic therapy	80 mg once a day	

*Owing to the risk of Reye's syndrome, aspirin is usually avoided in patients less than 18 years old.

lent effect on pH can be achieved by taking plain aspirin tablets with food or a glass of water. Buffered aspirin tablets are no different from plain tablets with respect to analgesic effects and gastric distress. Buffered tablets may dissolve faster than plain tablets, resulting in somewhat faster onset.

Buffered Aspirin Solution. A buffered aspirin solution is produced by dissolving effervescent aspirin tablets [Alka-Seltzer] in a glass of water. This solution has considerable buffering capacity due to its high content of sodium bicarbonate. Effects on gastric pH are sufficient to decrease the incidence of gastric irritation and bleeding. In addition, aspirin absorption is accelerated and peak blood levels are raised. Unfortunately, these benefits come with a price. The sodium content of buffered aspirin solution can be detrimental to individuals on a sodium-restricted diet. Also, absorption of bicarbonate can elevate urinary pH, which will accelerate aspirin excretion. Lastly, this highly buffered preparation is expensive. Because of this combination of benefits and drawbacks, the buffered aspirin solution is well suited for occasional use but is generally inappropriate for long-term therapy.

Enteric-Coated Preparations. Enteric-coated preparations dissolve in the intestine rather than the stomach, thereby reducing gastric irritation. Unfortunately, absorption from these formulations can be delayed and erratic. Patients should be advised not to crush or chew them.

Timed-Release Tablets. Timed-release tablets offer no advantage over plain aspirin tablets. Since the half-life of salicylic acid is long to begin with, and since aspirin produces irreversible inhibition of cyclooxygenase, timed-release tablets cannot prolong effects.

Rectal Suppositories. Rectal suppositories have been employed for patients who cannot take aspirin orally. Absorption can be variable, resulting in plasma drug levels that are insufficient in some patients and excessive in others. Also, rectal irritation can occur. Because of these undesirable properties, aspirin suppositories are not generally recommended.

Dosage and Administration

Aspirin is almost always administered by mouth. Gastric irritation can be minimized by dosing with water or food. Dosage depends on the age of the patient and the condition being treated. Adult and pediatric dosages for major indications are summarized in Table 71-4.

Nonaspirin First-Generation NSAIDs

In attempts to produce an aspirin-like drug with fewer GI, renal, and hemorrhagic effects than aspirin, the pharmaceutical industry has produced a large number of drugs with actions much like those of aspirin. In the United States, over 20 nonaspirin NSAIDs are available (Table 71-5). Like aspirin, all other first-generation NSAIDs inhibit both COX-1 and COX-2. However, in contrast to aspirin, which causes irre-

versible inhibition of cyclooxygenase, the other traditional NSAIDs cause reversible inhibition. All of these drugs have anti-inflammatory, analgesic, and antipyretic properties. In addition, they all can cause gastric ulceration, bleeding, and renal impairment—although the intensity of these effects may be less with some agents. Patients who are hypersensitive to aspirin are likely to experience cross-hypersensitivity with other NSAIDs. For most NSAIDs, safety during pregnancy has not been established, and hence use by pregnant women is discouraged.

The principal indications for the nonaspirin NSAIDs are rheumatoid arthritis and osteoarthritis. In addition, certain NSAIDs are used to treat fever, bursitis, tendinitis, mild to moderate pain, and dysmenorrhea (see Table 71-5).

In contrast to aspirin, the nonaspirin NSAIDs do not protect against MI and stroke. In fact, they increase the risk of thrombotic events. For the NSAIDs as a group, the increase in cardiovascular risk is relatively low—about 12%. Risk is highest with indomethacin (71%), sulindac (41%), and meloxicam (37%). However, although the increase in risk with these drugs appears high, it pales in comparison with smoking, which increases cardiovascular risk by 200% to 300%. To minimize cardiovascular risk, nonaspirin NSAIDs should be used in the lowest effective dosage for the shortest time needed. Also, these drugs should not be used prior to coronary artery bypass graft (CABG) surgery or for 14 days after. Other measures to reduce risk are discussed below under *AHA Statement on COX Inhibitors in Chronic Pain*.

Although individual NSAIDs differ chemically, pharmacokinetically, and to some extent pharmacodynamically, all are similar clinically: They all produce essentially equivalent antirheumatic effects and they all present a similar risk of serious adverse effects (gastric ulceration, bleeding, renal impairment, MI, and stroke). However, for reasons that are not understood, individual patients may respond better to one agent than another. Furthermore, individual patients may tolerate one NSAID better than another. Therefore, in order to optimize therapy for each patient, trials with more than one NSAID may be needed.

TABLE 71-5 • Clinical Pharmacology of the Oral Nonsteroidal Anti-inflammatory Drugs

Drug	Maximum Daily Dosage (mg)	Plasma Half-Life (hr)	Major Indications ^a				
			Arthritis	Moderate Pain	Fever	Dysmenorrhea	Bursitis/Tendinitis
FIRST-GENERATION NSAIDs							
Salicylates							
Aspirin (many trade names)	8000	0.2–0.3	A	A	A		
Magnesium salicylate [Doan's Tablets, others]	4800	2–30 ^b	A	A	A		
Sodium salicylate (generic)	3900	2–30 ^b	A	A	A		
Salsalate [Disalcid]	3000	2–30 ^b	A	A	A		
Propionic Acid Derivatives							
Fenoprofen [Nalfon]	3200	3	A	A			
Flurbiprofen (generic)	300	5.7	A	I	I	I	I
Ibuprofen [Advil, Motrin, others] ^c	3200	1.8–2	A	A	A	A	
Ketoprofen (generic)	300	2	A	A		A	
Naproxen [Aleve, others] ^d	1375	12–17	A	A	A	A	A
Oxaprozin [Daypro]	1800	42–50	A				
Others							
Diclofenac [Cambia, Cataflam, Voltaren, Zipsor] ^e	200	2	A	A		A	
Diflunisal (generic)	1500	11–15	A	A			
Etodolac (generic)	1200	7.3	A	A			I
Indomethacin [Indocin]	200	4.5	A				A
Ketorolac (generic) ^f	40	5–6	A ^g				
Meclofenamate (generic)	400	1.3	A	A		A	
Mefenamic acid [Ponstel, Ponstan ^h]	1000	2		A		A	
Meloxicam [Mobic, Mobicox ⁱ]	15	15–20	A				
Nabumetone (generic)	2000	22	A				
Piroxicam [Feldene]	20	50	A				
Sulindac [Clinoril]	400	7.8	A				A
Tolmetin (generic)	2000	2–7	A				
SECOND-GENERATION NSAIDs (COX-2 INHIBITORS)							
Celecoxib [Celebrex]	800	11	A	A		A	

^aA = FDA-approved indication, I = investigational use.

^bHalf-life increases with increasing dosage.

^cIbuprofen is also available in two *intravenous* formulations, sold as Caldolor and NeoProfen.

^dNaproxen is also available in a fixed-dose combination with esomeprazole sold as Vimovo.

^eDiclofenac is also available in three *topical* formulations, sold as Flector Patch, Pennsaid, and Voltaren Gel (see text). Also available in a fixed-dose combination with misoprostol sold as Arthrotec.

^fKetorolac is also available in an *intravenous* formulation, sold generically, and in an *intranasal* formulation, sold as Sprix (see text).

^gKetorolac is approved only for *acute* pain; use should not exceed 5 days.

Nonacetylated Salicylates: Magnesium Salicylate, Sodium Salicylate, and Salsalate

Similarities to Aspirin. The nonacetylated salicylates are similar to aspirin (an acetylated salicylate) in most respects. Like aspirin, these drugs inhibit COX-1 and COX-2 and are employed to treat arthritis, moderate pain, and fever. The most common adverse effects are GI disturbances. As with aspirin, these drugs should not be given to children with chickenpox or influenza owing to the possibility of precipitating Reye's syndrome.

Contrasts with Aspirin. In contrast to aspirin, the nonacetylated salicylates cause little or no suppression of platelet aggregation. As a result, these drugs cannot protect against MI and stroke, and may actually increase risk.

Because of its sodium content, *sodium salicylate* should be avoided in patients on a sodium-restricted diet (eg, patients with hypertension or heart failure).

Magnesium salicylate may accumulate to toxic levels in patients with chronic renal insufficiency, and hence should not be used by these people.

Salsalate is a prodrug that breaks down to release two molecules of salicylate in the alkaline environment of the small intestine. Because the stomach is not exposed to salicylate, salsalate produces less gastric irritation than aspirin.

Preparations, Dosage, and Administration. Magnesium salicylate [Doan's Tablets, others] is supplied in caplets (377 and 580 mg) and tablets (600 mg) for oral use. The usual dosage is 650 mg every 4 hours or 1090 mg every 8 hours. The maximum dosage is 4800 mg/day, administered in three or four doses.

Sodium salicylate (generic) is supplied in enteric-coated tablets (325 and 650 mg) for oral use. The usual dosage is 325 to 650 mg every 4 hours.

Salsalate [Disalcid] is supplied in capsules (500 mg) and tablets (500 and 750 mg) for oral use. The usual dosage is 3000 mg/day in divided doses.

Ibuprofen

Basic Pharmacology. Ibuprofen [Advil, Motrin, Caldolor, others] is the prototype of the propionic acid derivatives. Other members of the family are listed in Table 71-5 and discussed individually below. Like aspirin, ibuprofen inhibits cyclooxygenase and has anti-inflammatory, analgesic, and antipyretic actions. The drug is used to treat fever, mild to moderate pain, and arthritis. In addition, ibuprofen appears superior to most other NSAIDs for relief of primary dysmenorrhea, presumably because it produces good inhibition of cyclooxygenase in uterine smooth muscle. In clinical trials, ibuprofen was highly effective at promoting closure of the ductus arteriosus in preterm infants, a condition for which indomethacin is the current treatment of choice.

Ibuprofen is generally well tolerated, and the incidence of adverse effects is low. The drug produces less gastric bleeding than aspirin and less inhibition of platelet aggregation as well. Consequently, ibuprofen is among the safer NSAIDs for use with anticoagulants. Very rarely, ibuprofen has been associated with Stevens-Johnson syndrome, a severe hypersensitivity reaction that causes blistering of the skin and mucous membranes, and can result in scarring, blindness, and even death. Like other nonaspirin NSAIDs, ibuprofen may pose a risk of MI and stroke.

Oral Preparations and Dosages. Ibuprofen, *by itself*, is available in five oral formulations: (1) standard tablets (100, 200, 400, 600, and 800 mg); (2) chewable tablets (50 and 100 mg); (3) capsules (200 mg); (4) a 20-mg/mL oral suspension [Children's Advil, Children's Motrin, PediaCare Fever]; and (5) a 40-mg/mL oral suspension [Advil Pediatric Drops, Motrin Infant's, PediaCare Fever]. Administration with meals or milk can reduce gastric distress.

Dosages for adults are

- *Arthritis*—1.2 to 3.2 gm/day administered in three or four divided doses
- *Primary dysmenorrhea*—400 mg every 4 to 6 hours
- *Mild to moderate pain*—400 mg every 4 hours

Dosages for children are

- *Juvenile arthritis*—30 to 40 mg/kg/day in three or four divided doses.
- *Fever reduction*—5 mg/kg (for temperatures up to 102.5°F) or 10 mg/kg (for temperatures above 102.5°F). The total daily dose should not exceed 40 mg/kg.

Oral ibuprofen is also available in two fixed-dose combinations: (1) *ibuprofen/oxycodone* [Combunox] for short-term oral therapy of moderate to severe pain, and (2) *ibuprofen/famotidine* [Duexis] for treatment of rheumatoid arthritis and osteoarthritis, while reducing the risk of GI ulcers.

Intravenous Preparations and Dosages. Ibuprofen is available in two IV formulations, sold as Caldolor and NeoProfen. Indications and dosages for these products differ.

Caldolor is indicated for fever and pain in adults. The drug may be used alone for mild to moderate pain, or combined with an opioid for moderate to severe pain. *Caldolor* is supplied as a concentrated solution (100 mg/mL) that must be diluted (to 4 mg/mL or less) before use. Infusions are done slowly (over 30 minutes or longer). For patients with pain, the usual dosage is 400 to 600 mg every 6 hours. For patients with fever, treatment consists of an initial 400-mg dose, followed by either (1) 400 mg every 4 to 6 hours or (2) 100 to 200 mg every 4 hours.

NeoProfen (10 mg ibuprofen/mL) is indicated for closing a patent ductus arteriosus in premature infants. Treatment consists of an initial dose (10 mg/kg infused over 15 minutes) followed by two more doses (5 mg/kg each) given 24 and 48 hours later.

Fenoprofen

Fenoprofen [Nalfon] belongs to the propionic acid family of NSAIDs. Like other NSAIDs, the drug inhibits synthesis of prostanoids, thereby causing anti-inflammatory, analgesic, and antipyretic effects. Fenoprofen is indicated for arthritis and mild to moderate pain. The most common adverse effects are GI disturbances. Fenoprofen is supplied in tablets (600 mg) and capsules (200, 300, and 400 mg). The usual dosage for mild to moderate pain is 200 mg every 4 to 6 hours. The dosage range for rheumatoid arthritis is 300 to 600 mg every 6 to 8 hours, but should not exceed 3.2 gm/day.

Flurbiprofen

Flurbiprofen, formerly available as Ansaïd, is chemically related to ibuprofen and the other derivatives of propionic acid. The drug is approved for arthritis and has been used investigational for bursitis, tendinitis, moderate pain, fever, and primary dysmenorrhea. The most common adverse effects are GI disturbances (dyspepsia, nausea, diarrhea, abdominal pain). The risk of serious GI effects (ulceration, perforation, hemorrhage) may be greater than with ibuprofen. Like other NSAIDs, flurbiprofen can exacerbate renal impairment and may pose a risk of MI and stroke. The drug is supplied in tablets (50 and

100 mg) for oral use. The usual dosage for rheumatoid arthritis is 200 to 300 mg/day administered in two to four divided doses.

Ketoprofen

Ketoprofen belongs to the propionic acid family of NSAIDs. The drug inhibits synthesis of prostanoids and has anti-inflammatory, analgesic, and antipyretic effects. Indications are rheumatoid arthritis, osteoarthritis, mild to moderate pain, and primary dysmenorrhea. The most common adverse effects are dyspepsia (11.5%), nausea, vomiting, and abdominal pain. Ketoprofen is supplied in immediate-release capsules (50 and 75 mg) and extended-release capsules (100, 150, and 200 mg). The usual dosage for rheumatoid arthritis is 150 to 300 mg/day administered in three or four divided doses. The dosage for moderate pain or primary dysmenorrhea is 25 to 50 mg every 6 to 8 hours.

Naproxen

Actions and Uses. Naproxen [Aleve, Anaprox, Naprelan, Naprosyn], a member of the propionic acid family of NSAIDs, is highly selective for COX-1. The drug has a prolonged half-life (see Table 71-5), and hence can be administered less frequently than other propionic acid derivatives (eg, ibuprofen). Naproxen is approved for arthritis, bursitis, tendinitis, primary dysmenorrhea, fever, and mild to moderate pain. Like other NSAIDs, the drug acts primarily by inhibiting cyclooxygenase.

Adverse Effects. Naproxen is among the better tolerated NSAIDs. The most common adverse effects are GI disturbances. Like other NSAIDs, the drug can compromise renal function and may increase the risk of MI and stroke. However, because naproxen is COX-1 selective, the risk of MI and stroke appears lower than with other traditional NSAIDs. Bleeding time can be prolonged secondary to reversible inhibition of platelet aggregation.

Preparations, Dosage, and Administration. Naproxen is supplied in immediate-release tablets (200, 250, 375, and 500 mg) sold as Aleve, Anaprox, and Naprosyn; delayed-release enteric-coated tablets (375 and 500 mg) sold as EC-Naprosyn; controlled-release tablets (375 and 500 mg) sold as Naprelan; and an oral suspension (25 mg/mL) sold as Naprosyn and Naproxen. For all products, the usual dosage for rheumatoid arthritis is 250 to 500 mg of naproxen twice daily. The dosage for mild to moderate pain is 500 mg initially followed by 250 mg every 6 to 8 hours.

Naproxen/Esomeprazole [Vimovo]

Vimovo is a fixed-dose combination of naproxen plus esomeprazole, a proton pump inhibitor that blocks production of gastric acid (see Chapter 78), and thereby protects against naproxen-induced ulcers. A similar product—naproxen/lansoprazole [Prevacid NapraPAC]—has been withdrawn. Vimovo delayed-release tablets are available in two naproxen/esomeprazole strengths: 375 mg/20 mg and 500 mg/20 mg. For patients with osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis, the usual dosage is 1 tablet twice daily.

Oxaprozin

Oxaprozin [Daypro] belongs to the propionic acid family of NSAIDs. Approved uses are rheumatoid arthritis and osteoarthritis. As with other NSAIDs, benefits derive from inhibiting synthesis of prostanoids. Like other propionic acid derivatives, oxaprozin is generally well tolerated. The drug has an unusually long half-life (42 to 50 hours), and hence can be administered just once a day. Oxaprozin is available in 600-mg tablets and caplets. The dosage for arthritis is 1200 mg once a day. The maximum dosage is 1800 mg/day.

Diclofenac

Oral. Oral diclofenac [Voltaren, Cataflam, Cambia, Zipsor] is approved for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, mild pain, primary dysmenorrhea, and migraine. As with other NSAIDs, anti-inflammatory, analgesic, and antipyretic effects result from inhibiting cyclooxygenase. Diclofenac is well absorbed following oral administration, but undergoes extensive (40% to 50%) metabolism on its first pass through the liver. In the blood, about 99.5% of the drug is protein bound, primarily to albumin. Diclofenac is metabolized by the liver and excreted in the urine.

The most common adverse effects are abdominal pain, dyspepsia, and nausea. By impairing renal function, diclofenac can cause fluid retention, which can exacerbate hypertension and heart failure. Cardiovascular risk appears to equal that of rofecoxib, a COX-2 inhibitor that has been removed from the market owing to risk of MI and stroke.

Diclofenac can cause severe liver injury, even with topical therapy. Accordingly, patients should receive periodic tests of liver function, and should be instructed to report manifestations of liver injury (eg, jaundice, fatigue, nausea). If liver injury is diagnosed, diclofenac should be discontinued.

Diclofenac is supplied in immediate-release tablets (50 mg) as Cataflam, enteric-coated delayed-release tablets (25, 50, and 75 mg) as Voltaren.

extended-release tablets (100 mg) as Voltaren XR, liquid-filled capsules (25 mg) as Zipsor, and a powder for oral solution (50 mg) as Cambia. The dosage for rheumatoid arthritis is 150 to 200 mg/day administered in two or three divided doses. The dosage for osteoarthritis is 100 to 150 mg/day administered in two or three divided doses.

Topical. Diclofenac is available in three topical formulations—*Voltaren Gel*, *Flector Patch*, and *Pennsaid* (solution)—for treatment of pain and inflammation. *Voltaren Gel* is for osteoarthritis, *Flector Patch* is for minor pain, and *Pennsaid* is for osteoarthritis of the knee. A fourth topical formulation—*Solaraze*—is used for actinic keratoses (see Chapter 105). Topical diclofenac is more expensive than oral diclofenac, but also safer: With topical therapy, blood levels are only about 5% of those achieved with oral therapy, and hence the risk of systemic toxicity is low. Efficacy of topical diclofenac appears about equal to that of oral therapy. Whether topical diclofenac shares the drug interactions of oral diclofenac has not been determined.

Voltaren Gel (1% diclofenac sodium) was the first prescription topical NSAID for treating pain and inflammation. Application is done to the knees, elbows, and other amenable joints. For joints of the lower extremity (knees, ankles, feet), the dosage is 4 gm of gel applied 4 times a day. For joints of the upper extremity (elbows, wrists, hands), the dosage is 2 gm of gel applied 4 times a day. Total body exposure should not exceed 32 gm/day. Treated areas should be protected from sunlight (natural or artificial). Local dermatitis is the principal adverse effect.

Flector Patch (1.3% diclofenac epolamine) is the first prescription NSAID patch indicated for pain of strains, sprains, and contusions. One patch is applied over the injury twice a day—but only to skin that is intact. The patch should not be worn while bathing or showering. Local reactions—pruritus, dermatitis, burning—are the principal adverse effects.

Pennsaid is a 1.5% solution of diclofenac sodium, formulated with 45% dimethyl sulfoxide (DMSO) to facilitate skin penetration. The product has only one indication: osteoarthritis of the knee. Efficacy equals that of oral diclofenac. Application is done 4 times a day. For each application, 40 drops are spread around the entire knee (front, back, and sides). Application-site reactions are common. Among these are dry skin (32%), erythema and induration (9%), pruritus (4%), and contact dermatitis with vesicles (2%). Systemic effects are minimal. Patients may experience a garlicky odor or taste owing to the DMSO. As with *Voltaren Gel*, the treated area should not be exposed to sunlight, natural or artificial.

Diclofenac/Misoprostol [Arthrotec]

Oral diclofenac, in combination with misoprostol, is available under the trade name *Arthrotec*. Misoprostol is a prostaglandin analog that can protect against NSAID-induced ulcers. The combination product is approved for patients with rheumatoid arthritis or osteoarthritis who are at high risk for NSAID-induced gastric or duodenal ulcers. In patients with arthritis, the combination is as effective as diclofenac alone and produces significantly less GI ulceration. The most bothersome side effect is diarrhea (caused by misoprostol). Misoprostol can induce uterine contraction, and hence the product is contraindicated for use during pregnancy. Diclofenac/misoprostol is supplied in two strengths: 50 mg/200 mcg and 75 mg/200 mcg. For rheumatoid arthritis, the usual dosage is 50 mg/200 mcg 3 or 4 times a day.

Diflunisal

Diflunisal, formerly available as *Dolobid*, is a derivative of salicylic acid. However, unlike the salicylates, diflunisal is not converted to salicylic acid in the body. The drug is indicated for mild to moderate pain, rheumatoid arthritis, and osteoarthritis. Like other NSAIDs, the drug inhibits prostaglandin synthesis and can cause GI disturbances, suppression of platelet aggregation, and renal impairment, and may increase the risk of MI and stroke. Diflunisal has a prolonged half-life (11 to 15 hours), and hence can be administered only 2 or 3 times a day. Diflunisal is supplied in tablets (250 and 500 mg) for oral use. For treatment of arthritis and mild to moderate pain, the initial dose is 500 to 1000 mg. Maintenance doses of 250 to 500 mg are administered every 8 to 12 hours.

Etodolac

Etodolac is indicated for rheumatoid arthritis, osteoarthritis, and moderate pain. Investigational uses include bursitis and tendinitis. Like other NSAIDs, etodolac produces many of its effects by suppressing the synthesis of prostaglandins. The most common adverse effects are dyspepsia (10%), nausea, vomiting, diarrhea, and abdominal pain. Etodolac may cause less gastric ulceration and bleeding than other NSAIDs. The drug is supplied in immediate-release tablets (400 and 500 mg), extended-release tablets (400, 500, and 600 mg), and capsules (200 and 300 mg). The recommended dosage for arthritis is 800 to 1200 mg/day in divided doses. The dosage for moderate pain is 200 to 400 mg every 6 to 8 hours.

Indomethacin

Actions and Uses. Indomethacin [Indocin] is an effective anti-inflammatory agent approved for arthritis, bursitis, tendinitis, and, as discussed in Chapter 74, acute gouty arthritis. In addition, the drug can be given IV to preterm infants to promote closure of the ductus arteriosus. Although indomethacin is able to reduce pain and fever, it is not routinely used for these effects, owing to potential toxicity.

Pharmacokinetics. Indomethacin is well absorbed following oral administration and distributes to all body fluids and tissues. The drug is metabolized in the liver. Metabolites and parent drug are excreted in the urine and feces.

Adverse Effects. Untoward effects are seen in 35% to 50% of patients, causing about 20% to discontinue treatment. The most common adverse effect is severe frontal headache, which occurs in 25% to 50% of patients. Other CNS effects (dizziness, vertigo, confusion) are also common. Seizures and psychiatric changes (eg, depression, psychosis) have occurred. Mild GI reactions (nausea, vomiting, indigestion) develop in 3% to 9% of users. More severe GI effects (ulceration with perforation, hemorrhage) may also occur. Hematologic reactions (neutropenia, thrombocytopenia, aplastic anemia) have occurred but are rare. Indomethacin suppresses platelet aggregation.

Precautions and Contraindications. Because of its adverse effects, indomethacin is generally contraindicated for infants and children under the age of 14, patients with peptic ulcer disease, and women who are pregnant or breast-feeding. Caution is required in patients with epilepsy and psychiatric disorders, in patients involved in hazardous activities, and in patients receiving anticoagulant therapy.

Preparations, Dosage, and Administration. Indomethacin [Indocin] is available in immediate-release capsules (25 and 50 mg), sustained-release capsules (75 mg), an oral suspension (5 mg/mL), and rectal suppositories (50 mg). For treatment of rheumatoid arthritis, the initial dosage is 25 mg 2 or 3 times a day. The maximum daily dosage is 200 mg. Gastrointestinal reactions can be reduced by dosing with meals. Dosages for gout are presented in Chapter 74.

Ketorolac

Actions and Uses. Ketorolac is a powerful analgesic with minimum anti-inflammatory actions. Pain relief is equivalent to that produced by morphine and other opioids. Although ketorolac lacks the serious adverse effects associated with opioids (respiratory depression, tolerance, dependence, abuse potential), it nonetheless has serious adverse effects of its own. Accordingly, use should be short term and restricted to managing acute pain of moderate to severe intensity. Ketorolac is not indicated for chronic pain or for minor aches and discomfort. The usual indication is postoperative pain, for which ketorolac can be as effective as morphine. Like other NSAIDs, ketorolac suppresses prostaglandin synthesis. This action is thought to underlie analgesic effects.

Pharmacokinetics. Ketorolac is administered orally and parenterally (IM or IV). With parenteral administration, analgesia begins within 30 minutes, peaks in 1 to 2 hours, and persists 4 to 6 hours. The drug is eliminated by hepatic metabolism and urinary excretion. In young adults, ketorolac has a half-life of 4 to 6 hours. The half-life may be prolonged in the elderly and those with renal impairment.

Adverse Effects and Contraindications. Ketorolac can cause all of the adverse effects associated with other NSAIDs, including peptic ulcers, GI bleeding or perforation, prolonged bleeding time, renal impairment, hypersensitivity reactions, suppression of uterine contractions, and premature closure of the ductus arteriosus. Concurrent use with other NSAIDs increases the risk of these effects and hence is contraindicated. Other contraindications include active peptic ulcer disease, history of peptic ulcer disease or recent GI bleeding, advanced renal impairment, confirmed or suspected intracranial bleeding, use prior to major surgery, history of NSAID hypersensitivity reactions, and use during labor and delivery.

Preparations, Dosage, and Administration. Parenteral and Oral Therapy. Ketorolac is available in 10-mg tablets for oral dosing, and in solution (15 and 30 mg/mL) for IM or IV dosing. Dosing is parenteral initially, followed by oral dosing if needed. Owing to risks associated with prolonged use, treatment (parenteral plus oral) should not exceed 5 days.

Parenteral therapy can be accomplished with one injection or with several. When a single injection is used, the IM dose is 30 or 60 mg, and the IV dose is 15 or 30 mg. When multiple injections are given, the dosage (IM or IV) is 15 or 30 mg every 6 hours. In all cases, the smaller dosage option is employed for patients over 65 years, patients with impaired kidney function, and patients who weigh less than 50 kg (110 pounds). Intravenous doses should be administered over 15 seconds or longer. Intramuscular injections should be done slowly and deep in the muscle. Treatment should not exceed 5 days.

Oral ketorolac is indicated only as a follow-up to parenteral therapy. Initial oral doses are based on preceding parenteral doses. The usual oral maintenance dosage is 10 mg every 4 to 6 hours. Combined oral and parenteral treatment should not exceed 5 days.

Intranasal Therapy. Ketorolac [Sprix] is available in a metered-dose spray device (15.75 mg/actuation) for short-term, intranasal treatment of moderate to moderately severe pain. As with oral and parenteral therapy, treatment should not exceed 5 days. Dosage depends on weight, age, and renal function. For nonelderly patients with normal renal function who weigh more than 50 kg, the usual dosage is 2 sprays (one 15.75-mg spray in each nostril) every 6 to 8 hours. The dosage is lower—one 15.75-mg spray in one nostril every 6 to 8 hours—for patients who are elderly, have impaired kidney function, or weigh less than 50 kg.

Meclofenamate

Meclofenamate is indicated for rheumatoid arthritis, osteoarthritis, mild to moderate pain, and dysmenorrhea. As with other NSAIDs, benefits derive from inhibiting cyclooxygenase. Therapeutic effects are no better than with other NSAIDs, but adverse GI effects are greater: 3% to 9% of patients experience nausea, vomiting, abdominal pain, and cramps; worse yet, 10% to 33% develop diarrhea. Because of this poor benefit/risk profile, meclofenamate is not a drug of first choice. Meclofenamate is available in 50- and 100-mg capsules. Dosages are as follows: arthritis, 200 to 400 mg/day in three or four divided doses; moderate pain, 50 mg every 4 to 6 hours; and dysmenorrhea, 100 mg 3 times a day for up to 6 days.

Mefenamic Acid

Mefenamic acid [Ponstel, Ponstan] is indicated for relief of primary dysmenorrhea and moderate pain. The principal adverse effect is diarrhea, which can be severe. Mefenamic acid is supplied in 250-mg capsules. The dosage for primary dysmenorrhea is 500 mg initially followed by 250 mg every 6 hours. The drug should be administered with food or milk to reduce gastric distress. Usual treatment duration is 2 to 3 days.

Nabumetone

Nabumetone is a prodrug that undergoes hepatic conversion to its active form: 6-MNA. In contrast to most traditional NSAIDs, 6-MNA inhibits COX-2 more than COX-1. Although nabumetone has antipyretic, analgesic, and anti-inflammatory properties, the drug is approved only for osteoarthritis and rheumatoid arthritis. Principal adverse effects are diarrhea (14%), abdominal cramps (13%), dyspepsia (12%), and nausea (3% to 9%). Nabumetone causes much less GI ulceration than other first-generation NSAIDs, possibly because it preferentially inhibits COX-2. Nabumetone is supplied in 500- and 750-mg tablets. Dosing with food increases the rate of absorption. Treatment of arthritis begins with a single 1000-mg dose. After this, the daily dosage is 1500 to 2000 mg administered in one or two doses. Dosage should be reduced in patients with renal impairment.

Piroxicam

Piroxicam [Feldene] has anti-inflammatory, analgesic, and antipyretic properties, but is approved only for rheumatoid arthritis and osteoarthritis. The drug's most outstanding feature is its long half-life (about 50 hours). Because piroxicam is eliminated so slowly, therapeutic effects can be maintained with once-a-day dosing. In general, piroxicam is better tolerated than aspirin. Undesired effects are seen in 11% to 46% of patients, causing between 4% and 12% to discontinue therapy. Gastrointestinal reactions are most common, occurring in about 20% of patients. The incidence of gastric ulceration is about 1%. Like aspirin, piroxicam inhibits platelet aggregation and prolongs bleeding time. The drug is supplied in 10- and 20-mg capsules for oral use. The usual dosage is 20 mg once a day.

Sulindac

Sulindac [Clinoril] is a prodrug that undergoes conversion to its active form in the body. The drug is approved for rheumatoid arthritis, osteoarthritis, tendinitis, bursitis, and acute gouty arthritis. Principal adverse effects are abdominal distress, dyspepsia, nausea, vomiting, and diarrhea. Gastric ulceration is less common than with some other NSAIDs. Like other NSAIDs, sulindac causes reversible inhibition of platelet aggregation, prolongs bleeding time, and impairs renal function. The drug is supplied in 150- and 200-mg tablets. The usual dosage is 150 mg administered twice daily with meals. The maximum daily dosage is 400 mg.

Tolmetin

Tolmetin is approved for rheumatoid arthritis and osteoarthritis. The drug has analgesic and antipyretic properties but is not employed to relieve fever or pain unrelated to inflammation. Adverse effects occur in 25% to 40% of pa-

tients, causing between 5% and 10% to discontinue treatment. Gastrointestinal effects (nausea, vomiting, indigestion) are most common. Gastric ulceration has occurred, but less frequently than with aspirin. Nonetheless, caution should be exercised in patients with a history of peptic ulcer disease. Hypersensitivity reactions are more common than with aspirin. Effects on the CNS (headache, dizziness, anxiety, drowsiness) are less severe and less frequent than with indomethacin. Unlike most other NSAIDs, tolmetin does not augment the effects of warfarin, an oral anticoagulant. The drug is supplied in tablets (200 and 600 mg) and capsules (400 mg). For rheumatoid arthritis, the initial dosage is 400 mg 3 times a day. The maximum daily dosage is 2 gm. Gastrointestinal distress can be minimized by dosing with food.

Meloxicam

Meloxicam [Mobic, Mobicox] can inhibit COX-1 and COX-2, but shows selectivity for COX-2 at low doses. Like other NSAIDs, the drug has analgesic, anti-inflammatory, and antipyretic actions. Approved indications are osteoarthritis, rheumatoid arthritis, and pauciarticular/polyarticular-course juvenile rheumatoid arthritis (JRA). For osteoarthritis, meloxicam is as effective as first-generation NSAIDs. Direct comparison with true COX-2 inhibitors (eg, celecoxib) has not been made. Despite its COX-2 selectivity, meloxicam has a side effect profile like that of the first-generation NSAIDs. Gastrointestinal effects (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, and vomiting) occur in 20% to 25% of patients. More serious effects—GI ulceration, bleeding, perforation, and death—have also occurred. Meloxicam does not suppress platelet aggregation. The drug has a long half-life (15 to 20 hours) and undergoes elimination in the urine (50%) and feces (50%). Meloxicam is available in tablets (7.5 and 15 mg) and an oral solution (7.5 mg/5 mL). Both formulations can be taken with or without food. Because of its long half-life, meloxicam can be administered just once a day. The recommended dose for initial and maintenance therapy of osteoarthritis and rheumatoid arthritis is 7.5 mg/day. For patients with JRA, the recommended daily dosage is 0.125 mg/kg (but no more than 7.5 mg).

SECOND-GENERATION NSAIDS (COX-2 INHIBITORS, COXIBS)

The COX-2 inhibitors, also known as coxibs, were developed on the theory that selective inhibition of COX-2 should be able to suppress pain and inflammation while posing little or no risk of gastric ulceration. To some degree, theory and reality agree: Coxibs are just as effective as traditional NSAIDs at suppressing inflammation and pain, and they pose a somewhat lower risk of GI side effects. However, even with coxibs, patients can develop clinically significant gastroduodenal ulceration and bleeding. Furthermore, like traditional NSAIDs, coxibs can impair renal function, and can thereby cause hypertension and edema. Coxibs also increase the risk of MI and stroke.

The coxib story reads like a Greek tragedy. Following their introduction in December 1998, coxibs were prescribed for millions of patients, with hopes of relieving inflammation and pain while minimizing GI side effects. At their peak, combined annual sales for the three available coxibs exceeded \$5 billion. Within a few years, however, the story began to change. Protection from ulcers turned out to be less than hoped for, and evidence of serious cardiovascular risk began to emerge. By 2005, two coxibs—rofecoxib and valdecoxib—had been withdrawn from the market, and sales of the one remaining agent—celecoxib—had sharply declined.

Celecoxib

Therapeutic Use

Celecoxib [Celebrex], approved in December 1998, was the first selective COX-2 inhibitor to reach the market. The drug is indicated for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, and dysmenorrhea. In addition, cele-

market (see below). To minimize risk, celecoxib should be used in the lowest effective dosage for the shortest time needed. Also, the drug should be avoided in patients with existing heart disease and those who have just undergone CABG surgery, and should be used with caution in patients with cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia. Other measures to reduce risk are discussed below under *AHA Statement on COX Inhibitors in Chronic Pain*.

Why is the risk of MI and stroke increased? First, because celecoxib does not inhibit COX-1, platelet aggregation is not suppressed. Second, because celecoxib inhibits COX-2 in blood vessels, vasoconstriction is increased. These two factors—unimpeded platelet aggregation and increased vasoconstriction—increase the likelihood of vessel blockage once the process of thrombosis has begun.

Renal Impairment. Like conventional NSAIDs, celecoxib can impair renal function, thereby posing a risk to patients with hypertension, edema, heart failure, or kidney disease. Renal impairment apparently results from inhibiting COX-2.

Sulfonamide Allergy. Celecoxib contains a sulfur molecule and hence can precipitate an allergic reaction in patients allergic to sulfonamides. Accordingly, the drug should be avoided by patients with sulfa allergy.

Use in Pregnancy. Celecoxib and other NSAIDs can cause premature closure of the ductus arteriosus. Accordingly, these drugs are contraindicated during the third trimester of pregnancy.

Drug Interactions

Warfarin. Celecoxib may increase the anticoagulant effects of warfarin, and may thereby increase the risk of bleeding. Celecoxib itself does not inhibit platelet aggregation and does not promote bleeding. However, the drug may enhance the anticoagulant effects of warfarin (perhaps by increasing warfarin levels). Celecoxib may be combined with warfarin, but effects of warfarin should be monitored closely, especially during the first few days of treatment.

Other Interactions. Information on the interactions of celecoxib with other drugs is limited. Celecoxib may decrease the diuretic effects of furosemide as well as the antihypertensive effects of ACE inhibitors. Conversely, celecoxib may increase levels of lithium (a drug for bipolar disorder). Levels of celecoxib may be increased by fluconazole (an antifungal drug).

Preparations, Dosage, and Administration
Celecoxib [Celebrex] is available in capsules (50, 100, 200, and 400 mg). To minimize cardiovascular risk, the drug should be used in the lowest effective dosage for the shortest time needed. Approved dosages are as follows:

- **Osteoarthritis**—100 mg twice daily or 200 mg once daily
- **Rheumatoid arthritis**—100 or 200 mg twice daily
- **Acute pain**—On day 1, 400 mg initially plus another 200 mg if needed; on all subsequent days, 200 mg twice daily as needed
- **Primary dysmenorrhea**—Same as for acute pain
- **Familial adenomatous polyposis**—400 mg twice daily, taken with food

Rofecoxib and Valdecoxib

Rofecoxib [Vioxx] and valdecoxib [Bextra] have been withdrawn from the market. Both drugs greatly increase the risk of serious cardiovascular events. In addition, valdecoxib poses a risk of severe skin reactions. Rofecoxib was approved in May 1999 and withdrawn in September 2004. Concern about the drug began in March 2000, when data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial showed that patients who took rofecoxib experienced more MIs and other thrombotic events (eg, unstable angina, ischemic stroke, transient ischemic attacks) than did patients

celecoxib is approved for a rare genetic disorder known as familial adenomatous polyposis, which predisposes to developing colorectal cancer. For patients with arthritis, celecoxib is equal to naproxen (an NSAID) at relieving joint pain, stiffness, and swelling. Owing to concerns about cardiovascular safety, celecoxib is considered a last-choice drug for long-term management of pain (see below under *AHA Statement on COX Inhibitors in Chronic Pain*).

It is important to note that celecoxib does not provide the cardiovascular benefits of aspirin. Why? Because celecoxib does not inhibit COX-1 in platelets, and hence does not suppress platelet aggregation.

Mechanism of Action

Celecoxib causes selective inhibition of COX-2, the COX isoform whose products mediate inflammation and pain. At therapeutic doses, celecoxib does not inhibit COX-1, the COX isoform whose products protect the stomach, help maintain renal function, and promote platelet aggregation.

Pharmacokinetics

Celecoxib is well absorbed following oral administration. Plasma levels peak in 3 hours. Binding to plasma proteins is extensive (97%). The drug undergoes hepatic metabolism followed by renal excretion. The half-life is 11 hours.

Adverse Effects

In premarketing trials, celecoxib was well tolerated. The discontinuation rate owing to adverse effects was 7.1% for celecoxib versus 6.1% for placebo. The most common complaints were *dyspepsia* (8.8% vs. 6.2% for placebo) and *abdominal pain* (4.1% vs. 2.8% for placebo). Celecoxib does not decrease platelet aggregation and hence does not promote bleeding. Possible cardiovascular events are the biggest concern.

Gastrointestinal Ulceration.

Because celecoxib does not inhibit COX-1, the isoform of COX that protects the stomach, a low incidence of gastroduodenal ulceration would be expected. Some data support this expectation; others do not. When celecoxib was first approved, conclusions about its safety were based on 6-month data from the Celecoxib Arthritis Safety Study (CLASS), which indicated that celecoxib caused less GI toxicity than conventional NSAIDs (diclofenac, naproxen, ibuprofen). However, longer term (12-month) data from the same study showed *no difference* in GI toxicity between celecoxib and conventional NSAIDs. Other studies have shown that, compared with patients taking conventional NSAIDs, those taking celecoxib had a lower incidence of endoscopically detectable ulcers and a lower incidence of hospitalization for GI bleeding. What's the bottom line? Celecoxib may be safer than conventional NSAIDs, especially when used short term. However, convincing data of superior safety are lacking. Like traditional NSAIDs, celecoxib can be combined with a proton pump inhibitor (PPI) to reduce GI complications.

Cardiovascular Events. There is strong evidence that celecoxib, like other nonaspirin NSAIDs, increase the risk of MI, stroke, and other serious cardiovascular events. In the Adenoma Prevention with Celecoxib (APC) trial, patients who took 400 mg or 800 mg of celecoxib a day experienced more major fatal or nonfatal cardiovascular events than did patients who took placebo. With two other celecoxib-rofecoxib and valdecoxib—cardiovascular risk is even greater than with celecoxib, and hence these drugs have been removed from the

who took naproxen. However, it wasn't clear from these data whether rofecoxib actively promoted MI or naproxen protected against MI. Any doubts about the cardiovascular risks of rofecoxib were eliminated in September 2004, when data from the Adenomatous Polyp Prevention On Vioxx (APPROVE) trial showed that, in patients who took rofecoxib for more than 18 months, rates of MI and stroke were significantly greater than in patients who took a placebo. In response to the APPROVE data, the manufacturer—Merck—voluntarily withdrew rofecoxib from the market worldwide. By that time, however, more than 100 million prescriptions had been written in the United States alone, possibly resulting in thousands of excess cardiovascular deaths.

Valdecoxib was approved in November 2001 and withdrawn in April 2005. Why? Because of cardiovascular and hypersensitivity risks. Like other coxibs, valdecoxib increases the risk of cardiovascular events. In a study involving patients recovering from CABG surgery, those who took valdecoxib experienced more cardiovascular events (MI, stroke, deep vein thrombosis, pulmonary embolism) than did those who took a placebo. Valdecoxib can also cause severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, both of which can be fatal. Because of these risks, and because valdecoxib has no demonstrated advantage over other NSAIDs, the FDA asked the manufacturer (Pfizer) to suspend sales in the United States.

ACETAMINOPHEN

Acetaminophen [Tylenol, Ofirmev, many others] is like aspirin in some respects but different in others. Acetaminophen has *analgesic* and *antipyretic* properties equivalent to those of aspirin. However, in contrast to aspirin and the other NSAIDs, *acetaminophen is devoid of clinically useful anti-inflammatory and antirheumatic actions*. In addition, acetaminophen does not suppress platelet aggregation, does not cause gastric ulceration, and does not decrease renal blood flow or cause renal impairment. However, acetaminophen overdose can cause severe liver injury. In the United States, acetaminophen is used more than any other analgesic.

Mechanism of Action

Differences between the effects of acetaminophen and aspirin are thought to result from selective inhibition of cyclooxygenase, the enzyme needed to make prostaglandins and related compounds. Whereas aspirin can inhibit cyclooxygenase in both the CNS and the periphery, inhibition by acetaminophen is limited to the CNS; acetaminophen has only minimal effects on cyclooxygenase at peripheral sites. By decreasing prostaglandin synthesis in the CNS, acetaminophen is able to reduce fever and pain. The inability to inhibit prostaglandin synthesis outside the CNS may explain the absence of anti-inflammatory effects, gastric ulceration, and adverse effects on the kidneys and platelets.

Pharmacokinetics

Acetaminophen is readily absorbed following oral dosing and undergoes wide distribution. Most of each dose is metabolized by the liver, and the metabolites are excreted in the urine. The plasma half-life is approximately 2 hours.

Acetaminophen can be metabolized by two pathways; one is major and the other is minor (Fig. 71-2). In the major pathway, acetaminophen undergoes conjugation with glucuronic acid and other compounds to form nontoxic metabolites. In the minor pathway, acetaminophen is oxidized by a cytochrome P450-containing enzyme into a highly reactive toxic metabolite: *N*-acetyl-*p*-benzoquinoneimine. At therapeutic doses, practically all of the drug is converted to nontoxic metabolites via the major pathway. Only a small fraction is converted into the toxic metabolite via the minor pathway. Furthermore, under normal conditions, the toxic metabolite undergoes rapid conversion to a nontoxic form; glutathione is required for the conversion. When an overdose of acetaminophen is taken, a larger than normal amount is processed via the minor pathway, and hence a large quantity of the toxic metabolite is produced. As the liver attempts to clear the metabolite, glutathione is rapidly depleted, and further detoxification stops. As a result, the toxic metabolite accumulates, causing damage to the liver (see below).

Adverse Effects

Adverse effects are extremely rare at therapeutic doses. Acetaminophen does not cause gastric ulceration or renal impairment and does not inhibit platelet aggregation. In addition, there is no evidence linking acetaminophen with Reye's syndrome. Individuals who are hypersensitive to aspirin only rarely experience cross-hypersensitivity with acetaminophen. Overdose can cause severe *liver injury* (see below).

Data from the Nurses' Health Study show an association between daily use of *acetaminophen* (500 mg or more/day) and development of *hypertension*. However, a causal relationship has not been established. Nonetheless, it would be prudent to monitor blood pressure in women who take acetaminophen daily. The mechanism by which acetaminophen might raise blood pressure in women is unknown.

Studies have shown an association between acetaminophen and development of *asthma*. However, as with hypertension, a causal relationship has not been established. In fact, regarding asthma, the association may well be the other way around. That is, people may be taking acetaminophen *because* they have respiratory symptoms, rather than having respiratory symptoms because they took acetaminophen. To prove that

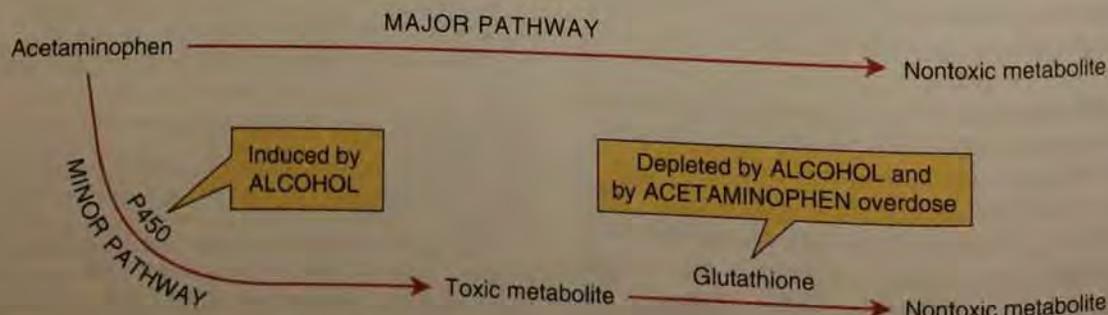


Figure 71-2 • Metabolism of acetaminophen.

acetaminophen actually does cause asthma, stronger data are needed.

Rarely, patients experience *anaphylaxis*, a severe hypersensitivity reaction characterized by breathing difficulty associated with swelling of the face, mouth, and throat. If these symptoms develop, patients should seek immediate medical help.

Drug and Vaccine Interactions

Alcohol. Regular alcohol consumption increases the risk of liver injury from acetaminophen—but only if acetaminophen dosage is excessive. Three mechanisms are involved. First, alcohol induces synthesis of the P450-containing enzyme in the minor metabolic pathway, thereby increasing production of acetaminophen's toxic metabolite (see Fig. 71-2). Second, stores of glutathione are depleted in chronic alcoholics. As a result, the liver is unable to convert the toxic metabolite to a nontoxic form (Fig. 71-2). Third, chronic alcohol abusers often have pre-existing liver damage, which renders them less able to tolerate injury from acetaminophen.

Does alcohol increase the risk of liver damage from acetaminophen taken in *therapeutic* doses? Probably not. Although *anecdotal* reports suggest that low-dose acetaminophen can cause liver injury in alcohol users, the results of a randomized controlled trial indicate otherwise: In alcoholics given therapeutic doses of acetaminophen, indices of liver damage were no greater than in alcoholics given a placebo. These data suggest that, even for people who consume alcohol in large amounts, *low* (therapeutic) doses of acetaminophen are safe. Nonetheless, some authorities recommend that, if you drink alcohol on a regular basis, you should consume no more than 2000 mg of acetaminophen a day (one-half the normal maximum).

Although therapeutic doses of acetaminophen may be safe for alcohol drinkers, *high* doses certainly are not. Accordingly, to alert the public to the potential risk of combining alcohol with acetaminophen, the FDA requires that acetaminophen labels bear the following statement: *Alcohol Warning: If you consume three or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers.*

Warfarin. There is evidence that acetaminophen may increase the risk of bleeding in patients taking warfarin (an oral anticoagulant), which is surprising. Why? Because unlike NSAIDs, acetaminophen does not suppress platelet aggregation, and hence should not promote bleeding. How, then, might acetaminophen cause a problem? The best guess is that acetaminophen may inhibit warfarin metabolism, which would cause warfarin levels to rise. Although this interaction has not been proved, caution is advised. Accordingly, for patients taking more than 1 gm of acetaminophen daily for several days, responses to warfarin should be monitored closely. Occasional use of acetaminophen is not a concern.

Vaccines. Acetaminophen and other analgesic/antipyretics can blunt the immune response to childhood vaccines. Accordingly, routine use of these drugs to prevent vaccine-associated pain and/or fever should be discouraged.

Therapeutic Uses

Acetaminophen is indicated for relief of pain and fever. Because acetaminophen is not associated with Reye's syndrome, the drug is preferred to NSAIDs for use by children suspected

of having chickenpox or influenza. Because it does not cause GI injury, acetaminophen is preferred to NSAIDs for patients with peptic ulcer disease. In addition, acetaminophen may be a safe alternative to aspirin for patients who have experienced aspirin hypersensitivity reactions. Because of its weak anti-inflammatory actions, acetaminophen is *not* useful for treating arthritis or rheumatic fever.

Acute Toxicity: Liver Damage

Overdose with acetaminophen can cause severe liver injury and death. The cause is accumulation of the toxic metabolite discussed above. In the United States, acetaminophen overdose—intentional or unintentional—is the leading cause of acute liver failure, accounting for about 50% of all cases. Risk of liver injury is increased by fasting, chronic alcohol use, and taking more than 4000 mg of acetaminophen a day.

Signs and Symptoms. The principal feature of acetaminophen overdose is *hepatic necrosis*. Severe poisoning can progress to hepatic failure, coma, and death. Early symptoms of poisoning (nausea, vomiting, diarrhea, sweating, abdominal discomfort) belie the severity of intoxication. It is not until 48 to 72 hours after drug ingestion that overt indications of hepatic injury appear.

Treatment. Liver damage can be minimized by giving *acetylcysteine* [Mucomyst, Acetadote], a specific antidote to acetaminophen. Acetylcysteine reduces injury by substituting for depleted glutathione in the reaction that converts the toxic metabolite of acetaminophen to its nontoxic form. When given within 8 to 10 hours of acetaminophen overdose, acetylcysteine is 100% effective at preventing severe liver injury. And even when administered as much as 24 hours after poisoning, it can still provide significant protection. Acetylcysteine may be administered PO or IV.

For oral therapy, acetylcysteine is supplied in solution (100 and 200 mg/mL), sold as *Mucomyst*, and should be diluted to 50 mg/mL with water, fruit juice, or a cola beverage. Conventional treatment consists of a loading dose (140 mg/kg) followed by 17 more doses (70 mg/kg) given every 4 hours for 72 hours. However, for most patients, treatment can be stopped after just 20 hours. Oral acetylcysteine has an extremely unpleasant odor and may induce vomiting.

For intravenous therapy, acetylcysteine is supplied in solution (200 mg/mL), sold as *Acetadote*, and should be diluted in 5% dextrose. Three doses are given in sequence. The first dose—150 mg/kg (in 200 mL of 5% dextrose)—is infused over 15 minutes to 1 hour. The second dose—50 mg/kg (in 500 mL of 5% dextrose)—is infused over 4 hours. And the third dose—100 mg/kg (in 1000 mL of 5% dextrose)—is infused over 16 hours. Rarely, IV acetylcysteine causes allergic reactions (rash, itching, angioedema, bronchospasm, hypotension), most often in response to the first dose. Fortunately, these reactions tend to be mild and self-limiting, and can be minimized by infusing the initial dose slowly (over a 1-hour interval).

Minimizing Risk. Risk of liver failure is very low with normal therapeutic doses (up to 4000 mg/day), except in people who drink alcohol, are undernourished, or have liver disease. Patient education can help reduce injury. Accordingly, you should:

- Inform patients about the risk of liver toxicity.
- Advise patients to consume no more than 4000 mg of acetaminophen a day, including the amount in combination prescription products (eg, Vicodin, Percocet) as well as over-the-counter (OTC) products.
- Advise patients who are undernourished (eg, owing to fasting or illness) to consume no more than 3000 mg of acetaminophen a day. Undernourished people are at risk be-

cause they have low stores of glutathione, the cofactor needed to convert the toxic metabolite of acetaminophen to a nontoxic form.

- Advise patients not to drink alcohol while taking acetaminophen.
- Advise patients who won't stop drinking alcohol (more than 3 drinks a day) to take no more than 2000 mg of acetaminophen a day.
- Advise patients with liver disease to ask their prescriber if acetaminophen is safe.

To help reduce overdosage, McNeil Consumer Healthcare, maker of the *Tylenol* brand of acetaminophen, changed the dosing recommendations on Tylenol labels. On the new labels, issued in 2011, the maximum daily dose of *Extra-Strength Tylenol* (500 mg/tablet) is stated as 3000 mg (6 tablets), and the maximum daily dose of *Regular Strength Tylenol* (325 mg/tablet) is stated as 3250 mg (10 tablets). Other manufacturers are expected to make similar changes. Please note, however, that the maximum daily dose recommended by the FDA is still 4000 mg, even though these product labels recommend a lower dose.

The FDA is also trying to help: In 2011, they requested that prescription combination analgesics (eg, Vicodin, Percocet, Lortab) contain no more than 325 mg of acetaminophen per tablet or capsule. Why was the request made? Because some prescription combinations contain acetaminophen in high doses. Vicodin ES, for example, contains 750 mg of acetaminophen, and Percocet brand products contain up to 650 mg of acetaminophen. Patients who take OTC acetaminophen along with one of these combination analgesics can easily exceed the safe daily limit. In fact, patients who just take a prescription combination product by itself can easily exceed 4000 mg of acetaminophen a day. You should note that the new limit applies only to prescription combination products. It does not apply to OTC combination products. The high-dose products will not be gone immediately. Rather, they will be phased out by 2014.

Preparations, Dosage, and Administration

Preparations. Numerous acetaminophen-containing products are on the market, including a wide assortment of fixed-dose combinations. The drug is available in rectal suppositories, solution for IV dosing, and multiple oral formulations (standard tablets, chewable tablets, effervescent granules, capsules, liquids, elixirs, and solutions). Many products are available over the counter, and many others require a prescription. Furthermore, product strengths vary widely. Why do I mention all these products? Because they create a significant risk of overdose—either from taking two or more products that both contain acetaminophen, or from taking too much of a single-ingredient product (owing to failure to carefully read the label). You should alert patients to these dangers.

Dosage and Administration. *Oral.* The recommended oral dosage for adults and children over 12 years is 325 to 650 mg every 4 to 6 hours, up to a maximum of 4000 mg/day. Dosages for younger children are based either on body weight—10 to 15 mg/kg/dose—or on age as follows:

- Up to 3 months—40 mg every 4 hours
- 4 to 11 months—80 mg every 4 hours
- 12 to 23 months—120 mg every 4 hours
- 2 to 3 years—160 mg every 4 hours
- 4 to 5 years—240 mg every 4 hours
- 6 to 8 years—320 mg every 4 to 6 hours
- 9 to 10 years—400 mg every 4 to 6 hours
- 11 years—480 mg every 4 to 6 hours
- 12 years—640 mg every 4 to 6 hours

Rectal. Acetaminophen suppositories [FeverAll, Acephen] are available in four strengths: 80, 120, 325, and 650 mg. The recommended dosage for adults and children over 12 years is 650 mg every 4 to 6 hours, up to a maximum of 3900 mg/day. Dosages for younger children vary with age as follows:

- 3 to 11 months—80 mg every 6 hours
- 12 to 36 months—80 mg every 4 hours
- 3 to 6 years—120 mg every 4 to 6 hours
- 6 to 12 years—325 mg every 4 to 6 hours

Intravenous. Intravenous acetaminophen [Ofirmev] is indicated for fever and mild to moderate pain (when used alone), and for moderate to severe pain (when combined with an opioid). Dosages are as follows:

- Adults and children 13 years and older who weigh more than 50 kg—1000 mg every 6 hours or 650 mg every 4 hours. Daily maximum is 4000 mg.
- Children 2 to 12 years old, and children 13 years and older who weigh less than 50 kg—15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours. Daily maximum is 75 mg/kg.

AHA STATEMENT ON COX INHIBITORS IN CHRONIC PAIN

Because most COX inhibitors—and especially COX-2 inhibitors—increase the risk of MI and stroke, the American Heart Association (AHA) recommends a stepped-care approach to their use, as discussed in a 2007 article titled *Use of Nonsteroidal Anti-inflammatory Drugs: An Update for Clinicians: A Scientific Statement from the American Heart Association*. Recommendations in the article apply specifically to managing musculoskeletal pain in patients with or at high risk of cardiovascular disease. However, the recommendations may also apply to patients who lack documented cardiovascular risk. The approach has four basic steps:

- Step 1.** Begin with nondrug measures. Options include physical therapy, exercise, weight loss, orthotics, and application of heat or cold.
- Step 2.** If nondrug measures don't work, initiate drug therapy using *acetaminophen* or *aspirin*, which do not increase cardiovascular risk. If these drugs can't control pain, an opioid or tramadol can be tried, but only short term.
- Step 3.** If step 2 drugs are ineffective or intolerable, try other nonselective NSAIDs, such as naproxen, ibuprofen, or a nonacetylated salicylate (eg, magnesium salicylate).
- Step 4.** As a *last resort*, try a selective COX-2 inhibitor (eg, celecoxib). Of all the NSAIDs, COX-2 inhibitors pose the greatest risk of cardiovascular harm, and hence are last-choice drugs for chronic pain.

Whenever these drugs are employed, patients should use the lowest effective dosage for the shortest time required. During steps 2, 3, and 4, if the patient is considered at high risk of a thrombotic event, low-dose aspirin (81 mg/day) plus a proton pump inhibitor (PPI) should be *added* to the regimen (except, of course, if high-dose aspirin is already in use).

KEY POINTS

- All of the drugs discussed in this chapter inhibit cyclooxygenase (COX), an enzyme that converts arachidonic acid into prostanoids (prostaglandins and related compounds).
- Cyclooxygenase has two forms: COX-1 and COX-2.
- The cyclooxygenase inhibitors fall into two major groups: nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (in a group by itself).
- The NSAIDs can be subdivided into two groups: (1) first-generation NSAIDs, which inhibit COX-1 and COX-2, and (2) second-generation NSAIDs, which selectively inhibit COX-2.
- Inhibition of COX-1 can cause gastric ulceration, renal impairment, and bleeding.
- Inhibition of COX-2 suppresses inflammation, pain, and fever, but can also cause renal impairment.
- Aspirin is the prototype of the first-generation NSAIDs.
- Aspirin has four major beneficial actions: suppression of inflammation, relief of mild to moderate pain, reduction of fever, and prevention of MI and stroke (secondary to suppressing platelet aggregation). All of these benefits result from inhibiting COX-2, except for prevention of MI and stroke, which results from inhibiting COX-1 (in platelets).
- Because aspirin inhibits COX-1 as well as COX-2, it cannot cause beneficial effects without posing a risk of gastric ulceration, bleeding, and renal impairment.
- Aspirin causes *irreversible* inhibition of cyclooxygenase. As a result, the effects of aspirin persist until cells can make more cyclooxygenase.
- Because platelets are unable to synthesize new cyclooxygenase, the antiplatelet effects of a single dose of aspirin persist for the life of the platelet (about 8 days).
- Anti-inflammatory doses of aspirin are much higher than analgesic or antipyretic doses.
- Aspirin is a useful drug for rheumatoid arthritis and other chronic inflammatory conditions.
- Aspirin is a very effective analgesic. It can be as effective as opioids for some types of postoperative pain.
- The risk of aspirin-induced gastric ulcers can be reduced by (1) testing for and eliminating *H. pylori* prior to starting therapy, and by (2) giving a proton pump inhibitor.
- Because of its antiplatelet actions, aspirin can protect against MI, stroke, and other thrombotic events.
- When taken for *primary prevention*, aspirin can reduce the risk of a first MI in men, and the risk of a first ischemic stroke in women.
- Ibuprofen, naproxen, and other nonaspirin NSAIDs can antagonize the antiplatelet actions of aspirin, and can thereby decrease protection against MI and stroke. To minimize this interaction, patients should take aspirin about 2 hours before other NSAIDs.
- Because of its antiplatelet actions, *high-dose* aspirin should be discontinued 1 week prior to elective surgery or parturition. In most cases, *low-dose* aspirin taken to protect against thrombosis can be continued.
- Because of its antiplatelet actions, aspirin can increase the risk of bleeding in patients taking warfarin, heparin, and other anticoagulants.
- By impairing renal function, aspirin can cause sodium and water retention, edema, and elevation of blood pressure. However, adverse outcomes are likely only in patients with additional risk factors: advanced age, pre-existing renal dysfunction, hypovolemia, hypertension, hepatic cirrhosis, or heart failure. Long-term aspirin use may lead to renal papillary necrosis and other forms of renal injury.
- Because of the risk of Reye's syndrome, aspirin should be avoided by children with influenza or chickenpox.
- Use of aspirin during labor and delivery can suppress spontaneous uterine contractions, induce premature closure of the ductus arteriosus, and intensify uterine bleeding.
- Although rarely fatal in adults, aspirin poisoning may prove lethal in children.
- Aspirin can cause hypersensitivity reactions, especially in adults with asthma, rhinitis, and nasal polyps. Severe reactions (anaphylaxis) can be treated with epinephrine.
- All of the nonaspirin first-generation NSAIDs are much like aspirin itself. All of these drugs inhibit COX-1 and COX-2; they all can suppress inflammation, pain, and fever; and they all can cause gastric ulceration, renal impairment, and bleeding.
- The nonaspirin NSAIDs differ from aspirin in three important ways. First, nonaspirin NSAIDs cause *reversible* inhibition of COX, and hence their effects decline as soon as their blood levels decline. Second, although they can suppress platelet aggregation, these drugs are not used to prevent MI and stroke. Third, these drugs actually *increase* the risk of MI and stroke, and hence should be used in the lowest effective dosage for the shortest possible time.
- By inhibiting COX-2, the second-generation NSAIDs (coxibs) can suppress inflammation, pain, and fever.
- By sparing COX-1, the coxibs *may* cause less gastric ulceration than the first-generation NSAIDs.
- Coxibs do not inhibit platelet aggregation, and hence do not pose a risk of bleeding.
- Like all first-generation NSAIDs (except aspirin), coxibs pose a risk of MI and stroke.
- Currently, celecoxib [Celebrex] is the only coxib on the market.
- Acetaminophen reduces pain and fever, but not inflammation.
- Acetaminophen inhibits prostaglandin synthesis in the CNS, but not in the periphery. As a result, acetaminophen differs from the NSAIDs in four ways: it (1) lacks anti-inflammatory actions, (2) does not cause gastric ulceration, (3) does not suppress platelet aggregation, and (4) does not impair renal function.
- Hepatic necrosis from acetaminophen overdose results from accumulation of a toxic metabolite. Risk is increased by undernourishment, alcohol, and pre-existing liver disease.
- Chronic alcohol consumption increases the risk of liver damage from acetaminophen *overdose*, but probably not from therapeutic doses. Two major mechanisms are involved: induction of cytochrome P450 (which increases

production of the toxic metabolite of acetaminophen) and depletion of glutathione stores (which reduces detoxification of the metabolite).

- Acetaminophen may increase the risk of warfarin-induced bleeding by inhibiting the metabolism of warfarin.
- Acetaminophen overdose is treated with PO or IV acetylcysteine, a drug that substitutes for depleted glutathione

in the reaction that clears the toxic metabolite of acetaminophen.

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Summary of Major Nursing Implications*

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

First-Generation NSAIDs

Aspirin
Diclofenac
Diflunisal
Etorolac
Fenoprofen
Flurbiprofen
Ibuprofen
Indomethacin
Ketoprofen
Ketorolac
Magnesium salicylate
Meclofenamate
Mefenamic acid
Meloxicam
Nabumetone
Naproxen
Oxaprozin
Piroxicam
Salsalate
Sodium salicylate
Sulindac
Tolmetin

Second-Generation NSAIDs (Coxibs)

Celecoxib

Except where noted, the nursing implications summarized below apply to aspirin and all other NSAIDs.

Preadministration Assessment

Therapeutic Goal

Major indications for the NSAIDs are inflammatory disorders (eg, rheumatoid arthritis, osteoarthritis), mild to moderate pain, fever, and primary dysmenorrhea. In addition, *aspirin* is used to prevent MI and stroke. Applications of individual NSAIDs are summarized in Table 71-5.

Identifying High-Risk Patients

NSAIDs are *contraindicated* for patients with a history of severe NSAID hypersensitivity.

NSAIDs (especially aspirin) are *contraindicated* for children with chickenpox or influenza.

Celecoxib is contraindicated for patients with sulfa allergy.

NSAIDs should be used with *extreme caution* by pregnant women and patients with peptic ulcer disease and bleeding disorders (eg, hemophilia, vitamin K deficiency, hypoprothrombinemia) and patients taking anticoagulants (eg, warfarin, heparin), glucocorticoids, ACE inhibitors, or ARBs. *Caution* is also needed when treating elderly patients and patients with heart failure, angina pectoris, history of MI, hypertension, hypovolemia, hepatic cirrhosis, renal dysfunction, asthma, hay fever, chronic urticaria, nasal polyps, or a history of alcoholism or heavy smoking.

Implementation: Administration

Routes

Oral. All NSAIDs.

Topical. Diclofenac (patch, solution, and gel).

Intranasal. Ketorolac.

Intramuscular. Ketorolac.

Intravenous. Ibuprofen, ketorolac.

Rectal Suppository. Aspirin, indomethacin.

Administration

- Advise patients to take oral NSAIDs with food, milk, or a glass of water to reduce gastric upset.
- Warn patients not to crush or chew enteric-coated or sustained-release formulations.
- Advise patients to discard aspirin preparations that smell like vinegar.
- Advise patients using topical diclofenac to apply the gel 4 times a day and to apply a new patch twice a day.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Gastrointestinal Effects. NSAIDs frequently cause mild GI reactions (dyspepsia, abdominal pain, nausea). To minimize GI effects, advise patients to take NSAIDs with food, milk, or a glass of water. Long-term therapy, even at moderate doses, can cause gastric ulceration, perforation, and hemorrhage. Several measures can reduce risk:

- Avoid NSAIDs in patients with a recent history of peptic ulcer disease and use NSAIDs with caution in patients with

*Patient education information is highlighted as **blue text**.

Summary of Major Nursing Implications*—cont'd

other risk factors (advanced age, previous intolerance to NSAIDs, heavy cigarette smoking, history of alcoholism). Test for and eliminate *H. pylori* prior to starting long-term therapy.

Give a proton pump inhibitor for prophylaxis in high-risk patients.

Use celecoxib instead of a traditional NSAID in high-risk patients.

Warn patients not to consume alcohol.

Instruct patients to notify the prescriber if gastric irritation is severe or persistent.

Manage ulcers by giving an antiulcer medication (eg, H₂-receptor antagonist, proton pump inhibitor).

Bleeding. Aspirin promotes bleeding by causing irreversible suppression of platelet aggregation. High-dose aspirin should be discontinued 7 to 10 days prior to elective surgery or anticipated date of parturition, but need not be stopped prior to minor dental, dermatologic, or cataract surgeries. Discontinuation of low-dose aspirin depends on circumstances. Specifically, low-dose aspirin should be discontinued in

- Patients considered at low risk of a cardiovascular (CV) event who require noncardiac surgery. Dosing should stop 7 to 10 days before surgery, and can resume 24 hours after the procedure.
- Patients undergoing intracranial surgery.

Conversely, low-dose aspirin should be continued in

- Patients undergoing coronary artery bypass surgery.
- Patients facing surgery within 6 weeks of receiving a bare metal coronary stent or within 12 months of receiving a drug-eluting coronary stent.
- Patients considered at high risk of a CV event who require noncardiac surgery or a percutaneous coronary intervention.
- Patients undergoing cataract surgery, minor dental procedures, or minor dermatologic procedures.

Exercise caution when using aspirin in conjunction with warfarin, heparin, and other anticoagulants. Avoid aspirin in patients with bleeding disorders (eg, hemophilia, vitamin K deficiency, hypoprothrombinemia).

Discontinue *ibuprofen* and other nonaspirin NSAIDs five half-lives prior to elective surgery and parturition.

The nonacetylated salicylates—sodium salicylate, magnesium salicylate, and salsalate—have minimal effects on platelet aggregation. Accordingly, these drugs are preferred for use in surgical patients and patients with bleeding disorders.

The risk of bleeding can be minimized by using celecoxib instead of a traditional NSAID.

Renal Impairment. NSAIDs can cause acute renal insufficiency in elderly patients and in patients with heart failure, hypovolemia, hepatic cirrhosis, or pre-existing renal dysfunction. Keep NSAID dosages as low as possible in these patients. Monitor high-risk patients for indications of renal im-

pairment (reduced urine output, weight gain despite diuretic therapy, rapid elevation of serum creatinine and blood urea nitrogen). Discontinue NSAIDs if these signs occur.

Prolonged NSAID therapy can cause renal papillary necrosis. Avoid prolonged NSAID use whenever possible.

Myocardial Infarction and Stroke. Nonaspirin NSAIDs—but not aspirin itself—increase the risk of MI and stroke. To minimize cardiovascular risk, nonaspirin NSAIDs should be used in the lowest effective dosage for the shortest time needed, and they should not be used before CABG surgery or for 14 days after. In patients with cardiovascular risk factors, use all NSAIDs (except aspirin) with caution, and use COX-2 inhibitors only as a last resort.

Hypersensitivity Reactions. Hypersensitivity reactions are most likely in adults with a history of asthma, rhinitis, and nasal polyps. Use NSAIDs with caution in these patients. If a severe hypersensitivity reaction occurs, parenteral epinephrine is the treatment of choice. As a rule, avoid NSAIDs in patients with a history of NSAID hypersensitivity. However, if an NSAID-like drug *must* be used, four are probably safe: celecoxib, salsalate, meloxicam (in low doses), and acetaminophen.

Salicylism. Aspirin and other salicylates can cause salicylism. Educate patients about manifestations of salicylism (tinnitus, sweating, headache, dizziness), and advise them to notify the prescriber if these occur. Aspirin should be withheld until symptoms subside, after which therapy can resume but at a slightly reduced dosage.

Reye's Syndrome. Use of NSAIDs, especially aspirin, by children with chickenpox or influenza may precipitate Reye's syndrome. Advise parents to avoid aspirin in these children and to use acetaminophen instead.

Use in Pregnancy. NSAIDs can cause maternal anemia and can prolong labor. In addition, they can promote premature closure of the ductus arteriosus. NSAIDs should be avoided by expectant mothers unless the potential benefits outweigh the risks. If NSAIDs are employed during pregnancy, they should be discontinued at least five half-lives before the anticipated day of delivery.

Liver Injury. *Diclofenac* can cause severe liver injury. Patients should receive periodic liver function tests. Inform patients about signs of liver damage (eg, jaundice, fatigue, nausea), and instruct them to report these immediately. If liver injury is diagnosed, diclofenac should be discontinued.

Sulfonamide Allergy. *Celecoxib* can cause severe allergic reactions in patients with sulfa allergy, and hence must not be given to these people.

Erectile Dysfunction. Regular NSAID use is associated with an increased risk of ED, although a causal relationship has not been established.

Minimizing Adverse Interactions

Anticoagulants. NSAIDs can increase the risk of bleeding in patients taking warfarin, heparin, and other anticoagulants. Monitor patients for signs of bleeding.

Glucocorticoids. Glucocorticoids increase the risk of gastric ulceration in patients taking NSAIDs. Prophylactic

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

therapy with a proton pump inhibitor can decrease the risk.

Alcohol. Alcohol increases the risk of gastric ulceration from NSAIDs. Exercise caution.

Aspirin-NSAID Interactions. Ibuprofen, naproxen, and other nonaspirin NSAIDs can antagonize the antiplatelet actions of aspirin, and can thereby decrease protection against MI and stroke. **Advise patients to take aspirin about 2 hours before taking another NSAID.**

ACE Inhibitors and ARBs. These drugs increase the risk of acute renal failure in patients taking NSAIDs. If possible, avoid all NSAIDs—except low-dose aspirin—in patients taking ACE inhibitors or ARBs.

Vaccines. NSAIDs may blunt the immune response to vaccines. **Advise parents to avoid routine use of NSAIDs to prevent vaccine-associated fever and pain.**

Managing Aspirin Toxicity

Aspirin poisoning is an acute medical emergency that requires hospitalization. Treatment is largely supportive and consists of external cooling (eg, sponging with tepid water), infusion of fluids (to correct dehydration and electrolyte loss), infusion of bicarbonate (to reverse acidosis and promote renal excretion of salicylates), and mechanical ventilation (if respiration is severely depressed). Absorption of aspirin can be reduced by gastric lavage and by giving activated charcoal. If necessary, hemodialysis or peritoneal dialysis can accelerate salicylate removal.

ACETAMINOPHEN

Preadministration Assessment

Therapeutic Goal

Acetaminophen is indicated for pain relief and lowering fever. The drug is preferred to NSAIDs for use in children with chickenpox or influenza, and for all patients with peptic ulcer disease.

Identifying High-Risk Patients

Use with *caution* in chronic alcohol abusers, patients who consume moderate amounts of alcohol daily, and patients taking warfarin.

Implementation: Administration

Routes

Oral, rectal, intravenous.

Administration

Do not exceed recommended doses.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Acetaminophen is largely devoid of significant adverse effects at usual therapeutic doses, except possibly in people who routinely consume alcohol. Overdose can cause liver damage (see below).

Hypertension. Taking at least 500 mg of acetaminophen per day is associated with an increased risk of hypertension in *women*, although a direct causal relationship has not been established. Nonetheless, prudence dictates monitoring blood pressure in women who take acetaminophen each day.

Asthma. Acetaminophen is associated with an increased risk of asthma, although a causal relationship has not been established.

Anaphylaxis. Rarely, acetaminophen causes anaphylaxis. **Inform patients about symptoms—breathing difficulty associated with swelling of the face, mouth, and throat—and advise them to seek immediate medical help if these develop.**

Liver Damage. Overdose can cause hepatic necrosis. Risk is increased by consuming high doses (more than 4000 mg/day), as well as by undernourishment, alcohol consumption, and pre-existing liver disease. To reduce risk:

- **Inform patients about the risk of liver injury.**
- **Advise patients to consume no more than 4000 mg of acetaminophen a day, including the amount in combination prescription products (eg, Vicodin, Percocet) as well as OTC products.**
- **Advise patients who are undernourished (eg, owing to fasting or illness) to consume no more than 3000 mg of acetaminophen a day.**
- **Advise patients not to drink alcohol while taking acetaminophen.**
- **Advise patients who won't stop drinking alcohol (more than 3 drinks a day) to take no more than 2000 mg of acetaminophen a day.**
- **Advise patients with liver disease to ask the prescriber if acetaminophen is safe.**

Acetylcysteine—given PO or IV—is a specific antidote to acetaminophen overdose. Oral acetylcysteine has an extremely unpleasant odor and may induce vomiting. If vomiting interferes with oral dosing, there are two options: give acetylcysteine IV or through an oroduodenal tube.

Minimizing Adverse Interactions

Alcohol. Chronic alcohol consumption increases the risk of liver injury from *excessive* doses of acetaminophen, but probably not from *therapeutic* doses. **Nonetheless, advise patients who consume 3 or more drinks a day that, to be safe, they should consume no more than 2000 mg of acetaminophen a day (one-half the normal daily maximum).**

Warfarin. Taking acetaminophen for several days may increase the risk of bleeding in patients on warfarin. Monitor warfarin effects closely.

Vaccines. Acetaminophen may blunt the immune response to vaccines. **Advise parents to avoid routine use of acetaminophen to prevent vaccine-associated fever and pain.**

*Patient education information is highlighted as blue text.

Glucocorticoids in Nonendocrine Disorders

Review of Glucocorticoid Physiology

Physiologic Effects

Control of Synthesis and Secretion

Pharmacology of the Glucocorticoids

Molecular Mechanism of Action

Pharmacologic Effects

Pharmacokinetics

Therapeutic Uses in Nonendocrine Disorders

Adverse Effects

Use in Pregnancy and Lactation

Drug Interactions

Summary of Precautions and Contraindications

Adrenal Suppression

Preparations and Routes of Administration

Dosage

The glucocorticoid drugs (eg, cortisone, prednisone), also known as *corticosteroids*, are nearly identical to the glucose-regulating steroids produced by the adrenal cortex. Accordingly, we can look on the glucocorticoids as having two kinds of effects: physiologic and pharmacologic. *Physiologic* effects, such as modulation of glucose metabolism, are elicited by *low* doses of glucocorticoids. In contrast, *pharmacologic* effects (eg, suppression of inflammation) require *high* doses.

As implied by the chapter title, glucocorticoids have both endocrine and nonendocrine applications. In low (physiologic) doses, glucocorticoids are used to treat adrenocortical insufficiency. In high (pharmacologic) doses, glucocorticoids are used to treat inflammatory disorders (eg, asthma, rheumatoid arthritis) and certain cancers and to suppress immune responses in organ transplant recipients. The endocrine applications of the glucocorticoids are discussed in Chapter 60. Nonendocrine uses are discussed here.

Toxicity of the glucocorticoids can be severe and is determined by the pattern of drug use. Glucocorticoids are devoid of toxicity when used in physiologic doses. However, when taken in pharmacologic doses, especially for extended periods, glucocorticoids can cause an array of serious adverse effects.

All of the glucocorticoid drugs can produce the same spectrum of therapeutic effects. Differences among individual agents pertain to time course and side effects. Because the similarities among these drugs are much more striking than the differences, we will not focus on a prototypic agent. Instead, we will discuss the glucocorticoids as a group.

REVIEW OF GLUCOCORTICOID PHYSIOLOGY

Physiologic Effects

Physiologic responses can be elicited with low doses of glucocorticoids. At higher doses, these effects are simply more intense. When glucocorticoids are used to treat nonendocrine disorders, physiologic responses occur as side effects. Physiologic effects are discussed at length in Chapter 60, and hence discussion here is brief.

Metabolic Effects. Glucocorticoids influence the metabolism of carbohydrates, proteins, and fats. The principal effect on carbohydrate metabolism is elevation of blood glucose. Glucocorticoids do this by promoting synthesis of glucose from amino acids, reducing peripheral glucose utilization, and reducing glucose uptake by muscle and adipose tissue. Glucocorticoids also promote storage of glucose in the form of glycogen.

Glucocorticoids have a negative impact on protein metabolism. Specifically, these drugs suppress synthesis of proteins from amino acids and divert amino acids for production of glucose. These actions can reduce muscle mass, decrease the protein matrix of bone, and cause thinning of the skin. Nitrogen balance becomes negative.

The most consistent effect of glucocorticoids on fat metabolism is stimulation of lipolysis (fat breakdown). Long-term, high-dose therapy can cause fat redistribution, resulting in the potbelly, “moon face,” and “buffalo hump” that characterize Cushing’s syndrome.

Cardiovascular Effects. Glucocorticoids are required to maintain the functional integrity of the vascular system. When levels of endogenous glucocorticoids are low, capillaries become more permeable, vasoconstriction is suppressed, and blood pressure falls. Glucocorticoids *increase* the number of circulating red blood cells and polymorphonuclear leukocytes, and *decrease* counts of lymphocytes, eosinophils, basophils, and monocytes.

Effects During Stress. At times of physiologic stress (eg, surgery, infection, trauma, hypovolemia), the adrenals secrete large quantities of glucocorticoids and epinephrine. Working together, these hormones help maintain blood pressure and blood glucose levels. If glucocorticoid release is insufficient, hypotension and hypoglycemia will occur. If the stress is especially severe, glucocorticoid insufficiency can result in circulatory failure and death.

Effects on Water and Electrolytes. To varying degrees, individual glucocorticoids can exert actions like those of aldosterone, the major mineralocorticoid released by the adrenals. Accordingly, glucocorticoids can act on the kidney to promote retention of sodium and water while increasing uri-

TABLE 72-1 ■ Systemic Glucocorticoids: Half-Lives, Relative Potencies, and Equivalent Doses

Drug	Biologic Half-Life (hr)	Relative Mineralocorticoid Potency*	Relative Glucocorticoid (Anti-inflammatory) Potency†	Equivalent Anti-inflammatory Dose (mg)‡
Short Acting				
Cortisone	8–12	2	0.8	25
Hydrocortisone	8–12	2	1	20
Intermediate Acting				
Prednisone	18–36	1	4	5
Prednisolone	18–36	1	4	5
Methylprednisolone	18–36	0	5	4
Triamcinolone	18–36	0	5	4
Long Acting				
Betamethasone	36–54	0	20–30	0.75
Dexamethasone	36–54	0	20–30	0.75

*Relative mineralocorticoid activity (sodium and water retention; potassium depletion): 0 = very low, 1 = moderate, 2 = high.

†Glucocorticoid potency values are relative to the potency of hydrocortisone.

‡Approximate *oral* or *intravenous* dose needed to produce equivalent anti-inflammatory effects.

nary excretion of potassium. The net result is hypernatremia, hypokalemia, and edema. Fortunately, most of the glucocorticoids employed as drugs have very low mineralocorticoid activity (Table 72-1).

Respiratory System Effects in Neonates. During labor and delivery, the adrenals of the full-term infant release a burst of glucocorticoids, which act to hasten maturation of the lungs. In the preterm infant, production of glucocorticoids is low, resulting in a high incidence of respiratory distress syndrome.

Control of Synthesis and Secretion

Synthesis and release of glucocorticoids are regulated by a negative feedback loop. The principal components of the loop are the hypothalamus, anterior pituitary, and adrenal cortex (Fig. 72-1). The loop is turned on when stress or some other stimulus from the central nervous system acts on the hypothalamus to cause release of corticotropin-releasing hormone (CRH). CRH then stimulates the pituitary to release adrenocorticotropic hormone (ACTH), which in turn acts on the adrenal cortex to promote synthesis and release of cortisol (the principal endogenous glucocorticoid). Cortisol has two basic effects: first, it stimulates physiologic responses; second, it acts on the hypothalamus and pituitary to suppress further release of CRH and ACTH. By inhibiting release of CRH and ACTH, cortisol suppresses its own production. As a result, this negative feedback loop keeps glucocorticoid levels within an appropriate range. When glucocorticoids are administered chronically in large doses, the feedback loop remains continuously suppressed. As discussed later, persistent suppression can be dangerous.

PHARMACOLOGY OF THE GLUCOCORTICOIDS

Molecular Mechanism of Action

Mechanistically, glucocorticoids differ from most drugs in two ways: (1) glucocorticoid receptors are located *inside* the cell, rather than on the cell surface; and (2) glucocorticoids modulate the production of regulatory proteins, rather than the activity of signaling pathways.

Here's how they do it. First, glucocorticoids penetrate the cell membrane, and then bind with receptors in the *cytoplasm*, thereby converting the receptor from an inactive form to an active form. Next, the receptor-steroid complex migrates to the cell *nucleus*, where it binds to chromatin in DNA, thereby altering the activity of target genes. In most cases, activity of the target gene is increased, causing increased transcription of messenger RNA molecules that code for specific regulatory proteins. However, in some cases, activity of the target gene is suppressed, and hence synthesis of certain regulatory proteins declines.

Pharmacologic Effects

When administered in the high doses employed to treat nonendocrine disorders, glucocorticoids produce anti-inflammatory and immunosuppressive effects—effects not seen at physiologic doses. Of course, these high doses also produce the physiologic effects seen at low doses.

Effects on Metabolism and Electrolytes

The effects of high-dose therapy on metabolism and electrolytes are like those seen with physiologic doses—but are more intense. Hence, with high doses, glucose levels rise, protein

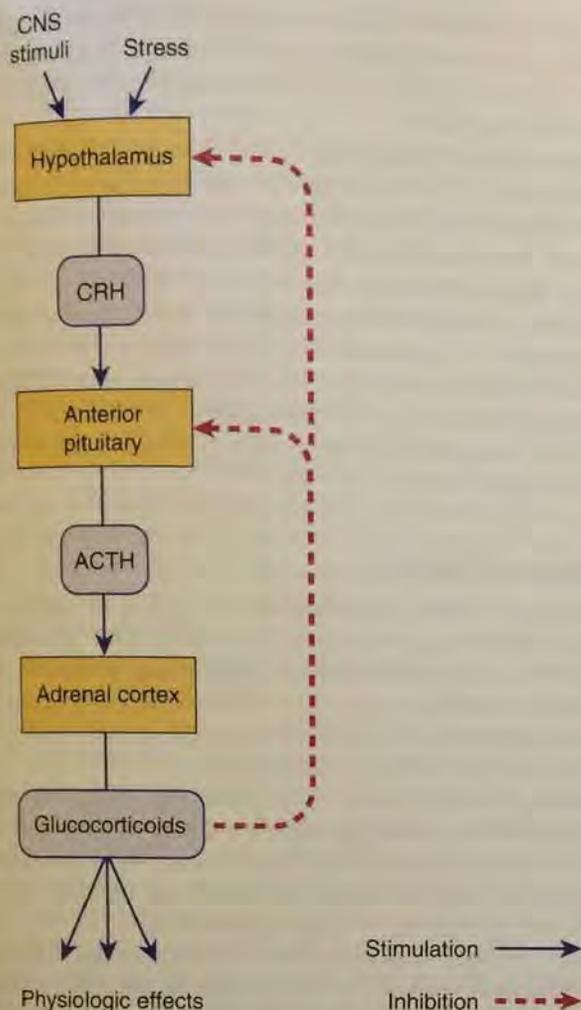


Figure 72-1 • Feedback regulation of glucocorticoid synthesis and secretion.

(ACTH = adrenocorticotrophic hormone, CNS = central nervous system, CRH = corticotropin-releasing hormone.)

synthesis is suppressed, and fat deposits are mobilized. As noted, most glucocorticoids have very little mineralocorticoid activity. Accordingly, these drugs do not usually induce significant sodium retention or potassium loss. However, these effects do occur in some patients and can be hazardous. In all patients, high-dose therapy can inhibit intestinal absorption of calcium, an effect not seen at physiologic doses.

Anti-inflammatory and Immunosuppressant Effects

The major clinical applications of the glucocorticoids stem from their ability to suppress immune responses and inflammation. Effects on the immune system and inflammation are interrelated, and hence we will consider them together.

Before discussing the actions of glucocorticoids, we need to review the process of inflammation. Characteristic symptoms of inflammation are pain, swelling, redness, and warmth. These are initiated by chemical mediators (prostaglandins, histamine, leukotrienes) and are amplified by the actions of lymphocytes and phagocytic cells (neutrophils and macrophages). Prostaglandins and histamine promote several symptoms of inflammation—swelling, redness, and warmth—by

causing vasodilation and increasing capillary permeability. Prostaglandins and histamine contribute to pain: histamine stimulates pain receptors directly; prostaglandins sensitize pain receptors to stimulation by histamine and other mediators. Neutrophils and macrophages heighten inflammation by releasing lysosomal enzymes, which cause tissue injury. Lymphocytes, which are important elements of the immune system, intensify inflammation by (1) causing direct cell injury and (2) promoting formation of antibodies that help perpetuate the inflammatory response.

Glucocorticoids act through several mechanisms to interrupt the inflammatory processes. These drugs can inhibit synthesis of chemical mediators (prostaglandins, leukotrienes, histamine) and can thereby reduce swelling, warmth, redness, and pain. In addition, they suppress infiltration of phagocytes. Hence, damage from lysosomal enzymes is averted. Lastly, glucocorticoids suppress proliferation of lymphocytes, and thereby reduce the immune component of inflammation.

It is important to appreciate that the mechanisms by which glucocorticoids suppress inflammation are more diverse than the mechanisms by which nonsteroidal anti-inflammatory drugs (NSAIDs) act. As discussed in Chapter 71, NSAIDs suppress inflammation primarily by inhibiting prostaglandin production. The glucocorticoids share this mechanism and act in other ways too. Because they act by multiple mechanisms, glucocorticoids have much greater anti-inflammatory effects than do NSAIDs.

Pharmacokinetics

Absorption. The rate of glucocorticoid absorption depends on the route of administration and the specific glucocorticoid. With oral administration, absorption of all glucocorticoids is rapid and nearly complete. Following IM injection, absorption is rapid with two types of glucocorticoid esters (sodium phosphates and sodium succinates) and relatively slow with other derivatives (eg, acetates, acetonides). Absorption from local sites of injection (eg, intra-articular, intrasynovial) is slower than from IM sites.

Duration of Action. Duration depends on dosage, route, and drug solubility. For glucocorticoids administered orally or IV, duration is determined largely by biologic half-life (see Table 72-1). With IM administration, duration is a function of water solubility: Highly soluble preparations have a shorter duration than less soluble preparations. For locally administered glucocorticoids, duration is determined by solubility and by the specific site of administration.

Metabolism and Excretion. Glucocorticoids are metabolized primarily by the liver. As a rule, the resulting metabolites are inactive. Excretion of metabolites is renal.

Therapeutic Uses in Nonendocrine Disorders

Glucocorticoids are used to treat endocrine disorders and nonendocrine disorders. Endocrine disorders (eg, Addison's disease) can be managed with low-dose therapy and are considered in Chapter 60. Nonendocrine applications, which require much higher doses, are discussed here. Because prolonged, high-dose therapy can produce serious adverse effects, the potential benefits of treatment must be weighed carefully against the very real risks.

Rheumatoid Arthritis. Glucocorticoids are indicated for adjunctive treatment of acute exacerbations of rheumatoid arthritis. These drugs can reduce inflammation and pain, but do not alter the course of the disease. Because of the risk of serious complications, prolonged systemic use should be avoided.

When arthritis is limited to just a few joints, intra-articular injections should be employed. Local injections can be highly effective and cause less toxicity than systemic therapy. Frequently, reductions in pain and inflammation may be so dramatic as to prompt vigorous use of joints that were previously immobile. Since excessive use of diseased joints can cause injury, patients should be warned against overactivity, even though symptoms have eased.

The use of glucocorticoids in rheumatoid arthritis is discussed further in Chapter 73.

Systemic Lupus Erythematosus. Systemic lupus erythematosus (SLE) is a chronic disease similar in many ways to rheumatoid arthritis. However, in SLE, inflammation is not limited to joints. Rather, it occurs throughout the body. Symptoms frequently include pleuritis, pericarditis, and nephritis. A severe episode can be fatal. Fortunately, manifestations of SLE can usually be controlled with prompt and aggressive glucocorticoid therapy.

Inflammatory Bowel Disease. Glucocorticoids are used to treat severe cases of ulcerative colitis and Crohn's disease, the two most common forms of inflammatory bowel disease. Administration may be oral or intravenous. Glucocorticoid therapy of these disorders is considered further in Chapter 80.

Miscellaneous Inflammatory Disorders. Glucocorticoids are useful in a variety of inflammatory disorders in addition to those discussed above. Conditions that respond include *bursitis*, *tendinitis*, *synovitis*, *osteoarthritis*, *gouty arthritis*, and *inflammatory disorders of the eye*.

Allergic Conditions. Glucocorticoids can control symptoms of allergic reactions. Responsive conditions include allergic rhinitis (see Chapter 77), bee stings, and drug-induced allergies. Because glucocorticoid responses are delayed, these drugs have little value as acute therapy for severe allergic reactions (eg, anaphylaxis). For life-threatening allergic reactions, epinephrine is the treatment of choice.

Asthma. Glucocorticoids are the most effective anti-asthma agents available. For treatment of asthma, they may be administered orally or by inhalation. Adverse effects are minimal with inhaled glucocorticoids. In contrast, oral therapy can cause serious toxicity, and hence should be reserved for patients who have failed to respond to safer treatments (eg, inhaled glucocorticoids, inhaled β_2 -adrenergic agonists, inhaled cromolyn sodium). The use of glucocorticoids in asthma is discussed at length in Chapter 76.

Dermatologic Disorders. Glucocorticoids are beneficial in a wide variety of skin diseases, including pemphigus, psoriasis, mycosis fungoides, seborrheic dermatitis, contact dermatitis, and exfoliative dermatitis. For mild disease, topical administration is usually adequate. For severe disorders, systemic therapy may be needed. It should be noted that topical glucocorticoids can be absorbed in amounts sufficient to produce systemic toxicity. Topical therapy is discussed further in Chapter 105.

Neoplasms. Glucocorticoids are used in conjunction with other anticancer agents to treat acute lymphocytic leukemia, Hodgkin's disease, and non-Hodgkin's lymphomas. Benefits derive from the direct toxicity of glucocorticoids to malignant lymphocytes. Treatment kills lymphoid cells and causes regression of lymphatic tissue. The use of glucocorticoids to treat cancers is discussed further in Chapter 103.

Suppression of Allograft Rejection. Glucocorticoids, together with other immunosuppressant agents, are used to

prevent rejection of organ transplants. Glucocorticoids are initiated at the time of surgery and continued indefinitely. The use of glucocorticoids for immunosuppression is discussed further in Chapter 69.

Prevention of Respiratory Distress Syndrome in Preterm Infants. Preterm infants are at high risk of respiratory distress syndrome. Why? Because their adrenals cannot produce the glucocorticoids needed for lung maturation. When preterm delivery is imminent, injecting the mother with glucocorticoids (usually dexamethasone or betamethasone) reduces the risk of neonatal respiratory distress. Steroids may also reduce the incidence of intraventricular hemorrhage and necrotizing enterocolitis (inflammation of the small intestine and colon). Antenatal use of glucocorticoids is discussed further in Chapter 107.

Adverse Effects

The adverse effects discussed below occur in response to *pharmacologic* doses of glucocorticoids. The intensity of these effects increases with dosage size and treatment duration. These toxicities are not seen when dosage is physiologic. Furthermore, most are not seen when treatment is brief (a few days or less), even when doses are high.

Adrenal Insufficiency. Pharmacologic doses of glucocorticoids can suppress production of glucocorticoids by the adrenals, resulting in adrenal insufficiency. The mechanism, consequences, and management of adrenal insufficiency are discussed below under *Adrenal Suppression*.

Osteoporosis. Development. Osteoporosis with resultant fractures is a frequent and serious complication of prolonged glucocorticoid therapy. Patients taking the equivalent of 5 mg/day or more of prednisone are at risk. The ribs and vertebrae are affected most. In some patients on high-dose glucocorticoids, vertebral compression fractures occur within weeks of beginning glucocorticoid use. Osteoporosis is most likely with systemic glucocorticoid therapy. In contrast, osteoporosis is uncommon when glucocorticoids are inhaled or administered topically. Patients should be observed for signs of compression fractures (back and neck pain) and for indications of fractures in other bones.

How do glucocorticoids cause bone loss? The most important mechanism is suppression of bone formation by osteoblasts. In addition, glucocorticoids accelerate bone resorption by osteoclasts. Also, these drugs reduce intestinal absorption of calcium, causing hypocalcemia. In response to hypocalcemia, release of parathyroid hormone increases, which increases mobilization of calcium from bone.

Management. Several measures can greatly reduce development of osteoporosis and subsequent fractures. Prior to glucocorticoid treatment, bone mineral density of the lumbar spine should be measured. This will identify patients at highest risk and provide a baseline for evaluating bone loss during treatment. When appropriate, glucocorticoids should be administered topically or by inhalation (because bone loss is less with these routes than with systemic therapy).

Drugs can help reduce bone loss. All patients should receive *calcium* and *vitamin D* supplements. Sodium restriction combined with a thiazide diuretic can enhance intestinal absorption of calcium and can decrease urinary excretion of calcium. There is solid evidence that a *bisphosphonate* can prevent glucocorticoid-induced bone loss. Dosing may be

done orally (eg, risedronate [Actonel], 5 mg/day) or by IV infusion (eg, zoledronate [Reclast], 5 mg once a year). How do bisphosphonates help? They inhibit bone resorption by osteoclasts. *Calcitonin* [Miacalcin, others], which also inhibits osteoclasts, is another option. For patients with significant bone loss, *teriparatide* [Forteo] may be preferred. Why? Because, unlike bisphosphonates and calcitonin, which only prevent bone resorption, teriparatide actively promotes new bone formation. In postmenopausal women, *estrogen* therapy is an effective way to reduce bone loss. However, as discussed in Chapter 61, the risks of estrogen therapy generally outweigh the benefits. The roles of calcium, vitamin D, bisphosphonates, calcitonin, teriparatide, and estrogen in the prophylaxis and treatment of osteoporosis are discussed fully in Chapter 75.

Infection. By suppressing host defenses (immune responses and phagocytic activity of neutrophils and macrophages), glucocorticoids can increase susceptibility to infection. The risk of acquiring a new infection is increased, as is the risk of reactivating a latent infection (eg, tuberculosis). In addition, since suppression of both the immune system and neutrophils reduces inflammation and other manifestations of infection, a fulminant infection may develop without detection. Hence, not only do glucocorticoids increase susceptibility to infection, they can mask the presence of an infection as it progresses. To minimize acquisition of infection, patients should avoid close contact with people who have a communicable disease. If a significant infection occurs, glucocorticoids should be continued only if absolutely necessary, and then only in combination with appropriate antimicrobial or antifungal therapy.

One infection—known as PCP (for *Pneumocystis pneumonia*)—deserves special mention. The causative organism is *Pneumocystis jirovecii* (formerly misidentified as *Pneumocystis carinii*). PCP occurs with alarming frequency in people receiving high doses of glucocorticoids (not just in people with AIDS, among whom PCP is the most common opportunistic infection). Accordingly, it has been suggested that PCP prophylaxis be considered for all people taking glucocorticoids long term in high doses.

Glucose Intolerance. Because of their effects on glucose production and utilization, glucocorticoids can increase plasma glucose levels, thereby causing hyperglycemia and glycosuria. Patients with diabetes may need to reduce caloric intake or increase the dosage of hypoglycemic medication (insulin or an oral agent). For patients with normal pancreatic function, significant elevation of blood glucose is unlikely. However, since glucocorticoids can unmask latent diabetes, nondiabetics should undergo periodic evaluation of blood glucose levels.

Myopathy. High-dose glucocorticoid therapy can cause myopathy (muscle injury), manifesting as weakness. The proximal muscles of the arms and legs are affected most. Damage to muscle may be sufficient to prevent ambulation. If myopathy develops, glucocorticoid dosage should be reduced. Myopathy then gradually resolves over several months.

Fluid and Electrolyte Disturbance. Because of their mineralocorticoid activity, glucocorticoids can cause sodium and water retention and potassium loss. Retention of water and sodium can cause hypertension and edema. Hypokalemia can predispose to dysrhythmias and toxicity from digitalis. Fortunately, most of the glucocorticoids in current use have minimal mineralocorticoid activity (see Table 72-1). Hence, serious fluid and electrolyte disturbance is rare. The risk of fluid and electrolyte disturbance can be reduced by (1) using

glucocorticoids that have low mineralocorticoid activity, (2) restricting sodium intake, and (3) taking potassium supplements or consuming potassium-rich foods (eg, potatoes, bananas, citrus fruits). Patients should be informed about signs of fluid retention (eg, weight gain, swelling of the lower extremities) and advised to contact the prescriber if these develop. Patients should also be alert for signs of hypokalemia (eg, muscle weakness or fatigue, irregular pulse).

Growth Retardation. Glucocorticoids can suppress growth in children. Growth retardation is probably the result of reduced DNA synthesis and decreased cell division. To assess effects on growth, height and weight should be measured at regular intervals. Growth suppression can be minimized with alternate-day therapy. This dosing schedule is discussed below.

Psychologic Disturbances. Systemic glucocorticoids can cause psychologic disturbances. About 60% of patients experience a mild reaction: insomnia, anxiety, agitation, or irritability. Another 6% experience a severe reaction: delirium, hallucinations, depression, euphoria, or mania. Of these, up to one-third may become suicidal. Of note, previous psychiatric illness does not seem to predispose patients to psychologic reactions—and a history of good mental health does not confer protection.

Psychologic reactions are dose and duration dependent. Long-term low-dose therapy is more likely to cause depression. In contrast, short-term high-dose therapy is more likely to cause mania and other psychoses. Cognitive impairment (eg, distractibility, memory loss) can occur with either dosing pattern.

Psychologic effects reverse when glucocorticoids are withdrawn. Delirium and hallucinations usually resolve quickly—within a few days to a week. Mood disturbances (depression, mania) resolve more slowly—over 6 weeks or longer.

Can we use drugs to manage symptoms? Yes. Depression can be treated with a mood stabilizer (eg, carbamazepine, valproic acid) or a selective serotonin reuptake inhibitor (eg, fluoxetine [Prozac]). Psychotic symptoms can be treated with an atypical antipsychotic. However, with all of these drugs, solid proof of efficacy against glucocorticoid-induced reactions is lacking.

Cataracts and Glaucoma. Cataracts are a common complication of long-term glucocorticoid therapy. Risk factors are in dispute; cataract development may be related to age, dosage, or individual susceptibility. To facilitate early detection, patients should undergo an eye exam every 6 months. Also, patients should be advised to contact the prescriber if vision becomes cloudy or blurred.

Oral glucocorticoids can cause open-angle glaucoma. Onset of ocular hypertension develops rapidly and reverses within 2 weeks of glucocorticoid cessation.

Peptic Ulcer Disease. Although glucocorticoids have actions that could lead to peptic ulcer disease, whether they actually cause GI ulceration is controversial. By inhibiting prostaglandin synthesis, glucocorticoids can augment secretion of gastric acid and pepsin, inhibit production of cytoprotective mucus, and reduce gastric mucosal blood flow. These actions predispose to GI ulceration. Making matters worse, glucocorticoids can decrease gastric pain, thereby masking ulcer development. As a result, perforation and hemorrhage can occur without warning. The risk of ulceration is increased by concurrent use of other ulcerogenic drugs, such as aspirin and other NSAIDs. To provide early detection of ulcer formation, stools should be periodically checked for occult blood. Patients should be instructed

to notify the prescriber if feces become black and tarry. If GI ulceration occurs, glucocorticoids should be slowly withdrawn (unless their continued use is considered essential to support life). Treatment with antiulcer medication is indicated.

Iatrogenic Cushing's Syndrome. Long-term glucocorticoid therapy can induce a cushingoid syndrome with symptoms identical to those of naturally occurring Cushing's syndrome. Prominent symptoms are hyperglycemia, glycosuria, fluid and electrolyte disturbances, osteoporosis, muscle weakness, cutaneous striations, and lowered resistance to infection. Redistribution of fat produces a potbelly, "moon face," and "buffalo hump."

Use in Pregnancy and Lactation

Pregnancy. Glucocorticoids can cross the placenta and affect the developing fetus. Studies in rats and other nonprimates indicate an increased incidence of cleft palate, spontaneous abortion, and low birth weight. In primates, high levels of prenatal glucocorticoids have impaired postnatal growth, impaired glucose-insulin homeostasis, increased blood pressure, and increased production of cortisol in response to mild stress. No adequate studies of these effects have been done in humans. Prolonged therapy with very large doses can cause fetal adrenal hypoplasia. Therefore, when large doses have been employed, the infant should be assessed for adrenal sufficiency and given replacement therapy if indicated. Whenever glucocorticoids are to be used during pregnancy, the benefits must be carefully weighed against the potential fetal risk.

Lactation. Glucocorticoids enter breast milk. When physiologic doses or low pharmacologic doses are used, the concentration achieved in milk is probably too low to affect the nursing infant. However, when large pharmacologic doses are employed (eg, doses greater than 5 mg/day of prednisone or its equivalent), the amount ingested by the infant may be sufficient to cause growth retardation and other adverse effects. Consequently, women receiving high-dose glucocorticoid therapy should be warned against breast-feeding.

Drug Interactions

Interactions Related to Potassium Loss. As noted, glucocorticoids can increase urinary loss of potassium, and can thereby induce hypokalemia. Consequently, glucocorticoids must be used with caution when combined with *digoxin* (because hypokalemia increases the risk of digoxin-induced dysrhythmias) and when combined with *thiazide* or *loop diuretics* (because these potassium-depleting diuretics will increase the risk of hypokalemia). When glucocorticoids are given together with any of the above drugs, it is advisable to monitor plasma potassium levels and be alert for signs of cardiotoxicity.

Nonsteroidal Anti-inflammatory Drugs. NSAIDs have the same effects on the gastrointestinal tract as do glucocorticoids. Accordingly, concurrent use of these agents increases the risk of ulceration.

Insulin and Oral Hypoglycemics. As noted, glucocorticoids promote hyperglycemia. To maintain glycemic control, diabetic patients may require increased doses of a glucose-lowering drug (insulin or another hypoglycemic agent).

Vaccines. Because of their immunosuppressant actions, glucocorticoids can decrease antibody responses to vaccines. Furthermore, if a live virus vaccine is employed, there is an in-

creased risk of developing viral disease. Accordingly, immunization should not be attempted while glucocorticoids are in use.

Summary of Precautions and Contraindications

Contraindications. Glucocorticoids are contraindicated for patients with *systemic fungal infections* and for those receiving *live virus vaccines*.

Precautions. Glucocorticoids must be used with caution in *pediatric patients* and in *women who are pregnant or breast-feeding*. Caution is also required in patients with *hypertension, heart failure, renal impairment, esophagitis, gastritis, peptic ulcer disease, myasthenia gravis, diabetes mellitus, osteoporosis, and infections that are resistant to treatment*. In addition, caution is required during concurrent therapy with *potassium-depleting diuretics, digoxin, insulin, oral hypoglycemics, and NSAIDs*.

Adrenal Suppression

Development of Adrenal Suppression. Like cortisol and other endogenous glucocorticoids, the glucocorticoids that we administer as drugs suppress release of CRH from the hypothalamus and ACTH from the anterior pituitary. By doing so, exogenous glucocorticoids inhibit the synthesis and release of endogenous glucocorticoids by the adrenals. During long-term therapy, the pituitary loses much of its ability to manufacture ACTH and, in response to the prolonged absence of ACTH, the adrenals atrophy and lose their ability to synthesize cortisol and other glucocorticoids. As a result, when prolonged glucocorticoid therapy is discontinued, there is a period during which the adrenals are unable to produce glucocorticoids. The time needed for adrenal recovery is highly variable: It may be as short as 5 days or as long as a year. The extent of adrenal suppression and the time required for recovery are determined primarily by the duration of glucocorticoid use; dosage size is less important. Development of adrenal suppression can be minimized through alternate-day dosing (see below).

Adrenal Suppression and Physiologic Stress. Because of adrenal suppression, patients taking glucocorticoids long term require increased doses at times of stress. Recall that, when stress occurs, the adrenals normally secrete large amounts of glucocorticoids. If the stress is sufficiently severe (eg, trauma, surgery), these glucocorticoids are essential for supporting life. Accordingly, *it is imperative that patients receiving long-term glucocorticoid therapy be given increased doses at times of stress* (unless the dosage is already very high). Furthermore, *once glucocorticoid use has ceased, supplemental doses are required whenever stress occurs until recovery of adrenal function is complete*. To ensure appropriate care in emergencies, patients should carry an identification card or bracelet to inform emergency personnel of their glucocorticoid needs. In addition, patients should always have an emergency supply of glucocorticoids on hand.

Glucocorticoid Withdrawal. To allow time for recovery of adrenal function, withdrawal of glucocorticoids should be done slowly. The withdrawal schedule is determined by the degree of adrenal suppression. A representative schedule is as follows: (1) taper the dosage to a physiologic range over 7 days; (2) switch from multiple daily doses to single doses administered each morning; (3) taper the dosage to 50% of

physiologic values over the next month; and (4) monitor for production of endogenous cortisol and, when basal levels have returned to normal, cease routine glucocorticoid dosing (but be prepared to give supplemental doses at times of stress). As a rule, tapering is unnecessary when oral glucocorticoids have been used for less than 2 to 3 weeks.

In addition to unmasking adrenal insufficiency, stopping glucocorticoids may produce a withdrawal syndrome. Symptoms include hypotension, hypoglycemia, myalgia, arthralgia, and fatigue. In patients being treated for arthritis and certain other disorders, these symptoms may be confused with return of the underlying disease. Discomfort of withdrawal can be minimized by gradual dosage reduction and by concurrent treatment with NSAIDs.

Preparations and Routes of Administration

Preparations

The glucocorticoids employed clinically include hydrocortisone (cortisol) and synthetic derivatives of hydrocortisone. Individual glucocorticoids differ with respect to (1) biologic half-life, (2) mineralocorticoid potency, and (3) glucocorticoid (anti-inflammatory) potency (see Table 72-1).

The term *biologic half-life* refers to the time required for glucocorticoids to leave body tissues. In most cases, these drugs are cleared from tissues more slowly than from the blood. Hence, the biologic half-life is usually longer than the plasma half-life. When glucocorticoids are administered by mouth or by IV injection, it is the biologic half-life, and not the plasma half-life, that determines duration of action. Because of differences in their biologic half-lives, individual glucocorticoids can be classified as short acting, intermediate acting, or long acting (see Table 72-1).

Glucocorticoids with high *mineralocorticoid potency* (cortisone, hydrocortisone) can cause significant retention of sodium and water, coupled with depletion of potassium. These effects can be especially hazardous for patients with hypertension or heart failure and for those taking digoxin. Because of the potential dangers of sodium retention and potassium loss, glucocorticoids with high mineralocorticoid activity should not be administered systemically for long periods.

The differences in *glucocorticoid potency* summarized in Table 72-1 are reflected in the doses required to produce anti-inflammatory effects—not mineralocorticoid effects. As with other drugs, potency is relatively unimportant. However, it is important to appreciate that, in order to produce equivalent therapeutic effects, dosages for some glucocorticoids must be much larger than for others.

Routes of Administration

Glucocorticoids can be administered *orally*, *parenterally* (IV, IM, subQ), *topically*, and *intranasally* and by *local injection* (eg, intra-articular, intralesional) or *inhalation*. Topical application is used for dermatologic disorders (see Chapter 105), inhalation therapy is used for asthma (see Chapter 76), and intranasal therapy is used for allergic rhinitis (see Chapter 77). Since local therapy (topical, intranasal, inhalation, local injection) minimizes systemic toxicity, this form of treatment is preferred to systemic therapy (oral, parenteral). When systemic effects are needed, oral administration is preferred to parenteral. It is important to note that, even when glucocorti-

coids are administered for local effects, absorption can be sufficient to produce systemic effects. That is, local administration does not eliminate toxicity risk.

Individual glucocorticoids are available as various esters (eg, acetate, sodium phosphate). When glucocorticoids are administered by routes other than oral or IV, the particular ester employed is a major determinant of duration of action. As indicated in Table 72-2, not all esters can be administered by all routes. Hence, when preparing to give a glucocorticoid, you should verify that the ester ordered is appropriate for the intended route.

Dosage

General Guidelines for Dosing

For most patients, the therapeutic objective is to reduce symptoms to an acceptable level. Complete relief is usually not an appropriate goal.

Dosages are highly individualized and, for any patient with any disorder, dosage must be determined empirically (by trial and error). For patients whose disorder is not an immediate threat to life, the dosage should be low initially and then increased gradually until symptoms are under control. In the event of a life-threatening disorder, a large initial dose should be used, and, if a response does not occur rapidly, the dose should be doubled or even tripled. When glucocorticoids are used for a long time, the dosage should be reduced until the smallest effective amount has been established. Prolonged treatment with high doses should be done only if the disorder (1) is life threatening or (2) has the potential to cause permanent disability. During long-term treatment, an increase in dosage will be needed at times of stress (unless the dosage is very high to begin with). If disease status changes, appropriate adjustment of dosage must be made.

As noted, abrupt termination of long-term therapy may unmask adrenal insufficiency. To minimize the impact of adrenal insufficiency, glucocorticoid withdrawal should be gradual. Patients must be warned against abrupt discontinuation.

Alternate-Day Therapy

In alternate-day therapy, a large dose (of an intermediate-acting glucocorticoid) is given every other morning. This dosing schedule contrasts with traditional therapy, in which multiple smaller doses are administered daily. Benefits of alternate-day therapy are (1) reduced adrenal suppression, (2) reduced risk of growth retardation, and (3) reduced toxicity overall. Adrenal insufficiency is decreased because, over the extended interval between doses, plasma glucocorticoids decline to a level that is low enough to permit some production of ACTH, thereby promoting some synthesis of cortisol by the adrenals. To allow maximal recovery of endocrine function, doses should be administered prior to 9:00 in the morning, and long-acting agents should be avoided. Early-morning administration is also helpful in that it mimics (sort of) the burst of glucocorticoids normally released by the adrenals at dawn.

Unfortunately, alternate-day therapy does have one drawback: In the long interval between doses, drug levels may fall to a subtherapeutic value, thus permitting flare-up of symptoms. Symptoms are likely to be most intense late on the second day after a dose is given. If symptoms become intolerable, switching to a single daily dose may be sufficient to provide control. As with alternate-day treatment, patients taking single daily doses should administer their medicine before 9:00 AM.

TABLE 72-2 ■ Glucocorticoid Routes of Administration*

Drug	Routes of Administration†									
	Systemic				Local					
	PO	IM	IV	SubQ	IA	IB	IL	IS	ST	
Betamethasone	✓									
Betamethasone sodium phosphate		✓	✓		✓		✓			✓
Betamethasone acetate/sodium phosphate		✓			✓		✓	✓		✓
Cortisone acetate	✓	✓								
Dexamethasone	✓									
Dexamethasone sodium phosphate		✓	✓		✓		✓	✓		✓
Hydrocortisone	✓									
Hydrocortisone acetate					✓	✓	✓	✓		✓
Hydrocortisone sodium succinate		✓	✓							
Methylprednisolone	✓									
Methylprednisolone acetate		✓			✓		✓			✓
Methylprednisolone sodium succinate		✓	✓							
Prednisolone	✓									
Prednisolone acetate	✓									
Prednisolone acetate/sodium phosphate		✓			✓	✓			✓	✓
Prednisolone sodium phosphate	✓									
Prednisone	✓									
Triamcinolone acetonide		✓			✓	✓	✓			
Triamcinolone hexacetonide					✓		✓			

*Glucocorticoids for topical, inhalational, and intranasal use are listed in Tables 105-1, 76-3, and 77-2, respectively.

†IA = intra-articular, IB = intrabursal, IL = intralesional, IM = intramuscular, IS = intrasynovial, IV = intravenous, PO = oral, ST = soft tissue, SubQ = subcutaneous.

KEY POINTS

- Glucocorticoids are used in low (physiologic) doses to treat endocrine disorders (see Chapter 60) and in high (pharmacologic) doses to treat nonendocrine disorders (eg, arthritis, asthma).
- Glucocorticoids are beneficial in nonendocrine disorders primarily because they suppress inflammatory and immune responses.
- Glucocorticoids produce their effects by penetrating the cell membrane and activating cytoplasmic receptors, which then travel to the cell nucleus, where they modulate the activity of genes that code for specific regulatory proteins.
- Glucocorticoids reduce inflammation by multiple mechanisms, including suppressing the (1) synthesis of inflammatory mediators (prostaglandins, leukotrienes, histamine), (2) infiltration of phagocytes, (3) release of lysosomal enzymes, and (4) proliferation of lymphocytes.
- Important nonendocrine indications for glucocorticoids include arthritis, allergic disorders, asthma, cancer, and suppression of allograft rejection.
- When used in pharmacologic doses, especially for prolonged times, glucocorticoids can cause severe adverse effects. These are not seen at physiologic doses.
- Adverse effects of the glucocorticoids include adrenal insufficiency, osteoporosis, increased vulnerability to infection, muscle wasting, thinning of the skin, fluid and electrolyte imbalance, glucose intolerance, psychologic disturbances, and, possibly, peptic ulcer disease.
- By causing potassium loss, glucocorticoids can increase the risk of toxicity from digoxin, and they can exacerbate hypokalemia caused by thiazide and loop diuretics.
- Concurrent use of NSAIDs with glucocorticoids increases the risk of peptic ulcer disease.
- Prolonged glucocorticoid use causes adrenal insufficiency.
- Patients with adrenal insufficiency must be given supplemental doses of glucocorticoids at times of stress (eg, surgery, trauma). Failure to do so may be fatal!
- To minimize expression of adrenal insufficiency when glucocorticoids are discontinued, doses should be tapered very gradually.
- Following glucocorticoid withdrawal, supplemental glucocorticoids are needed at times of stress until adrenal function has fully recovered.
- Alternate-day dosing can help minimize development of adrenal insufficiency.
- Glucocorticoids should be administered before 9:00 AM. Why? Because this helps minimize adrenal insufficiency and mimics (sort of) the burst of glucocorticoids released naturally by the adrenals each morning.

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Summary of Major Nursing Implications*

GLUCOCORTICOIDS

Betamethasone
Cortisone
Dexamethasone
Hydrocortisone
Methylprednisolone
Prednisolone
Prednisone
Triamcinolone

The nursing implications summarized here apply to all glucocorticoids, but only to their use for *nonendocrine disorders*. Implications that apply specifically to their use for *replacement therapy* are summarized in Chapter 60. Implications specific to *asthma therapy* are summarized in Chapter 76.

Preadministration Assessment

Therapeutic Goal

Glucocorticoids are used to suppress rejection of organ transplants, and to treat a variety of inflammatory, allergic, and neoplastic disorders. When treating inflammatory and allergic disorders, the goal is to suppress signs and symptoms to an acceptable level, not to eliminate them.

Baseline Data

Make a full assessment of the specific disorder (eg, rheumatoid arthritis, asthma, psoriasis) being treated. These data are used to determine the initial dosage and to guide dosage adjustments as treatment proceeds. Determine bone mineral density of the lumbar spine.

Identifying High-Risk Patients

Glucocorticoids are *contraindicated* for patients with systemic fungal infections and for individuals receiving live virus vaccines.

Use glucocorticoids with *caution* in pediatric patients and in women who are pregnant or breast-feeding. In addition, exercise *caution* in patients with hypertension, open-angle glaucoma, heart failure, renal impairment, esophagitis, gastritis, peptic ulcer disease, myasthenia gravis, diabetes mellitus, osteoporosis, and infections that are resistant to treatment, and in patients receiving potassium-depleting diuretics, digoxin, insulin, oral hypoglycemics, or NSAIDs.

Implementation: Administration and Dosage

Routes and Administration

Glucocorticoids are administered orally, parenterally (IV, IM, subQ), topically (to skin and mucous membranes), intranasally, by inhalation, and by local injection (eg, intra-articular, intralesional). Routes for specific preparations are summarized in Table 72-2. (Glucocorticoids administered topically, intranasally, and by inhalation are presented in Chapters 105, 77, and 76, respectively.) When getting ready to administer a glucocorticoid, verify that the preparation is appropriate for the intended route.

Dosage

Dosage is determined empirically. For patients whose disorder does not threaten life, dosage should be low initially and then gradually increased, until the desired response is achieved. For a life-threatening disorder, initial doses should be as large as needed to control symptoms. During prolonged therapy, the dosage should be reduced to the smallest effective amount. Supplemental doses are needed at times of stress, unless the dosage is very high to begin with.

Alternate-Day Therapy

Alternate-day dosing reduces adrenal suppression and other toxicities. **Instruct patients to take their medicine before 9:00 AM every other day.**

Drug Withdrawal

Glucocorticoids taken chronically must be withdrawn gradually. **Warn the patient against abrupt discontinuation of treatment.** Following termination, supplemental doses are needed during times of stress until adrenal function has recovered fully.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Evaluate therapy by making periodic comparisons of current signs and symptoms with the pretreatment assessment. Dosage adjustment is based on these evaluations.

Minimizing Adverse Effects

General Measures. (1) Keep the dosage as low as possible and the duration of treatment as short as possible. (2) Use alternate-day therapy if possible. (3) When appropriate, administer glucocorticoids topically, intranasally, by inhalation, or by local injection, rather than systemically.

Adrenal Insufficiency. Long-term therapy suppresses the ability of the adrenal glands to make glucocorticoids. Increase the dosage when stress occurs (eg, surgery, trauma, infection) unless the dosage is very high to begin with. Following termination of therapy, supplemental doses are required at times of stress until adrenal recovery is complete. **Advise the patient to carry identification (eg, Medic Alert bracelet) to ensure proper dosing in emergencies. Advise the patient to always have an emergency supply of glucocorticoids on hand.** Expression of adrenal insufficiency can be reduced by withdrawing glucocorticoids gradually. Adrenal insufficiency can be minimized through alternate-day dosing and use of glucocorticoids that have an intermediate duration of action.

Osteoporosis. Glucocorticoid-induced osteoporosis predisposes the patient to fractures, especially of the ribs and vertebrae. Monitor patients for signs of compression fractures (neck or back pain) and for indications of other fractures. Evaluate status with bone densitometry. Several drugs can help prevent osteoporosis. Important among these are calcium supplements, vitamin D supplements, thiazide diuretics (combined with salt restriction), bisphosphonates (eg, risedronate, zoledronate), teriparatide, and calcitonin.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Estrogen therapy can reduce bone loss in postmenopausal women, but the benefits are not likely to outweigh the risks.

Infection. Glucocorticoids increase the risk of morbidity from infection. **Warn patients to avoid close contact with persons who have a communicable disease. Inform patients about early signs of infection (eg, fever, sore throat), and instruct them to notify the prescriber if these occur.** Treat established infections with appropriate antimicrobial drugs, and withdraw glucocorticoids unless they are absolutely required.

Glucose Intolerance. Glucocorticoids can cause hyperglycemia and glycosuria. Diabetic patients may need to decrease their caloric intake and use higher doses of hypoglycemic medication (insulin or an oral hypoglycemic).

Fluid and Electrolyte Disturbance. Glucocorticoids can cause sodium and water retention and loss of potassium. These effects can be minimized by (1) using glucocorticoids that have low mineralocorticoid activity, (2) restricting sodium intake, and (3) taking potassium supplements or consuming potassium-rich foods (eg, bananas, citrus fruits). **Educate patients about signs and symptoms of fluid retention (eg, weight gain, swelling of the lower extremities) and hypokalemia (eg, muscle weakness, irregular pulses, cramping), and instruct them to notify the prescriber if these develop.**

Growth Retardation. Glucocorticoids can suppress growth in children. Evaluate growth by making periodic measurements of height and weight. Alternate-day therapy minimizes effects on growth.

Cataracts and Glaucoma. Cataracts are a common complication of long-term therapy. Open-angle glaucoma may also develop. The patient should be given an eye exam every 6 months. **Instruct the patient to notify the prescriber if vision becomes cloudy or blurred.**

Peptic Ulcer Disease. Glucocorticoids may increase the risk of ulcer formation and can mask ulcer symptoms. **Instruct the patient to notify the prescriber if stools become black and tarry.** Have stools checked periodically for occult blood. If ulcers develop, glucocorticoids should be slowly withdrawn—unless their continued use is considered essential for life—and antiulcer therapy should be instituted.

Psychologic Disturbances. Systemic glucocorticoids can cause psychologic disturbances, both mild (insomnia, anxiety, agitation, irritability) and severe (delirium, hallucinations, depression, euphoria, mania). Depression is more likely with low-dose, long-term therapy, whereas psychoses (mania, delirium) are more likely with high-dose, short-term therapy. Psychologic disturbances are reversible, and usually resolve within days to weeks after drug withdrawal. Depression may respond to a mood stabilizer (eg, carbamazepine, valproic acid) or a selective serotonin reuptake inhibitor (eg, fluoxetine [Prozac]). Psychotic symptoms may respond to an atypical antipsychotic. **Inform patients about possible psychologic reactions, and instruct them to report disturbing symptoms.** Monitor for suicidal ideation.

Use in Pregnancy and Lactation. Glucocorticoids can induce adrenal hypoplasia in the developing fetus. When large doses have been employed, the newborn should be assessed for adrenal insufficiency, and given replacement therapy if indicated.

During high-dose therapy, the glucocorticoid content of breast milk may become high enough to affect the nursing infant. **Warn women who are receiving high-dose therapy not to breast-feed.**

Other Adverse Effects. *Myopathy* and *Cushing's syndrome* can be minimized by implementing the general measures noted at the beginning of this section. There are no specific measures to prevent these complications.

Minimizing Adverse Interactions

Minimizing Adverse Interactions

Interactions Related to Potassium Loss. Glucocorticoid-induced potassium loss can be augmented by *potassium-depleting diuretics* (thiazides, loop diuretics) and can increase the risk of toxicity from *digoxin*. If digoxin and glucocorticoids are used concurrently, potassium levels should be monitored. Also, be alert for indications of cardiotoxicity.

Nonsteroidal Anti-inflammatory Drugs. NSAIDs can increase the risk of gastric ulceration during glucocorticoid therapy. Exercise caution when this combination is employed.

Insulin and Other Hypoglycemics. Glucocorticoids can elevate blood levels of glucose. Diabetic patients may need to increase their dosage of insulin or other hypoglycemic drugs.

Vaccines. Glucocorticoids can decrease antibody responses to vaccines and can increase the risk of infection from live virus vaccines. Immunization should not be done while glucocorticoids are in use.

*Patient education information is highlighted as blue text.

Drug Therapy of Rheumatoid Arthritis

Pathophysiology of Rheumatoid Arthritis

Overview of Therapy

Nondrug Measures

Drug Therapy

Nonsteroidal Anti-inflammatory Drugs

Glucocorticoids

Nonbiologic (Traditional) DMARDs

Methotrexate

Sulfasalazine

Leflunomide

Hydroxychloroquine

Minocycline

Other Nonbiologic DMARDs

Biologic DMARDs

Tumor Necrosis Factor Antagonists

Rituximab, a B-Lymphocyte-Depleting Agent

Abatacept, a T-Cell Activation Inhibitor

Tocilizumab, an Interleukin-6 Receptor Antagonist

Anakinra, an Interleukin-1 Receptor Antagonist

Rheumatoid arthritis (RA) is an autoimmune, inflammatory disorder that affects about 1% of the American population. Each year, the disease results in more than 9 million physician visits and over 250,000 hospitalizations. Although RA can develop at any age, initial symptoms usually appear during the third and fourth decades. Among younger patients, the incidence of RA in females is 3 times greater than in males. However, among patients over age 60, the incidence in men and women is equal. Rheumatoid arthritis follows a progressive course, and can eventually cripple its victim. In many cases, drug therapy can delay disease progression. In others, benefits are limited to symptomatic relief. Some of the drugs used for RA were introduced in preceding chapters. Additional drugs are introduced here.

PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

Onset of RA is heralded by symmetric joint stiffness and pain. Symptoms are most intense in the morning and abate as the day advances. Joints become swollen, tender, and warm. For some patients, periods of spontaneous remission occur. For others, injury progresses steadily. In addition to joint injury, RA has systemic manifestations, including fever, weakness,

fatigue, weight loss, thinning of the skin, scleritis (inflammation of the sclera), corneal ulcers, vasculitis (which can be severe), and nodules under the skin and periosteum (connective tissue that surrounds all bones).

The progression of joint deterioration is depicted in Figure 73-1. Inflammation begins in the synovium—the membrane that encloses the joint cavity. As inflammation intensifies, the synovial membrane thickens and begins to envelop the articular cartilage. This overgrowth is referred to as pannus. Damage to the cartilage is caused by enzymes released from the pannus and by chemicals and enzymes produced by the inflammatory process raging within the synovial space. Ultimately, the articular cartilage undergoes total destruction, resulting in direct contact between bones of the joint, followed by eventual bone fusion. After this, inflammation subsides.

Joint destruction is caused by an autoimmune process in which the immune system mounts an attack against synovial tissue. During the attack, mast cells, macrophages, and T lymphocytes produce cytokines and cytotoxins—compounds that promote inflammation and joint destruction. The cytokines of greatest importance are tumor necrosis factor, interleukin-1, interleukin-6, interferon gamma, platelet-derived growth factor, and granulocyte-macrophage colony-stimulating factor. Why the immune system attacks joints is unclear.

OVERVIEW OF THERAPY

Treatment is directed at (1) relieving symptoms (pain, inflammation, and stiffness), (2) maintaining joint function and range of motion, (3) minimizing systemic involvement, and (4) delaying disease progression. To achieve these goals, a combination of pharmacologic and nonpharmacologic measures is used.

Nondrug Measures

Nondrug measures for managing RA include physical therapy, exercise, and surgery. Physical therapy may consist of massage, warm baths, and applying heat to the affected regions. These procedures can enhance mobility and reduce inflammation. A balanced program of rest and exercise can decrease joint stiffness and improve function. However, excessive rest and excessive exercise should be avoided: Too much rest will foster stiffness, and too much activity can intensify inflammation.

Orthopedic surgery has made marked advances. For patients with severe disease of the hip or knee, total joint replacement can be performed. When joints of the hands or wrists have been damaged severely, function can be improved

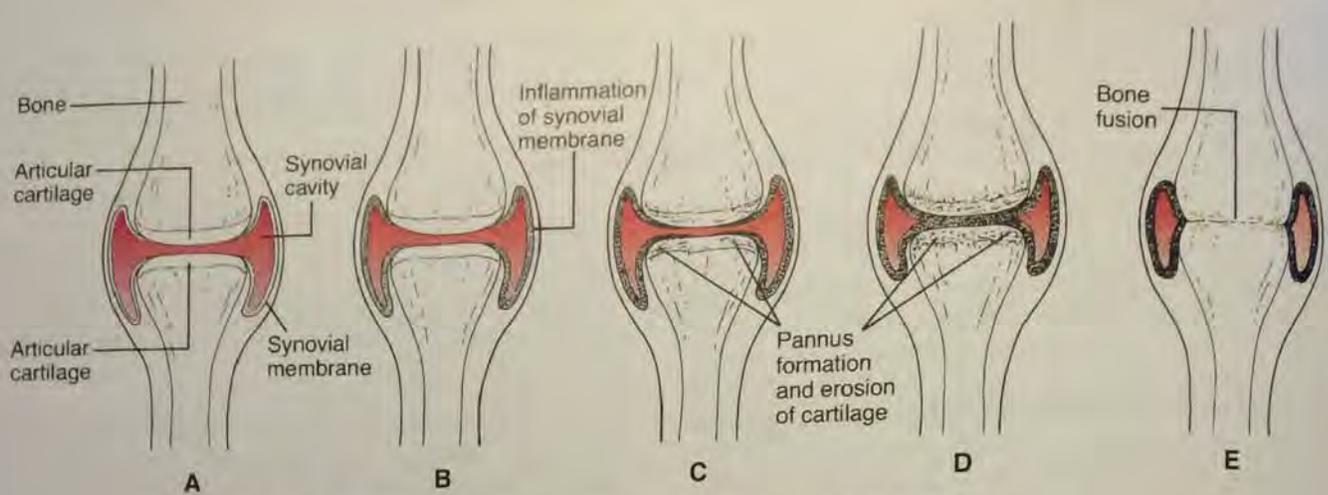


Figure 73-1 • Progressive joint degeneration in rheumatoid arthritis.

A, Healthy joint. B, Inflammation of synovial membrane. C, Onset of pannus formation and cartilage erosion. D, Pannus formation progresses and cartilage deteriorates further. E, Complete destruction of joint cavity together with fusion of articulating bones.

through removal of the diseased synovium and repair of ruptured tendons. Plastic implants can help correct deformities.

A complete program of treatment should include patient education and counseling. The patient should be informed about the nature of RA, the possible consequences of joint degeneration, management measures, and the benefits and limitations of drug therapy. If loss of mobility limits function at home, on the job, or in school, consultation with a social worker, occupational therapist, or specialist in vocational rehabilitation may be appropriate.

Drug Therapy

Antiarthritic drugs can produce symptomatic relief, and some drugs, if started very early in the disease process, can induce protracted remission. However, remission is rarely complete, and the disease typically advances steadily. As a result, drug therapy is chronic, and hence success requires patient motivation and cooperation.

Classes of Antiarthritic Drugs

The antirheumatic drugs fall into three major groups:

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Glucocorticoids (adrenal corticosteroids)
- Disease-modifying antirheumatic drugs (DMARDs)

These major groups differ with respect to time course of effects, toxicity, and ability to slow RA progression.

The NSAIDs provide rapid relief of symptoms but do not prevent joint damage and do not slow disease progression. The NSAIDs are safer than DMARDs and glucocorticoids, and hence treatment requires less vigorous monitoring.

Like the NSAIDs, glucocorticoids provide rapid relief of symptoms. In addition, they can slow disease progression. Unfortunately, although glucocorticoids are effective, with long-term use they can cause serious toxicity. As a result, treatment is usually limited to short courses.

By definition, DMARDs are drugs that reduce joint destruction and retard disease progression. However, benefits develop more slowly than with the NSAIDs. The DMARDs

are more toxic than NSAIDs, and therefore close monitoring is required. In the discussion below, DMARDs are subdivided into two basic groups—*nonbiologic DMARDs* (traditional DMARDs) and *biologic DMARDs*—based on their molecular size and method of production. The nonbiologic DMARDs are small molecules that are synthesized using conventional chemical techniques. In contrast, the biologic DMARDs are large molecules that are produced through recombinant DNA technology.

Drug Selection

Drug therapy of RA is evolving. In the past, treatment followed a simple protocol: (1) Start with an NSAID (eg, aspirin, ibuprofen, celecoxib). (2) If symptoms can't be controlled with an NSAID, add a DMARD (eg, methotrexate), and continue the NSAID until the DMARD takes effect. And (3) if necessary, provide a short course of glucocorticoid therapy while responses to the DMARD are developing, and to supplement treatment any time that symptoms flare. Note that, in this protocol, DMARDs are used only if NSAIDs are insufficient.

Today, treatment is more aggressive. Current guidelines recommend starting a DMARD *early*—within 3 months of RA diagnosis for most patients. The aim is to delay joint degeneration. Recall that NSAIDs only provide symptomatic relief; they do not retard disease progression. In contrast, DMARDs may be able to arrest the disease process. Hence, by instituting DMARD therapy early—rather than waiting until joint degeneration has advanced to the point where NSAIDs can no longer control symptoms—it is possible to delay or even prevent serious joint injury. Because the effects of DMARDs take weeks or months to develop, whereas the effects of NSAIDs are immediate, an NSAID is given until the DMARD has had time to act, after which the NSAID can be withdrawn. As in the past, glucocorticoids are generally reserved for short-course management of symptom flare-ups and to control symptoms until DMARDs take effect. If joint injury progresses despite treatment with an initial DMARD (typically methotrexate), another DMARD can be added or substituted.

You can find detailed information on the diagnosis and management of RA in two documents sponsored by the American College of Rheumatology (ACR):

- *Guidelines for the Management of Rheumatoid Arthritis: 2002 Update*, available online at <http://onlinelibrary.wiley.com/doi/10.1002/art.10148/pdf>
- *American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis*, available online at <http://www.rheumatology.org/practice/clinical/guidelines/recommendations.pdf>

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The basic pharmacology of the NSAIDs is discussed in Chapter 71. Consideration here is limited to their role in RA.

Therapeutic Role. NSAIDs are drugs of first choice for RA, owing to their efficacy and rapid onset. Benefits derive primarily from anti-inflammatory actions, although analgesic actions help too. Both actions result from inhibiting cyclooxygenase (COX). NSAIDs only provide symptomatic relief; they do not slow disease progression. Accordingly, they are usually combined with a DMARD.

NSAID Classification. As discussed in Chapter 71, there are two main classes of NSAIDs: (1) *first-generation NSAIDs*, which inhibit COX-1 and COX-2; and (2) *second-generation NSAIDs*

(coxibs), which selectively inhibit COX-2. Anti-inflammatory and analgesic effects result from inhibiting COX-2, whereas major adverse effects—especially gastroduodenal ulceration—result from inhibiting COX-1. Because of their selectivity, the coxibs may cause less GI ulceration than the first-generation NSAIDs, while producing equal therapeutic effects.

Drug Selection. Selection of an NSAID is based largely on efficacy, safety, and cost.

Efficacy. All of the NSAIDs have essentially equal anti-rheumatic effects. However, individual patients may respond better to one NSAID than to another. Accordingly, it may be necessary to try more than one agent to achieve an optimal response.

Safety and Cost. The COX-2 inhibitors (eg, celecoxib [Celebrex]) appear somewhat safer than the first-generation NSAIDs, but are also more expensive. Hence, selection must balance these factors. If symptoms are controlled with a first-generation NSAID, and the drug is well tolerated, cost considerations would dictate using that drug. However, if a first-generation NSAID produces serious gastric ulceration, then switching to a COX-2 inhibitor might be appropriate—despite the increased cost.

Dosage. Dosages employed for anti-inflammatory effects are considerably higher than those required for analgesia or fever reduction. For example, treatment of RA may require 5.2 gm (16 standard tablets) of aspirin a day, compared with only 2.6 gm for aches, pain, and fever. Dosages for RA are summarized in Table 73-1.

TABLE 73-1 ■ Nonsteroidal Anti-inflammatory Drugs: Oral Dosage for Rheumatoid Arthritis

Generic Name	Trade Name	Daily Dosage
First-Generation NSAIDs		
Salicylates		
Aspirin (extended release)	Many trade names	800 mg 4 times/day
Magnesium salicylate	Magan	1090 mg 3 times/day
Salsalate	Disalcid, others	3–4 gm/day (in 2 or 3 doses)
Sodium salicylate	generic	3.6–5.4 gm/day (in divided doses)
Nonsalicylates		
Diclofenac	Cambia, Cataflam, Voltaren, Zipsor	150–200 mg/day (in 3 or 4 doses)
Diclofenac/misoprostol	Arthrotec	50 mg diclofenac/200 mcg misoprostol 3 or 4 times daily
Diflunisal	generic	250–500 mg twice daily
Etodolac	generic	600–1200 mg/day (in 2–4 doses)
Fenoprofen	Nalfon	300–600 mg 3 or 4 times/day
Flurbiprofen	generic	200–300 mg/day (in 2–4 doses)
Ibuprofen	Motrin, Advil, others	600–800 mg 3 or 4 times/day
Indomethacin	Indocin	25–50 mg 3 times/day
Ketoprofen	generic	150–300 mg/day (in 3 or 4 doses)
Meclofenamate	generic	200–400 mg/day (in 3 or 4 doses)
Meloxicam	Mobic, Mobicox	7.5 mg once a day
Nabumetone	generic	1.5–2 gm/day (in 1 or 2 doses)
Naproxen	Naprosyn	250–500 mg twice daily
Naproxen sodium	Aleve, others	250–500 mg twice daily
Naproxen/esomeprazole	Vimovo	375–500 mg (naproxen) twice daily
Oxaprozin	Daypro	1.2 gm once a day
Piroxicam	Feldene	20 mg once a day
Sulindac	Clinoril	150–200 mg twice daily
Tolmetin	generic	200–400 mg 3 times/day
Second-Generation NSAIDs (COX-2 Inhibitors)		
Celecoxib	Celebrex	100–200 mg twice daily

GLUCOCORTICOIDS

The glucocorticoids are powerful anti-inflammatory drugs that can relieve symptoms of severe RA, and may also retard disease progression. For patients with generalized symptoms, oral glucocorticoids are indicated. However, if only one or two joints are affected, *intra-articular injections* may be employed. Because long-term oral therapy can cause serious toxicity (eg, osteoporosis, gastric ulceration, adrenal suppression), short-term therapy should be used whenever possible. Most often, glucocorticoids are used for temporary relief until drugs with more slowly developing effects (eg, methotrexate) can provide control. Long-term therapy should be limited to patients who have failed to respond adequately to all other options. The most commonly employed oral glucocorticoids are *prednisone* and *prednisolone*. When symptoms flare, patients may be given 10 to 20 mg/day until symptoms are controlled, followed by gradual drug withdrawal over 5 to 7 days. The pharmacology of the glucocorticoids is discussed at length in Chapter 72 (Glucocorticoids in Nonendocrine Disorders).

NONBIOLOGIC (TRADITIONAL) DMARDS

As noted, the nonbiologic DMARDs are small molecules produced using conventional synthetic procedures. With several of these drugs, benefits result from immunosuppression. Unlike the NSAIDs, whose benefits are limited to symptomatic relief, the nonbiologic DMARDs can retard disease progression. These drugs are much more toxic than the NSAIDs, and clinical responses develop more slowly. The nonbiologic DMARDs cost much less than the biologic DMARDs, largely because the nonbiologic agents are easier to make.

Methotrexate

Methotrexate [Rheumatrex, Trexall] acts faster than all other DMARDs. Therapeutic effects may develop in 3 to 6 weeks. At least 80% of patients improve with this drug. Benefits are the result of immunosuppression secondary to reducing the activity of B and T lymphocytes. Many rheumatologists consider methotrexate the DMARD of first choice, owing to its efficacy, relative safety, low cost, and extensive use in RA. Major toxicities are hepatic fibrosis, bone marrow suppression, GI ulceration, and pneumonitis. Periodic tests of liver and kidney function are mandatory, as are complete blood cell and platelet counts. Methotrexate can cause fetal death and congenital abnormalities, and therefore is contraindicated during pregnancy. Recent data suggest that patients using methotrexate for RA may have a reduced life expectancy, owing to increased deaths from cardiovascular disease, infection, and certain cancers (melanoma, lung cancer, and non-Hodgkin's lymphoma). For treatment of RA, methotrexate is administered once a *week*, either orally or by injection. Oral dosage is 10 to 15 mg/wk initially, and then increased by 5 mg/wk every 2 to 4 weeks, up to a maintenance level of 20 to 30 mg/wk. Dosing with folic acid (at least 5 mg/wk) is recommended to reduce GI and hepatic toxicity. Methotrexate is discussed at length in Chapter 102 (Anticancer Drugs I: Cytotoxic Agents).

Sulfasalazine

Sulfasalazine [Azulfidine, Azulfidine EN-tabs] has been used for decades to treat inflammatory bowel disease (see Chapter 80) and is now used for RA too. Benefits may result from anti-inflammatory and immunomodulatory actions. In patients with RA, sulfasalazine can slow the progression of joint deterioration, sometimes with just 1 month of treatment. Gastrointestinal reactions (nausea, vomiting, diarrhea, anorexia, abdominal pain) are the most common reasons for stopping treatment. These reactions can be minimized by using an enteric-coated formulation and by dividing the daily dosage. Dermatologic reactions (pruritus, rash, urticaria) are also common. Fortunately, serious adverse effects—hepatitis and bone marrow suppression—are rare. To ensure early detection, periodic monitoring for hepatitis and bone marrow function (complete blood counts, platelet counts) should be performed. Because of its structure, sulfasalazine should not be given to patients with sulfa allergy. The initial dosage for RA is 1000 mg/day. The usual maintenance dosage is 1000 mg 2 or 3 times a day. Sulfasalazine is discussed further in Chapter 80 (Other Gastrointestinal Drugs).

Leflunomide

Actions and Uses. Leflunomide [Arava] is a powerful immunosuppressant indicated for adults with active RA. In clinical trials, the drug decreased signs and symptoms and slowed disease progression. Compared with methotrexate, leflunomide is about equally effective, but more dangerous and more expensive. Accordingly, the drug is often reserved for second-line use.

Leflunomide is a prodrug that undergoes conversion to its active form—metabolite 1 (M1)—in the body. Metabolite 1 inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme needed for *de novo* synthesis of pyrimidines, which in turn are needed for T-cell proliferation and antibody production. *In vitro*, leflunomide inhibits T-cell proliferation. In animals, it suppresses inflammation.

Pharmacokinetics. Following oral dosing, leflunomide is converted to M1 by enzymes in the intestine and liver. Levels of M1 peak in 6 to 12 hours. The active form undergoes further metabolism followed by excretion in the urine and bile. The half-life is prolonged: 16.5 days. As a result, a series of loading doses is needed to achieve steady state quickly.

Adverse Effects. The most common adverse effects are diarrhea (17%), respiratory infection (15%), reversible alopecia (10%), rash (10%), and nausea (9%). The drug has also been associated with much more serious reactions: pancytopenia, Stevens-Johnson syndrome, and severe hypertension.

Leflunomide is *hepatotoxic*. Elevation of liver enzymes occurs in about 10% of patients. In postmarketing reports, the drug has been associated with over 130 cases of severe liver injury, including 14 that were fatal. Liver function should be assessed at baseline, every month for the first 6 months of treatment, and every 6 to 8 weeks thereafter. Leflunomide should be avoided in patients with liver impairment, hepatitis B, or hepatitis C. Patients should be informed about signs of liver injury—abdominal pain, fatigue, dark urine, and jaundice—and advised to report them immediately.

Leflunomide may increase the risk of *serious infection*. The drug is immunosuppressive and can suppress the bone marrow. Rarely, patients experience sepsis and other severe infections, including tuberculosis. Deaths have occurred. If an infection develops, it may be necessary to interrupt leflunomide use. To reduce risk, platelet counts and blood cell counts should be conducted at baseline, every month for the first 6 months of treatment, and every 6 to 8 weeks thereafter. If evidence of bone marrow suppression is detected, leflunomide should be discontinued. Patients should be screened for tuberculosis before starting this drug.

Leflunomide is carcinogenic in animals, but has not been associated with cancer in humans.

Leflunomide and Pregnancy. Leflunomide is contraindicated during pregnancy. The drug is teratogenic and embryotoxic in animals and has been classified in Food and Drug Administration (FDA) Pregnancy Risk Category X. Women of child-bearing age must use a reliable form of contraception.

Patients who wish to become pregnant must first clear leflunomide from the body. A three-step protocol is followed:

Step 1: Discontinue leflunomide.

Step 2: Take cholestyramine (8 gm 3 times a day) for 11 days. (Cholestyramine binds leflunomide and its metabolites in the intestine, and thereby accelerates their excretion. Without cholestyramine, safe levels might not be achieved for 2 years.)

Step 3: Verify that plasma drug levels are below 20 mcg/L.

To minimize any risk of fetal injury, men using leflunomide who wish to father a child should undergo the same clearance procedure.

Drug Interactions. Leflunomide can inhibit the metabolism of certain NSAIDs (eg, ibuprofen, diclofenac), causing their levels to rise. In addition, leflunomide can intensify liver damage from other hepatotoxic drugs (eg, methotrexate), and hence should not be combined with such agents. Rifampin (a drug for tuberculosis) can raise leflunomide levels by 40%. Conversely, two other agents—cholestyramine and activated charcoal—can rapidly lower leflunomide levels.

Preparations, Dosage, and Administration. Leflunomide [Arava] is available in 10- and 20-mg tablets for oral dosing. Treatment begins with a series of loading doses (100 mg once a day for 3 days) followed by daily maintenance doses of 10 or 20 mg.

Hydroxychloroquine

Hydroxychloroquine [Plaquenil], a drug with antimalarial actions, is considered a preferred DMARD in the 2008 ACR treatment guidelines. As a rule, the drug is usually combined with methotrexate. By itself, hydroxychloroquine does not slow disease progression, but early use *can* improve long-term outcomes. Like other DMARDs, hydroxychloroquine has a delayed onset; full therapeutic effects take 3 to 6 months to develop. Concurrent therapy with anti-inflammatory agents (NSAIDs or glucocorticoids) is indicated during the latency period. How hydroxychloroquine works in RA is unknown.

Retinal damage, which is rare, is the most serious toxicity. Retinopathy may be irreversible and can produce blindness. Visual loss is directly related to dosage. Low doses may be used in long-term treatment with little risk. When dosage has been excessive, retinal damage may appear after treatment has ceased and may progress in the absence of continued drug use. Patients should undergo a thorough ophthalmologic exam prior to treatment and every 6 months thereafter. Hydroxychloroquine should be discontinued at the first sign of retinal injury. Patients should be advised to contact the prescriber if any visual disturbance is noted.

Minocycline

Minocycline [Minocin], an antibiotic in the tetracycline family, can improve symptoms in patients with RA. The drug was originally tried because of suspicions that RA may have an infectious basis in some patients. However, it now appears that the most likely mechanism underlying benefits is inhibition of collagenase, an enzyme that promotes joint destruction. Other potential mechanisms include inhibition of phospholipase A₂, interleukins, leukocyte infiltration, and lymphocyte proliferation.

In patients with RA, minocycline can improve morning stiffness, joint pain and tenderness, and activities of daily living. In addition, it may delay disease progression in some patients. The usual dosage is 100 mg twice daily. Increasing the dosage increases adverse effects but does not increase benefits. Symptoms begin improving within 12 weeks, but may not be maximal until 12 months. Adverse effects include dizziness and skin rash. Minocycline is an experimental therapy, and hence should be reserved for patients who have not responded to other DMARDs.

Other Nonbiologic DMARDs

Several drugs that are FDA approved for RA are used infrequently, largely because of adverse effects. These drugs are discussed briefly below. For more information, refer to the 6th edition of this book.

Penicillamine. Penicillamine [Cuprimine, Depen] can relieve symptoms of RA and can retard disease progression. Unfortunately, treatment may be associated with serious toxicity, especially bone marrow suppression and autoimmune disorders. Therapeutic effects take 3 to 6 months to develop. The pharmacology of penicillamine is discussed further in Chapter 109 (Management of Poisoning).

Gold Salts. Gold salts—gold sodium thiomalate [Aurolate, Myochryline] and auranofin [Ridaura]—have been used in RA for decades. Treatment can relieve pain and stiffness, and may also retard disease progression. The mechanism underlying these benefits is unknown. Unfortunately, adverse ef-

fects are common. Potential reactions include intense pruritus, rashes, stomatitis, kidney damage, severe blood dyscrasias, encephalitis, hepatitis, peripheral neuritis, pulmonary infiltrates, and profound hypotension.

Azathioprine. Azathioprine [Imuran] is an older DMARD with immunosuppressive and anti-inflammatory actions. Serious toxicities include hepatitis and blood dyscrasias (leukopenia, thrombocytopenia, anemia). Also, azathioprine is teratogenic in animals and should not be used during pregnancy. The drug may also pose a small risk of malignancy. As discussed in Chapter 69 (Immunosuppressants), azathioprine is also used to prevent rejection of kidney transplants.

Cyclosporine. Cyclosporine, an immunosuppressive drug used to prevent rejection of transplanted organs, can reduce symptoms of RA. Because it can cause kidney damage and other serious adverse effects, cyclosporine should be reserved for severe, progressive RA that has not responded to safer DMARDs. In patients with an inadequate response to methotrexate, adding cyclosporine may produce significant improvement. Cyclosporine is discussed at length in Chapter 69 (Immunosuppressants).

Protein A Column [ProSORba]. The *ProSORba* column, used in combination with plasmapheresis, decreases the titer of circulating immune complexes that promote symptoms of RA. The column contains an adsorbent compound—*protein A*—that binds to antibodies of the immunoglobulin G (IgG) class and to IgG-antigen complexes. When the patient's plasma is passed through the column, these antibodies and immune complexes are removed. Treatment should be reserved for patients with moderate to severe RA who have been refractory to or intolerant of methotrexate and other DMARDs. The most common adverse effects are transient increases in joint swelling, joint pain, and fatigue.

BIOLOGIC DMARDs

The biologic DMARDs are immunosuppressive drugs that target specific components of the inflammatory process (Table 73-2). These drugs are usually combined with methotrexate. Of the biologic agents available, only seven are used routinely. Five of these—etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol—interfere with tumor necrosis factor (TNF). One agent—rituximab—promotes destruction of B lymphocytes. And one agent—abatacept—inhibits activation of T lymphocytes. Since these drugs suppress immune function, they all pose a risk of serious infections, and perhaps cancer. As noted, the biologic DMARDs are so named because they are manufactured using recombinant DNA technology, an expensive process that is reflected in the cost of these drugs, which can range from \$14,000 to more than \$35,000 a year.

Tumor Necrosis Factor Antagonists

The drugs in this group work by neutralizing TNF, an important immune mediator of joint injury in RA. Five TNF antagonists are available. In patients with RA, all five are highly and equally effective. Unfortunately, all five pose a risk of serious infections, including bacterial sepsis, invasive fungal infections, hepatitis B infection, and tuberculosis (TB). Rarely, patients experience severe allergic reactions, heart failure, liver failure, hematologic disorders, neurologic disorders, or cancer. The principal differences among these drugs concern dosing schedule and route of administration:

- Etanercept [Enbrel]—subQ once a week
- Adalimumab [Humira]—subQ every 2 weeks
- Certolizumab pegol [Cimzia]—subQ every 2 or 4 weeks
- Golimumab [Simponi]—subQ every 4 weeks
- Infliximab [Remicade]—IV every 8 weeks

In addition to their use in RA, these drugs are approved for other inflammatory disorders, including psoriatic arthritis, ankylosing spondylitis, and Crohn's disease (Table 73-3).

TABLE 73-2 ■ Disease-Modifying Antirheumatic Drugs (DMARDs)

NONBIOLOGIC (TRADITIONAL) DMARDs

Major Drugs

- Methotrexate [Rheumatrex, Trexall]
- Sulfasalazine [Azulfidine]
- Leflunomide [Arava]
- Minocycline [Minocin]
- Hydroxychloroquine [Plaquenil]

Minor Drugs

- Azathioprine [Imuran]
- Cyclosporine [Neoral, Sandimmune]
- Penicillamine [Cuprimine, Depen]
- Protein A [Prosorba]
- Gold salts:
 - Gold sodium thiomalate [Aurolate, Myochrysine]
 - Auranofin [Ridaura]

BIOLOGIC DMARDs

Tumor Necrosis Factor Antagonists

- Adalimumab [Humira]
- Certolizumab pegol [Cimzia]
- Etanercept [Enbrel]
- Golimumab [Simponi]
- Infliximab [Remicade]

B-Lymphocyte-Depleting Agents

- Rituximab [Rituxan]

T-Cell Activation Inhibitors

- Abatacept [Orencia]

Interleukin-6 Receptor Antagonists

- Tocilizumab [Actemra]

Interleukin-1 Receptor Antagonists

- Anakinra [Kineret]

Etanercept

Etanercept [Enbrel], approved in 1998, was the first TNF antagonist available, and will serve as our prototype for the group. Like all other TNF antagonists, etanercept is highly effective at reducing RA symptoms and disease progression, but may also promote serious infections and other adverse effects.

Mechanism of Action. Etanercept suppresses inflammation by neutralizing TNF. As noted above, TNF is an important contributor to RA pathophysiology. In patients with RA,

TNF binds with receptors on cells in the synovium, and thereby stimulates production of chemotactic factors and endothelial adhesion molecules, which in turn promote infiltration of neutrophils and macrophages. The result is inflammation and joint destruction.

How does etanercept neutralize TNF? Etanercept is a large molecule composed of two receptors for TNF that are linked to the Fc component of immunoglobulin G (IgG). The TNF receptors, which are produced through recombinant DNA technology, are identical to the TNF receptors found on human cells. Like the TNF receptors on our cells, etanercept binds tightly with TNF, and thereby prevents TNF from interacting with its natural receptors on cells.

Therapeutic Uses. Etanercept is indicated for patients with moderately to severely active RA. In clinical trials, the drug was slightly superior to methotrexate at delaying progression of joint damage, and it suppressed signs and symptoms of RA more rapidly. Among patients who had failed to respond to methotrexate, addition of etanercept for 6 months reduced symptoms in 61%, compared with 27% who continued taking methotrexate alone.

In addition to RA, etanercept is approved for ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and juvenile idiopathic arthritis.

Pharmacokinetics. Etanercept is administered by subQ injection. Plasma levels peak about 3 days after dosing. The drug is cleared from the plasma with a half-life of 115 hours (about 5 days). The mode of elimination is unknown.

Adverse Effects. Mild Effects. Injection-site reactions—itching, erythema, swelling, pain—occur in 37% of patients, but usually subside in a few days. Other mild but less common reactions include headache, rhinitis, dizziness, cough, and abdominal pain.

Serious Infections. Etanercept increases the risk of serious infections, including invasive fungal infections (eg, histoplasmosis, coccidioidomycosis, candidiasis), and infections caused by *Mycobacterium tuberculosis* and other opportunistic pathogens, such as *Legionella pneumophila* and *Listeria monocytogenes*. Why do these infections develop? Under normal conditions, TNF plays a crucial role in our immune response to infection, especially those caused by *M. tuberculosis* and other intracellular pathogens. Accordingly, when we neutralize TNF with etanercept, the risk of infections goes up. Infection risk is further increased by diabetes, HIV infection, and concurrent use of immunosuppressant drugs, including glucocorticoids and methotrexate.

TABLE 73-3 ■ Approved Indications for TNF Antagonists

Approved Indications	Etanercept [Enbrel]	Infliximab [Remicade]	Adalimumab [Humira]	Golimumab [Simponi]	Certolizumab [Cimzia]
Rheumatoid arthritis	✓	✓	✓	✓	✓
Ankylosing spondylitis	✓		✓	✓	
Juvenile idiopathic arthritis	✓		✓		
Psoriatic arthritis	✓	✓	✓	✓	
Plaque psoriasis	✓	✓	✓		
Crohn's disease		✓	✓		✓
Ulcerative colitis		✓			

Tuberculosis is a special concern. When TB develops in patients taking etanercept, the disease is often extrapulmonary and disseminated. To reduce risk, potential users should be tested for latent TB and, if the test is positive, should undergo TB treatment before etanercept is used. During etanercept treatment, patients should be monitored closely for TB development.

Etanercept may promote reactivation of latent infection with hepatitis B virus (HBV). Fatalities have occurred. Candidates for etanercept therapy should be tested for latent HBV, and those who test positive should be monitored closely. If reactivation of HBV infection occurs, etanercept should be stopped and the patient given antiviral drugs.

To reduce infection risk, etanercept should not be given to patients with active infection, including infections that are chronic or localized. Patients who develop a new infection should be monitored closely. Etanercept should be used with caution in patients with a history of recurrent infection or any condition that predisposes them to acquiring infection (eg, advanced or poorly controlled diabetes). If a severe infection develops, etanercept should be discontinued.

Severe Allergic Reactions. Rarely, etanercept has been associated with severe allergic reactions, including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), and toxic epidermal necrolysis (TEN). As of 2006, 22 such cases had been reported. The median onset was 28 days after starting etanercept. Patients and providers should be alert for these reactions.

Heart Failure. Etanercept may pose a risk of heart failure. In patients using the drug, existing cases of heart failure have gotten worse, and new cases have developed. Exercise caution in patients with existing heart failure, and monitor them closely for disease progression.

Cancer. Etanercept and other TNF antagonists may increase the risk of lymphoma and other malignancies, primarily in children, adolescents, and young adults.

Hematologic Disorders. Etanercept may pose a small risk of hematologic disorders, including neutropenia, thrombocytopenia, and aplastic anemia, which can be fatal. Advise patients who develop signs or symptoms of a blood disorder (persistent fever, bruising, bleeding, pallor) to seek immediate medical attention. If a significant hematologic abnormality is diagnosed, discontinuing etanercept should be considered.

Liver Injury. Rarely, etanercept has been associated with severe liver injury, including acute liver failure. Some patients have required a liver transplant, and some have died. Patients should be informed about symptoms of liver injury—fatigue, yellow skin, yellow eyes, anorexia, right-side abdominal pain, dark brown urine—and advised to seek medical attention if these develop. If severe liver injury is diagnosed, discontinuation of etanercept should be considered. Etanercept should be used with caution in patients with pre-existing liver dysfunction.

Central Nervous System (CNS) Demyelinating Disorders. Etanercept has been associated with rare cases of CNS demyelinating disorders, including multiple sclerosis, myelitis, and optic neuritis. However, a causal relationship has not been established. Nonetheless, caution is advised, especially in patients with a pre-existing or recent-onset demyelinating disorder.

Drug Interactions. By neutralizing TNF, etanercept may increase the risk of acquiring or transmitting infection follow-

ing immunization with a *live vaccine*. Accordingly, live vaccines should be avoided. In pediatric patients, vaccinations should be up to date before starting the drug.

Immunosuppressant drugs—including glucocorticoids, methotrexate, tocilizumab, anakinra, and abatacept—increase the risk of serious infection. Use these combinations with caution.

Preparations, Dosage, and Administration. Etanercept [Enbrel] is available in three formulations: (1) single-use pre-filled syringes (25 and 50 mg), (2) single-use *SureClick* auto-injectors (50 mg), and (3) a 25-mg powder to be reconstituted in 1 mL of sterile bacteriostatic water (supplied by the manufacturer). Administration is by subQ injection, usually into the abdomen or anterior thigh, but avoiding areas that are tender, bruised, red, or hard. Solutions that are discolored or cloudy or contain particles should not be used. The usual adult dosage is 50 mg subQ once a week. The dosage for children 4 to 17 years old is 0.8 mg/kg (up to a maximum of 50 mg) once a week. Etanercept is expensive: The cost for a 12-month course of treatment is about \$23,400.

Infliximab

Actions and Uses. Infliximab [Remicade], formulated for IV use, was the second TNF antagonist approved for RA. Like etanercept, infliximab binds to and thereby neutralizes TNF. However, the two drugs are structurally different: whereas etanercept is composed of two TNF receptors, infliximab is a TNF antibody.

Infliximab has several approved uses. In patients with RA, the drug is approved for combined use with methotrexate to reduce symptoms and delay disease progression. Infliximab is also approved for psoriasis (see Chapter 105) and two intestinal disorders: Crohn's disease and ulcerative colitis (see Chapter 80).

Adverse Effects. Like etanercept, infliximab has immunosuppressant actions, and hence can increase the risk of serious infection, including bacterial sepsis, invasive fungal infections, HBV infection, and TB. Accordingly, the drug should not be given to patients with chronic infections, and should be temporarily withdrawn if an acute infection develops. Patients should receive a TB test and HBV test to rule out latent infection prior to treatment.

Like other TNF inhibitors, infliximab has been associated with rare cases of heart failure, liver failure, hematologic disorders, neurologic disorders, severe allergic reactions, and cancer.

Preparations, Dosage, and Administration. Infliximab is supplied as a powder (100 mg in single-use vials) to be dissolved in 10 mL of sterile water, followed by dilution in 0.9% sodium chloride to a final volume of 250 mL. The solution should be clear, and either colorless or pale yellow. Solutions that are discolored or contain particles should not be used. Administration is by slow IV infusion (over 2 hours or more)—starting within 3 hours of preparing the solution—using an infusion set with an in-line filter. The dosage is 3 mg/kg at weeks 0, 2, and 6, and then every 8 weeks thereafter. Patients should also receive methotrexate (oral or subQ).

Infusion reactions are common, manifesting as flu-like symptoms, headache, fever, chills, dyspnea, hypotension, skin reactions, and GI disturbance. Rarely, patients experience anaphylaxis. Symptoms can be reduced by pretreatment with an antihistamine, acetaminophen, and/or a glucocorticoid. Mild reactions can be managed by slowing or interrupting the infusion. If anaphylaxis develops, the infusion should be stopped.

Infliximab is expensive: Depending on dosage and dosing schedule, treatment costs between \$14,000 and \$37,000 a year.

Adalimumab

Like infliximab, adalimumab [Humira] is a monoclonal antibody that binds to and thereby neutralizes TNF. The drug is indicated for adults with moderate to severe RA who have not responded adequately to one or more DMARDs. In these patients, adalimumab can reduce symptoms and slow progression of joint damage. The drug may be used alone or in combination with methotrexate or other DMARDs. In addition to RA, adalimumab is approved for ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, and Crohn's disease.

Adalimumab is generally well tolerated. The most common side effects are injection-site reactions (rash, erythema, itching, pain, swelling), which develop in about 20% of patients. Like other TNF inhibitors, adalimumab can promote serious infections (eg, bacterial sepsis, invasive fungal infections, HBV infection, TB), and has been associated with rare cases of heart failure, liver failure, hematologic disorders, neurologic disorders, severe allergic reactions, and cancer.

Adalimumab [Humira] is supplied in single-use, pre-filled syringes (40 and 80 mg) and single-use, pre-filled auto-injectors (80 mg). Administration is by subQ injection in the anterior thigh or abdomen. The injection giver—physician, nurse, patient, or caregiver—should rotate the injection site and avoid areas where the skin is tender, bruised, red, or hard. The recommended dosage for RA in adults is 40 mg every 2 weeks. If adalimumab is being used without methotrexate, giving it more frequently (40 mg once a week) may improve results. The drug should be stored cold -2°C to 8°C (36°F to 46°F)—and protected from light. Like other TNF inhibitors, adalimumab is expensive: For patients taking 40 mg every 2 weeks, the annual cost is about \$19,200.

Golimumab

In 2009, golimumab [Simponi] became the fourth TNF antagonist approved for RA—but only in combination with methotrexate. Like infliximab, golimumab is a monoclonal antibody that binds with and thereby neutralizes TNF. In addition to RA, golimumab is approved for ankylosing spondylitis and psoriatic arthritis. For both conditions, golimumab may be used alone or combined with methotrexate. For all indications, treatment is done by monthly subQ injections.

In clinical trials, the most common adverse effects were injection-site reactions, upper respiratory tract infections, and nasopharyngitis. However, except for injection-site reactions, the incidence of these adverse effects was only slightly higher than in patients receiving placebo. Like other TNF inhibitors, golimumab can promote serious infections (eg, bacterial sepsis, invasive fungal infections, HBV infection, TB), and has been associated with rare cases of heart failure, liver failure, hematologic disorders, neurologic disorders, severe allergic reactions, and cancer.

Golimumab [Simponi] is supplied as a solution (50 mg/0.5 mL) in single-dose, pre-filled syringes and single-dose, pre-filled *SmartJet* auto-injectors. Syringes and auto-injectors should be stored cold (36° to 46°F), and allowed to warm up at room temperature for 30 minutes prior to use. The usual dosage is 50 mg subQ once a month, usually into the abdomen or anterior thigh. Sites that are tender, bruised, red, or hard should not be used. Like other TNF inhibitors, golimumab is expensive, costing about \$24,000 a year.

Certolizumab Pegol

Certolizumab pegol [Cimzia] is a monoclonal antibody derivative designed to neutralize TNF. The drug consists of a recombinant humanized Fab antibody fragment that has been covalently bound to polyethylene glycol (PEG). Because of this “pegylation,” the drug is eliminated slowly, with a half-life of 17 days. Certolizumab has two approved indications: (1) treatment of adults with moderate to severe RA, and (2) treatment of Crohn’s disease (see Chapter 80). In patients with RA, the combination of certolizumab plus methotrexate is more effective than methotrexate alone.

Certolizumab can cause serious adverse effects. In clinical trials, the most common events were upper respiratory tract infections, urinary tract infections, and arthralgia. Like other TNF inhibitors, certolizumab can promote serious infections (eg, bacterial sepsis, invasive fungal infections, HBV infection, TB), and has been associated with rare cases of heart failure, liver failure, hematologic disorders, neurologic disorders, severe allergic reactions, and cancer.

Certolizumab [Cimzia] is available in two formulations: (1) a 200-mg pre-filled syringe (for injection by the patient or caregiver) and (2) a 200-mg powder (for reconstitution and injection by a healthcare provider). Solutions prepared from the powder should be used within 2 hours (if held at room temperature) or within 24 hours (if refrigerated). For RA, treatment starts with 3 doses, given at weeks 0, 2, and 4. Each dose consists of two subQ injections (200 mg each, 400 mg total) made at separate sites on the abdomen or thigh. After that, patients receive maintenance doses of 200 mg (or sometimes 400 mg) every 2 weeks. Treatment costs about \$23,400 per year.

Rituximab, a B-Lymphocyte-Depleting Agent

Actions and Uses

Rituximab [Rituxan] reduces the number of B lymphocytes, cells that play an important role in the autoimmune attack on joints. As a result, rituximab can reduce symptoms of RA and slow disease progression. How does it work? Rituximab is a monoclonal antibody directed against CD20, an antigen found exclusively on the surface of B lymphocytes. When rituximab binds with CD20, the immune system attacks the rituximab-B-cell complex, causing B-cell lysis and death.

Rituximab, in combination with methotrexate, is indicated for IV therapy of adults with moderate to severe RA who have not responded to one or more TNF antagonists. In addition, rituximab is indicated for two inflammatory disorders of blood vessels—Wegener’s granulomatosis and microscopic polyangiitis—and for two types of cancer: B-cell non-Hodgkin’s lymphoma and B-cell chronic lymphocytic leukemia (see Chapter 103).

Adverse Effects

Infusion Reactions. Rituximab can cause severe infusion-related hypersensitivity reactions, beginning within 30 to 120 minutes. The immediate reaction and its sequelae include hypotension, bronchospasm, angioedema, hypoxia, pulmonary infiltrates, myocardial infarction, and cardiogenic shock. Deaths have occurred within 24 hours. To reduce the risk of these events, patients should be premedicated with an antihistamine and acetaminophen, and monitored during the infusion. If a severe reaction occurs, management includes giving glucocorticoids, epinephrine, bronchodilators, and oxygen.

Mucocutaneous Reactions. Rituximab has been associated with severe mucocutaneous reactions, including SJS, lichenoid dermatitis, vesiculobullous dermatitis, and TEN. Deaths have occurred. Reaction onset is typically 1 to 3 weeks after rituximab exposure. Patients who experience these reactions should seek immediate medical attention, and should not receive rituximab again.

Hepatitis B Reactivation. There have been reports of hepatitis B virus (HBV) reactivation, leading to fulminant hepatitis, hepatic failure, and death. Patients at high risk of HBV should be screened before getting rituximab. Asymptomatic carriers should be closely monitored for clinical and laboratory signs of active HBV infection while taking rituximab, and for several months after stopping.

Progressive Multifocal Leukoencephalopathy (PML). Rituximab has been associated with rare cases of PML, a severe infection of the CNS caused by reactivation of the JC virus, an opportunistic pathogen resistant to all available drugs. Most cases have occurred in patients being treated for non-Hodgkin’s lymphoma. Patients and prescribers should be alert for any new neurologic signs and symptoms. If PML is diagnosed, rituximab should be discontinued immediately.

Other Adverse Effects. Like other monoclonal antibodies, rituximab can cause a flu-like syndrome, especially during the initial infusion. Symptoms include fever, chills, nausea, vomiting, and myalgia. Rituximab causes transient neutropenia, but this does not appear to increase the risk of infection.

Preparations, Dosage, and Administration

Rituximab [Rituxan] is supplied in solution (10 mg/mL) in 10- and 50-mL single-use vials. The concentrated solution should be diluted in 0.9% sodium chloride or 5% dextrose in water to a final concentration of 1 to 4 mg/mL, and then administered by IV infusion. To reduce the risk of infusion reactions, patients should be premedicated with an antihistamine and acetaminophen. For RA, dosing consists of two 1000-mg infusions given 2 weeks apart. The first infusion should start at 50 mg/hr, and then, if no infusion reaction occurs, the rate may be slowly increased to a maximum of 400 mg/hr. If the first infusion is well tolerated, the second can be started at 100 mg/hr, and then, if well tolerated, gradually increased to 400 mg/hr.

Abatacept, a T-Cell Activation Inhibitor

Abatacept [Orencia], a first-in-class T-cell activation inhibitor, reduces symptoms of RA and disease progression. Patients who have not responded adequately to methotrexate or TNF antagonists have experienced significant improvement with this drug. Like other biologic DMARDs, abatacept poses a risk of serious infections, and may also pose a small risk of cancer.

Therapeutic Uses. Abatacept has two approved indications. In 2006, the drug was approved for reducing symptoms and delaying disease progression in adults with moderately to severely active RA. For these patients, abatacept may be used alone or in combination with most other DMARDs, but not with TNF antagonists or anakinra. In 2007, abatacept was approved for decreasing symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in children 6 years and older. For these patients, the drug may be used alone or in combination with methotrexate.

Mechanism of Action. In patients with RA, activated T lymphocytes play a key role in the autoimmune attack on joints. Abatacept prevents T-cell activation. Here’s how. For T cells to achieve full activity, they must be stimulated by antigen-presenting cells (APCs). Abatacept—a complex molecule composed of a ligand (cytotoxic T-lymphocyte-associated antigen 4) linked to immunoglobulin G1—binds with receptors on APCs, and thereby prevents the APCs from activating T cells. The result is reduced T-cell proliferation, and reduced production of interferon gamma, interleukins, and TNF.

Adverse Effects. Abatacept is generally well tolerated. The most common adverse effects are headache, upper respiratory infection, nasopharyngitis, and nausea.

Because abatacept suppresses immune function, the drug can increase the risk of serious infections. Infections seen most often are pneumonia, cellulitis, bronchitis, diverticulitis, pyelonephritis, and urinary tract infections. Patients should be told about infection risk and advised to report suspected in-

infection immediately. If a serious infection develops, abatacept should be discontinued.

Abatacept may blunt the effect of all vaccines, and may increase the risk of infection from live vaccines. Before abatacept is given to children, all vaccinations should be up to date. Live vaccines should not be used in children or adults during abatacept use and for 3 months after stopping.

Drug Interactions. Abatacept should not be used in conjunction with TNF antagonists. Why? Because the combination increases the risk of serious infection, and offers no benefit over abatacept alone.

Preparations, Dosage, and Administration. For treatment of RA, abatacept is available in IV and subQ formulations.

Intravenous. Abatacept for IV use is supplied as a 250-mg powder to be reconstituted with sterile water, using the disposable *silicon-free* syringe provided. To minimize foam formation, the vial should be rotated with gentle swirling until the contents are completely dissolved. Following reconstitution, the solution should be diluted to a final volume of 100 mL. Solutions that are discolored or contain particles should be discarded. Administer using an infusion set with a sterile, nonpyrogenic, low-protein-binding filter (pore size 0.2 to 1.2 micrometer). Each dose should be infused over a 30-minute span. No other agents should be given through the same line.

The dosage for RA in adults is based on body weight as follows: less than 60 kg, give 500 mg; 60 to 100 kg, give 750 mg; and over 100 kg, give 1000 mg. Dosing is done on days 0, 14, and 28, and every 4 weeks thereafter.

The dosage for polyarticular juvenile idiopathic arthritis is based on body weight as follows: less than 75 kg, give 10 mg/kg; 75 to 100 kg, give 750 mg; and over 100 kg, give 1000 mg. In adults, dosing is done on days 0, 14, and 28, and every 4 weeks thereafter.

Subcutaneous. Abatacept for subQ dosing is supplied in single-dose, pre-filled syringes (125 mg in 1 mL of solution). All patients receive the same dose: 125 mg subQ every week, preferably following a single IV loading dose (10 mg/kg). Patients switching from monthly IV abatacept should get their first subQ dose 4 weeks after their last IV dose. Subcutaneous abatacept may be administered at home or in the provider's office.

Tocilizumab, an Interleukin-6 Receptor Antagonist

In patients with RA, interleukin-6 (IL-6) helps amplify the autoimmune attack on joints. Accordingly, drugs that block the actions of IL-6 can reduce RA symptoms and disease progression. At this time, tocilizumab is the only drug that works by this mechanism.

Actions and Therapeutic Use

Tocilizumab [Actemra] is a first-in-class IL-6 receptor antagonist. In 2010, the FDA approved tocilizumab for IV therapy of adults with moderately to severely active RA. However, owing to the risk of infection and other serious adverse effects, tocilizumab is indicated only for patients who have not responded adequately to a TNF antagonist. In five clinical trials involving over 4000 patients, tocilizumab was significantly more effective than placebo at reducing joint tenderness and swelling. Tocilizumab may be combined with methotrexate, but not with TNF inhibitors or other DMARDs that increase the risk of infection.

How does tocilizumab work? The drug is a monoclonal antibody that blocks receptors for IL-6, a proinflammatory cytokine that helps mediate the autoimmune attack against the joints of patients with RA. By blocking IL-6 receptors, tocilizumab prevents IL-6 from promoting injury. Tocilizumab is the first drug to work by this mechanism.

Adverse Effects

The most serious adverse effects are infections, GI perforation, liver injury, and hematologic effects: neutropenia and thrombocytopenia. Other adverse effects include headache, nasopharyngitis, hypertension, and increased cholesterol levels.

Serious Infections. Owing to its immunosuppressant actions, tocilizumab increases the risk of life-threatening infections. Infections seen in clinical trials include TB, invasive fungal infections, and opportunistic infections caused by bacteria, viruses, protozoa, and other pathogens. Before

starting tocilizumab, patients should be tested for latent TB and treated as indicated. During tocilizumab therapy, patients should be closely monitored for signs and symptoms of infection and, if an infection develops, tocilizumab should be interrupted until the infection is under control.

GI Perforation. In clinical trials, perforation of the colon occurred at a rate of 0.26 events per 100 patient-years. Most cases were complications of pre-existing diverticulitis (ie, inflammation of diverticula [small outpouchings] along the colon wall). Patients at high risk for perforation—especially those with diverticulitis—should be closely monitored. Patients should be instructed to contact their prescriber in the event of severe, persistent abdominal pain.

Liver Injury. Tocilizumab can cause liver injury, as indicated by elevation of circulating liver transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]). Tocilizumab should not be initiated if transaminase levels are more than 2 times the upper limit of normal (ULN). Transaminase levels should be monitored every 4 to 8 weeks during treatment and, if the levels exceed 5 times the ULN, tocilizumab should be discontinued.

Neutropenia and Thrombocytopenia. Tocilizumab can reduce counts of neutrophils and platelets. Neutrophil reduction increases the risk of infection. In clinical trials, reduction of platelets was *not* associated with increased bleeding. Neutrophil and platelet counts should be determined at baseline and every 4 to 8 weeks during treatment. Tocilizumab should not be initiated if the absolute neutrophil count (ANC) is below 2000/mm³, or if the platelet count is below 100,000/mm³. Patients taking tocilizumab should discontinue the drug if the ANC falls below 500/mm³, or if the platelet count falls below 50,000/mm³.

Drug Interactions

In general, tocilizumab should not be combined with other *strong immunosuppressants*, owing to an increased risk of serious infections. Antirheumatic drugs to avoid include the TNF antagonists (eg, etanercept), T-cell inhibitors (eg, abatacept), interleukin-1 antagonists (eg, anakinra), and drugs that block the CD20 antigen (eg, rituximab).

Tocilizumab can reduce blood levels of other drugs. Here's how. Under normal circumstances, IL-6 suppresses the activity of several cytochrome P450 drug-metabolizing isozymes. By blocking receptors for IL-6, tocilizumab can negate that suppression, and can thereby increase rates of drug metabolism. Drugs whose levels may be diminished include oral contraceptives, warfarin (an anticoagulant), proton pump inhibitors (which reduce gastric acidity), and HMG-CoA reductase inhibitors (which reduce cholesterol levels). Dosages for all of these agents may need to be increased.

Preparations, Dosage, and Administration

Tocilizumab [Actemra] is supplied in single-use vials (4, 10, and 20 mL) as a concentrated solution (20 mg/mL) for dilution in 0.9% sodium chloride to a final volume of 100 mL. The initial dosage is 4 mg/kg every 4 weeks, given as a single 60-minute IV drip infusion. The dosage can be increased to 8 mg/kg every 4 weeks based on the clinical response. The maximum single dose is 800 mg. In the event of certain laboratory changes—increased transaminase levels, reduced neutrophil counts, or reduced platelet counts—tocilizumab should be given in reduced dosage or discontinued, depending on the magnitude of the change. Treatment should be interrupted if the patient develops a serious infection. Tocilizumab should be stored cold (36°F to 46°F), but not frozen.

Anakinra, an Interleukin-1 Receptor Antagonist

Anakinra [Kineret], approved in 2001, reduces symptoms of RA by blocking receptors for interleukin-1, a proinflammatory cytokine that plays a central role in synovial inflammation and joint destruction. The drug is indicated for patients with moderate to severe RA that has not responded to one or more nonbiologic DMARDs (eg, methotrexate). Like the TNF antagonists, anakinra poses a risk of serious infections. Accordingly, the drug should not be given to patients with active infection, and should be stopped if a serious infection develops. Because both anakinra and the TNF antagonists increase infection risk, these drugs should not be combined.

KEY POINTS

- The objectives of RA therapy are to (1) reduce symptoms (pain, inflammation, stiffness), (2) maintain joint function and range of motion, (3) minimize systemic involvement, and (4) delay disease progression.
- RA is treated with three classes of drugs: (1) nonsteroidal anti-inflammatory drugs (NSAIDs), (2) glucocorticoids, and (3) disease-modifying antirheumatic drugs (DMARDs).
- DMARDs can be divided into two groups: (1) nonbiologic (traditional) DMARDs, which are small molecules produced by conventional chemical techniques; and (2) biologic DMARDs, which are large molecules produced by recombinant DNA technology.
- NSAIDs act quickly to relieve symptoms, but do not prevent joint injury and do not delay disease progression.
- Glucocorticoids act quickly and may delay disease progression.
- DMARDs delay disease progression and reduce joint injury, but onset of benefits is delayed.
- In the past, treatment of RA was initiated with NSAIDs alone; DMARDs were added only after NSAIDs could no longer control symptoms. Today, guidelines recommend initiating DMARDs within 3 months of RA diagnosis; the rationale is to delay joint degeneration and retard disease progression. During the DMARD latency period, NSAIDs (and sometimes glucocorticoids) are used to control symptoms.
- NSAIDs are much safer than glucocorticoids and DMARDs.
- Because glucocorticoids cause serious toxicity when used long term, they are generally reserved for short-term use to (1) control symptoms while responses to DMARDs are developing or (2) supplement other drugs when symptoms flare.
- Second-generation NSAIDs (COX-2 inhibitors, or coxibs) may cause less GI ulceration than first-generation NSAIDs, but are more expensive.
- The doses of NSAIDs used for RA are much higher than the doses used to relieve pain or fever.
- Methotrexate, a nonbiologic DMARD, acts relatively quickly and is considered the DMARD of first choice by most rheumatologists.
- Etanercept, a biologic DMARD, neutralizes TNF, and thereby suppresses the autoimmune attack on joints.
- Etanercept and other TNF antagonists pose a significant risk of serious infections (eg, bacterial sepsis, invasive fungal infections, TB, HBV infection), and are associated with rare cases of heart failure, liver failure, hematologic disorders, neurologic disorders, severe allergic reactions, and cancer.

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Summary of Major Nursing Implications*

TUMOR NECROSIS FACTOR ANTAGONISTS

Adalimumab
Certolizumab pegol
Etanercept
Golimumab
Infliximab

The nursing implications summarized below pertain only to the use of TNF antagonists for rheumatoid arthritis.

Preadministration Assessment

Therapeutic Goal

TNF inhibitors are used to reduce symptoms and delay disease progression in patients with moderate to severe RA.

Identifying High-Risk Patients

TNF inhibitors are *contraindicated* in patients with demyelinating disorders, severe heart failure, and active infections, including TB and HBV infection.

Exercise *caution* in patients who are immunosuppressed (eg, owing to HIV infection or immunosuppressant drugs), and in those with diabetes, mild heart failure, liver dysfunction, latent TB, latent HBV infection, a history

of recurrent infection, and any condition that predisposes to acquiring an infection.

Implementation: Administration

Routes

Subcutaneous. Adalimumab, certolizumab, etanercept, golimumab.

Intravenous. Infliximab.

Administration

Adalimumab, Certolizumab, Etanercept, Golimumab. Teach patients and caregivers how to make subQ injections, using either a syringe (adalimumab, certolizumab, etanercept, golimumab) or an auto-injector (adalimumab, etanercept, golimumab). Instruct patients to (1) make injections into the abdomen or anterior thigh, (2) rotate the injection site, and (3) avoid areas where the skin is tender, bruised, red, or hard.

Infliximab. To prepare the infusion solution, dissolve infliximab powder (100 mg) in 10 mL of sterile water, and then dilute this solution with 0.9% sodium chloride to a final volume of 250 mL. Discard solutions that are discolored or contain particles. Administer by slow IV infusion (over

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

2 hours or more)—starting within 3 hours of preparing the solution—using an infusion set with an in-line filter. All patients should also receive methotrexate (oral or subQ). Pretreat with acetaminophen, an antihistamine, and/or a glucocorticoid to reduce infusion reactions (see below).

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Serious Infections. TNF antagonists increase the risk of serious infections, including invasive fungal infections (eg, histoplasmosis, coccidioidomycosis, candidiasis), reactivated HBV infection, and infections caused by *M. tuberculosis* and other opportunistic pathogens. Risk is increased by diabetes, HIV infection, and concurrent use of immunosuppressant drugs.

In general, avoid TNF antagonists in patients with active infections, and closely monitor those who develop a new infection. Use caution in patients with a history of recurrent infection or any condition that predisposes them to acquiring an infection (eg, advanced or poorly controlled diabetes). If a severe infection develops, TNF antagonists should be discontinued. **Inform patients about the risk of infection, and instruct them to seek medical attention if signs of infection develop.**

To minimize the risk of TB, test patients for latent TB (using a blood test or tuberculin skin test) and, if the test is positive, treat for TB before starting the TNF antagonist. During TNF antagonist treatment, monitor closely for development of TB.

To minimize the risk of HBV reactivation, test for HBV before starting the TNF antagonist. Closely monitor patients with a positive result. If reactivation of HBV infection occurs, stop the TNF antagonist and treat with antiviral drugs.

Allergic Reactions. Rarely, TNF antagonists have been associated with severe allergic reactions, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis. **Inform patients about the risk of a severe reaction, and instruct them to seek medical attention if one develops.**

Heart Failure. TNF antagonists may cause new-onset heart failure, and may worsen existing heart failure. Exercise caution in patients with mild heart failure, and monitor them closely for heart failure progression. Avoid TNF antagonists in patients with severe heart failure.

Cancer. TNF antagonists may increase the risk of lymphoma and other malignancies, primarily in children, adolescents, and young adults. **Counsel patients about cancer risk.**

Hematologic Disorders. TNF antagonists may pose a risk of hematologic disorders, including neutropenia, thrombocytopenia, and aplastic anemia. **Inform patients about signs of a blood disorder (persistent fever, bruising, bleeding, pallor) and advise them to seek medical attention if these develop.** If a significant hematologic abnormality is diagnosed, discontinuing the TNF antagonist should be considered.

Liver Injury. Rarely, TNF inhibitors have been associated with severe liver injury, including acute liver failure. Some patients have required a liver transplant, and some have died. **Inform patients about symptoms of liver injury—fatigue, yellow skin, yellow eyes, anorexia, right-sided abdominal pain, dark brown urine—and advise them to seek medical attention if these develop.** If severe liver injury is diagnosed, discontinuing the TNF antagonist should be considered. Exercise caution in patients with pre-existing liver dysfunction.

CNS Demyelinating Disorders. TNF antagonists have been associated with rare cases of CNS demyelinating disorders, including multiple sclerosis, myelitis, and optic neuritis. Avoid TNF antagonists in patients with a pre-existing or recent-onset demyelinating disorder.

Injection-Site Reactions: Adalimumab, Certolizumab Pegol, Etanercept, and Golimumab. Injection-site reactions—redness, swelling, itching, pain—are common with these drugs. **Inform patients that symptoms usually subside in a few days, and advise them to contact the prescriber if the reaction persists.**

Infusion Reactions: Infliximab. Infusion reactions—flu-like symptoms, headache, fever, chills, dyspnea, hypotension, skin reactions, GI disturbance—are common with *infliximab*. To reduce symptoms, pretreat with an antihistamine, acetaminophen, and/or a glucocorticoid. Manage mild reactions by slowing or interrupting the infusion. In the event of a severe reaction (eg, anaphylaxis), stop the infusion and don't use *infliximab* again.

Minimizing Adverse Interactions

Immunosuppressants. Drugs that suppress immune function (eg, glucocorticoids, methotrexate, tocilizumab, anakinra, abatacept) increase the risk of infections. Use these drugs with caution.

Live Vaccines. TNF antagonists may increase the risk of acquiring or transmitting infection following immunization with a live vaccine. Accordingly, live vaccines should be avoided. **Inform parents that pediatric vaccinations should be current before therapy with a TNF antagonist starts.**

*Patient education information is highlighted as blue text.

Pathophysiology of Gout**Overview of Drug Therapy****Drugs for Acute Gouty Arthritis****Nonsteroidal Anti-inflammatory Drugs****Glucocorticoids****Colchicine****Drugs for Hyperuricemia (Urate-Lowering Therapy)****Xanthine Oxidase Inhibitors: Allopurinol and Febuxostat****Probenecid, a Uricosuric Agent****Pegloticase, a Recombinant Form of Uric Acid Oxidase**

Our topic for the chapter is gout, a painful inflammatory disorder seen mainly in men. Symptoms result from deposition of uric acid crystals in joints. We begin by discussing the pathophysiology of gout, after which we discuss the drugs used for treatment.

PATHOPHYSIOLOGY OF GOUT

Gout is a recurrent inflammatory disorder characterized by *hyperuricemia* (high blood levels of uric acid) and episodes of *severe joint pain*, typically in the large toe. Hyperuricemia—defined as blood uric acid above 7 mg/dL in men, or 6 mg/dL in women—can occur through two mechanisms: (1) excessive production of uric acid and (2) impaired renal excretion of uric acid. Acute attacks are precipitated by crystallization of sodium urate (the sodium salt of uric acid) in the synovial space. Deposition of urate crystals promotes inflammation by triggering a complex series of events. A key feature of the inflammatory process is infiltration of leukocytes, which, once inside the synovial cavity, phagocytize urate crystals and then break down, causing release of destructive lysosomal enzymes. When hyperuricemia is chronic, large and gritty deposits, known as *tophi*, may form in the affected joint. Also, deposition of urate crystals in the kidney may cause renal damage. Fortunately, when gout is detected and treated early, the disease can be arrested and these chronic sequelae avoided.

OVERVIEW OF DRUG THERAPY

In patients with gout, drugs are used in two ways. First, they are given short term to relieve symptoms of an acute gouty attack. Second, they are given long term to lower blood levels of uric acid.

In patients with infrequent flare-ups (less than three per year), treatment of symptoms may be all that is needed. Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered first-line agents for relieving pain of an acute gouty attack. Glucocorticoids are an acceptable option. In the past, colchicine was considered a drug of choice for acute gout—even though it has a poor risk/benefit ratio. Today, colchicine is generally reserved for patients who are unresponsive to or intolerant of safer agents.

In patients with chronic gout, tophaceous gout, or frequent gouty attacks (three or more per year), drugs for hyperuricemia are indicated. Three types of drugs may be employed: agents that decrease uric acid production, agents that increase uric acid excretion, and agents that convert uric acid to allantoin. Agents that increase urate excretion are known as *uricosuric* drugs.

DRUGS FOR ACUTE GOUTY ARTHRITIS

Nonsteroidal Anti-inflammatory Drugs

For acute gouty arthritis, NSAIDs are considered agents of first choice. Compared with colchicine, NSAIDs are better tolerated and their effects are more predictable. Benefits derive from suppressing inflammation. Treatment should start as soon as possible after symptom onset. Most patients experience marked relief within 24 hours; swelling subsides over the next few days. Adverse effects of NSAIDs include GI ulceration, impaired renal function, fluid retention, and increased risk of cardiovascular events. However, since the duration of treatment is brief, the risk of these complications is low. Which NSAID should be used? There is no good evidence that any NSAID is superior to the others for treatment of gout. Commonly used drugs and dosages are as follows:

- Indomethacin [Indocin]—50 mg 4 times daily for 3 to 6 days
- Naproxen [Naprosyn]—500 mg 2 or 3 times daily for 3 to 6 days
- Diclofenac sodium [Voltaren]—50 mg 3 times daily for 3 to 6 days

NSAIDs are discussed at length in Chapter 71.

Glucocorticoids

Glucocorticoids (eg, prednisone), given PO or IM, are highly effective for relieving an acute gouty attack—although NSAIDs are generally preferred. Candidates for glucocorticoid therapy include patients who are hypersensitive to NSAIDs, patients who have medical conditions that contraindicate use of NSAIDs, and patients with severe gout that is unresponsive to NSAIDs. Because of their effects on carbohy-

urate metabolism, glucocorticoids should be avoided in patients prone to hyperglycemia. For oral therapy, prednisone can be used. The dosage is 20 to 40 mg on day 1, followed by progressively smaller doses over the next 8 days. For IM therapy, triamcinolone acetonide can be used. The dosage is 60 mg every 1 to 4 days as needed. Glucocorticoids are discussed at length in Chapter 72.

Colchicine

Colchicine [Colcryst] is an anti-inflammatory agent with effects specific for gout. The drug is not active against other inflammatory disorders. Colchicine is not an analgesic and does not relieve pain in conditions other than gout. The drug's most common adverse effect is GI toxicity. In the past, colchicine was considered a first-line drug for gout. However, owing to the availability of safe and effective alternatives, its use has declined.

Therapeutic Use

Colchicine has two applications in gout. First, it can be used short term to treat an acute gouty attack. Second, it can be used long term to prevent attacks from recurring.

Acute Gouty Arthritis. High-dose colchicine can produce dramatic relief of an acute gouty attack. Within hours, patients whose pain had made movement impossible are able to walk. Inflammation disappears completely within 2 to 3 days. Administration is oral only. Colchicine for IV use has been withdrawn.

Prophylaxis of Gouty Attacks. When taken during asymptomatic periods, low-dose colchicine (0.6 mg once or twice daily) can decrease the frequency and intensity of acute flare-ups. Colchicine is also given for prophylaxis when urate-lowering therapy is initiated. Why? Because there is a tendency for gouty episodes to increase at this time.

Mechanism of Action

We do not fully understand how colchicine relieves or prevents episodes of gout. We do know that colchicine does *not* decrease urate production or removal. How then might it work? At least in part, by inhibiting leukocyte infiltration: In the absence of leukocytes, there is no phagocytosis of uric acid and no subsequent release of lysosomal enzymes. How does colchicine inhibit leukocyte migration? It disrupts microtubules, the structures required for cellular motility. Because microtubules are also required for cell division, colchicine is toxic to any tissue that has a large percentage of proliferating cells. Disruption of cell division in the GI tract and bone marrow underlies major toxicities of the drug.

Pharmacokinetics

Colchicine is readily absorbed following oral dosing, both in the presence and absence of food. Large amounts re-enter the intestine via the bile and intestinal secretions, and then undergo reabsorption. Final elimination occurs primarily through two processes: metabolism by hepatic CYP3A4 (the 3A4 isozyme of cytochrome P450) and renal excretion of intact drug.

Adverse Effects

Gastrointestinal Effects. The most characteristic side effects are nausea, vomiting, diarrhea, and abdominal pain. These responses, which occur during treatment of acute gouty attacks, result from injury to the rapidly proliferating cells of the GI epithelium. With the high doses used in the past, these GI effects developed in nearly all patients. However, with the lower doses used today, GI toxicity is less common, but still develops in 25% of patients. If GI symptoms occur, colchicine should be discontinued immediately, regardless of the status of joint pain.

Myelosuppression. Injury to rapidly proliferating cells can suppress bone marrow function, and can thereby cause leukopenia, granulocytopenia, thrombocytopenia, and pancytopenia. Accordingly, colchicine should be used with caution in patients with hematologic disorders.

Myopathy. Colchicine can cause rhabdomyolysis (muscle breakdown) during long-term low-dose therapy. Risk is increased in patients with renal and hepatic impairment, and in those taking statin drugs (eg, atorvastatin, simvastatin), which can cause rhabdomyolysis on their own. Patients should be monitored for sign of muscle injury (tenderness, pain, weakness).

Drug Interactions

Statins. As noted, atorvastatin, simvastatin, and other statins can increase the risk of colchicine-induced muscle injury. If possible, combined use of statins and colchicine should be avoided.

Drugs That Can Increase Colchicine Levels. Life-threatening reactions have occurred when combining colchicine with two classes of drugs: *P-glycoprotein* (PGP) inhibitors and inhibitors of *CYP3A4*. Recall from Chapter 4 that PGP is a transporter protein that can reduce plasma drug levels through effects in the liver, kidney, and intestine. Hence, by inhibiting PGP, drugs such as cyclosporine and ranolazine can cause colchicine to accumulate to toxic levels. Similarly, by inhibiting *CYP3A4*, drugs such as ketoconazole, clarithromycin, and the HIV protease inhibitors (eg, nelfinavir, ritonavir) can cause colchicine levels to rise. Accordingly, combined use of colchicine with strong inhibitors of either PGP or *CYP3A4* should generally be avoided, and is contraindicated in patients with hepatic or renal impairment.

Precautions and Contraindications

Colchicine should be used with care in elderly and debilitated patients, and in patients with cardiac, renal, hepatic, and GI disease.

As noted, combined use of colchicine with strong inhibitors of PGP or *CYP3A4* should generally be avoided, and is contraindicated in patients with hepatic or renal impairment.

High-dose colchicine is teratogenic in mice. Adequate studies of colchicine during human pregnancy have not been conducted. At this time, oral colchicine is classified in FDA Pregnancy Risk Category C, and hence should be avoided during pregnancy, unless the perceived benefits outweigh the potential risks.

Preparations, Dosage, and Administration

Preparations. Colchicine is available alone in 0.6-mg oral tablets sold as *Colcryst*, and in a fixed-dose combination with probenecid (1.5 mg/500 mg), sold as *ColBenemid*. Dosing may be done with or without food.

Dosage. Dosage recommendations for an acute gouty attack have recently changed. The current recommendation is 1.2 mg at the first sign of the flare, followed by 0.6 mg 1 hour later, for a maximum of 1.8 mg. Much higher doses were used in the past—for example, 1.2 mg initially followed by 0.6 mg every hour until pain is relieved or diarrhea ensues.

The recommended dosage for prophylaxis of flares is 0.6 mg once or twice daily.

For both acute therapy and long-term prophylaxis, dosage should be adjusted on the basis of liver function, kidney function, and usage of interacting drugs.

DRUGS FOR HYPERURICEMIA (URATE-LOWERING THERAPY)

Urate-lowering therapy (ULT) is indicated for patients who experience relatively frequent acute gouty attacks. The goal is to promote dissolution of urate crystals, prevent new crystal formation, prevent disease progression, reduce the frequency of acute attacks, and improve quality of life. For most patients, ULT must continue lifelong.

Four drugs—*allopurinol*, *febuxostat*, *probenecid*, and *pegloticase*—are used to reduce uric acid levels. Three mechanisms are involved. Allopurinol and febuxostat inhibit uric acid formation. Probenecid accelerates uric acid excretion. And pegloticase converts uric acid to allantoin, a compound that is readily excreted by the kidney. With all four drugs, the goal is to reduce plasma uric acid to 6 mg/dL or less. These drugs lack anti-inflammatory and analgesic actions, and hence are not useful against an acute gouty attack. The effects of all four drugs on uric acid are depicted in Figure 74-1.

Xanthine Oxidase Inhibitors: Allopurinol and Febuxostat

Two xanthine oxidase inhibitors are now available: allopurinol and febuxostat. Both seem equally effective. Allopurinol has been in use for decades, whereas febuxostat is new. Because experience with allopurinol is more extensive, and because the new drug is much more expensive (aren't they always), allopurinol is preferred.

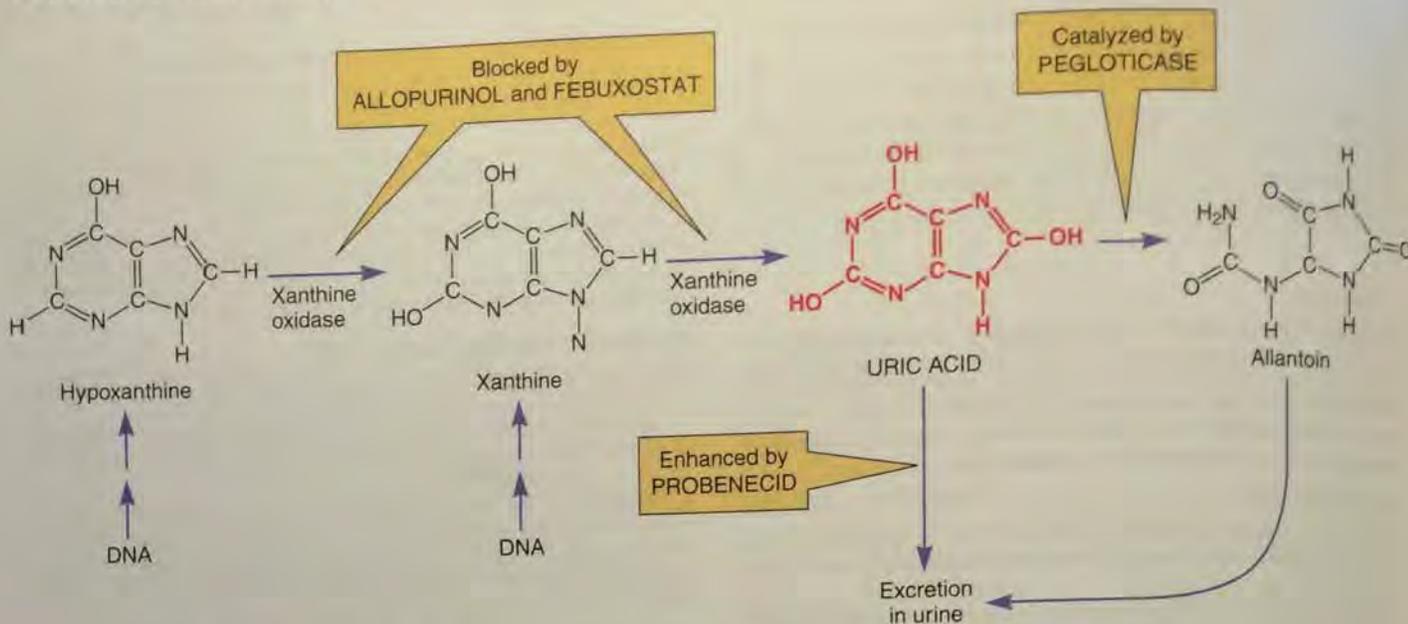


Figure 74-1 = Drugs that lower plasma levels of uric acid.

These drugs lower plasma urate by three mechanisms: Allopurinol and febuxostat reduce uric acid formation, pegloticase catalyzes conversion of uric acid to allantoin, and probenecid facilitates uric acid excretion by the kidney.

Allopurinol

Therapeutic Uses. Allopurinol [Zyloprim] is the current drug of choice for *chronic tophaceous gout*. By reducing blood uric acid levels, allopurinol prevents new tophus formation and causes regression of tophi that have already formed, thereby allowing joint function to improve. Reversal of hyperuricemia also decreases the risk of nephropathy from deposition of urate crystals in the kidney. During the initial months of treatment, allopurinol may *increase* the incidence of acute gouty arthritis. The risk of an attack can be reduced by concurrent treatment with colchicine or an NSAID.

Allopurinol can be used for hyperuricemia that develops secondary to cancer chemotherapy and to certain blood dyscrasias, such as polycythemia vera, myeloid metaplasia, and leukemia. Why does hyperuricemia develop during chemotherapy? Because, when cells die, breakdown of DNA releases uric acid. To minimize hyperuricemia, allopurinol should be administered before chemotherapy starts.

Mechanism of Action. Allopurinol and its major metabolite (alloxanthine) inhibit *xanthine oxidase* (XO), an enzyme required for uric acid formation. As indicated in Figure 74-1, XO catalyzes the final two reactions that lead to formation of uric acid from breakdown products of DNA.

Pharmacokinetics. Allopurinol is well absorbed following oral dosing, and then undergoes rapid conversion to alloxanthine, an active metabolite. Alloxanthine is then eliminated slowly by renal excretion. Because alloxanthine has a prolonged half-life (about 25 hours), therapeutic effects are long lasting. Consequently, once-a-day dosing is adequate.

Adverse Effects. Allopurinol is generally well tolerated. The most serious toxicity is a rare but potentially fatal *hypersensitivity syndrome*, characterized by rash, fever, eosinophilia, and dysfunction of the liver and kidneys. If rash or fever develops, allopurinol should be discontinued immediately. Many patients recover spontaneously; others may require hemodialysis or glucocorticoid therapy.

As noted, initial therapy may elicit an *acute gouty attack*. This can be prevented by giving colchicine (0.6 mg once or twice daily), or a low-dose NSAID (eg, 25 mg indomethacin twice daily, or 250 mg naproxen twice daily).

Mild side effects seen occasionally include *GI reactions* (nausea, vomiting, diarrhea, abdominal discomfort) and *neurologic effects* (drowsiness, headache, metallic taste). Prolonged use (more than 3 years) may cause *cataracts*; periodic ophthalmic examinations are recommended.

Drug Interactions. Allopurinol can inhibit hepatic drug-metabolizing enzymes, thereby delaying the inactivation of other drugs. This interaction is of particular concern for patients taking *warfarin*, whose dosage should be reduced. If possible, combined use with *mercaptopurine* or *azathioprine* should be avoided. Why? Because both of these anticancer drugs are substrates for XO, and hence could accumulate to toxic levels in the presence of allopurinol. If combined use can't be avoided, then dosages of mercaptopurine and azathioprine should be greatly reduced (by as much as 75%). *Theophylline*, a drug for asthma, is also a substrate for XO, and hence should not be combined with allopurinol. The combination of allopurinol plus *ampicillin* is associated with a high incidence of rash; if rash develops, allopurinol should be discontinued immediately.

Preparations, Dosage, and Administration. Allopurinol [Zyloprim] is supplied in 100- and 300-mg tablets for oral dosing, with or without food.

For *chronic tophaceous gout*, the objective is to decrease plasma urate to 6 mg/dL. Dosages should be individualized. In patients with normal renal function, the usual initial dosage is 100 mg once a day. Dosage is then increased by 50- to 100-mg increments every few weeks until the urate target level has been reached. The standard maintenance dose is 300 mg a day. However, higher doses are often needed. The maximum approved dosage is 800 mg/day. To prevent renal injury, fluid intake should be sufficient to maintain a urine flow of at least 2 L/day. Since allopurinol is eliminated by the kidneys, dosage should be reduced in patients with renal impairment.

For *secondary hyperuricemias in adults*, dosages range from 100 to 800 mg/day. For *children* ages 6 to 10 years who are undergoing cancer chemotherapy, the recommended dosage is 300 mg daily. The dosage for children under 6 years is 150 mg/day.

Febuxostat

Febuxostat [Uloric], approved in 2009, is an expensive alternative to allopurinol. Like allopurinol, febuxostat lowers urate levels by inhibiting XO. In clinical trials, febuxostat (40 or 80 mg/day) was at least as effective as allopurinol. As with allopurinol, symptoms of gout may flare during initial therapy. Accordingly, patients should receive prophylactic NSAIDs or colchicine for up to 6 months after starting treatment. Adverse effects of febuxostat, which are uncommon, include liver function abnormalities (4.6% to 6.6%), nausea (1.2%), arthralgia (0.7% to 1.1%), and rash (0.5% to 1.6%). High

doses (80 mg/day) are associated with a small increase in cardiovascular events. Like allopurinol, febuxostat should not be combined with drugs that are substrates for XO, especially theophylline, mercaptopurine, and azathioprine. In contrast to allopurinol, which is eliminated entirely by the kidneys, febuxostat is eliminated by hepatic metabolism, followed by renal excretion. Febuxostat is supplied in 40- and 80-mg tablets. Dosage is 40 mg/day initially, and can be increased to 80 mg/day if needed. No dosage adjustment is needed for patients with mild to moderate renal or hepatic impairment.

Probenecid, a Uricosuric Agent

Actions and Uses. Probenecid (generic only) acts on renal tubules to inhibit reabsorption of uric acid. As a result, excretion of uric acid is increased and hyperuricemia is reduced. By lowering plasma urate levels, probenecid prevents formation of new tophi and facilitates regression of existing tophi. The drug may exacerbate acute episodes of gout, and hence treatment should be delayed until the acute attack has been controlled. During the initial months of therapy, probenecid may induce acute attacks of gout. If an attack occurs, colchicine or indomethacin can be added for relief. In addition to its use in gout, probenecid may be employed to prolong the effects of penicillins and cephalosporins (by delaying their excretion by the kidneys).

Adverse Effects. Probenecid is well tolerated by most patients. Mild *GI effects* (nausea, vomiting, anorexia) occur occasionally. These can be reduced by taking the drug with food. *Hypersensitivity reactions*, usually manifesting as rash, develop in about 4% of patients. *Renal injury* may occur from deposition of urate in the kidney. The risk of kidney damage can be minimized by alkalinizing the urine and consuming 2.5 to 3 L of fluid daily during the first few days of treatment.

Drug Interactions. Aspirin and other *salicylates* interfere with the uricosuric action of probenecid. Accordingly, probenecid should not be used concurrently with these drugs. Probenecid inhibits the renal excretion of several drugs, including *indomethacin* and *sulfonamides*; dosages of these agents may require reduction.

Preparations, Dosage, and Administration. Probenecid is supplied in 500-mg tablets. The initial dosage for adults is 250 mg twice daily for 1 week. The maintenance dosage is 500 mg twice daily. Administration with food decreases GI upset. Therapy should not be initiated during an acute gouty attack.

Pegloticase, a Recombinant Form of Uric Acid Oxidase

Therapeutic Use. Pegloticase [Krystexxa], approved in 2010, is indicated for IV therapy of chronic gout in patients who have not responded to oral ULT (eg, allopurinol, proben-

ecid). Although pegloticase is quite effective, the drug is expensive (over \$20,000 a year) and carries a significant risk of severe adverse effects. Accordingly, pegloticase is considered a treatment of last resort.

Mechanism of Action. How does pegloticase reduce urate levels? The drug is a recombinant form of *uricase* (urate oxidase), an enzyme that catalyzes the conversion of uric acid to allantoin, an inert, water-soluble compound that is readily excreted by the kidney. Uricase is present in nearly all mammals—but not in humans and higher primates. The actions of pegloticase are depicted in Figure 74-1.

Adverse Effects. As with other drugs for ULT, patients are likely to experience *gout flare* during the first few months of treatment. To reduce flare intensity, patients should take colchicine or an NSAID during this time.

During premarketing trials, pegloticase triggered *anaphylaxis* in 6.5% of patients. Symptoms include wheezing, perioral or lingual edema, hemodynamic instability, and rash. To reduce risk, patients should be pretreated with an antihistamine and glucocorticoid. Administration should be done in a setting equipped to manage a severe reaction.

During premarketing trials, *infusion reactions* were seen in 26% to 41% of patients. Symptoms include urticaria, dyspnea, chest discomfort, erythema, and pruritus. These reactions were seen despite pretreatment with an antihistamine, acetaminophen, and an IV glucocorticoid. If a reaction develops, slowing the infusion rate may reduce symptom intensity.

Pegloticase is *contraindicated* for patients with inherited *glucose-6-phosphate dehydrogenase (G6PD) deficiency*, owing to a risk of hemolysis and methemoglobinemia. Patients at higher risk (eg, those of African or Mediterranean ancestry) should be screened for G6PD deficiency before receiving the drug.

Preparations, Dosage, and Administration. Pegloticase [Krystexxa] is supplied as a concentrated solution (8 mg/mL in 2-mL single-use vials) to be diluted for IV infusion. The dosage is 8 mg infused over 2 or more hours every 2 weeks. Owing to the risk of anaphylaxis and infusion reactions, patients should be premedicated with an antihistamine and a glucocorticoid, and monitored closely during the infusion. In the event of a moderate reaction, the infusion should be slowed. In the event of a severe reaction, the infusion should be stopped.

KEY POINTS

- Gout is an inflammatory disorder characterized by hyperuricemia and episodic joint pain, typically in the big toe.
- NSAIDs and glucocorticoids are preferred drugs for treating acute gouty attacks. Benefits derive mainly from anti-inflammatory actions.
- Colchicine is a second-choice drug for treating an acute gouty attack.
- Four drugs—allopurinol, febuxostat, probenecid, and pegloticase—are used long term to prevent gouty attacks. Benefits derive from lowering plasma uric acid levels. These drugs lack anti-inflammatory and analgesic actions, and hence are not effective against acute gouty attacks.
- Allopurinol is the drug of choice for ULT.

- Allopurinol lowers plasma uric acid by decreasing uric acid production. How? By inhibiting xanthine oxidase, an enzyme that forms uric acid from breakdown products of DNA.
- Probenecid lowers plasma uric acid by promoting renal uric acid excretion. How? By inhibiting tubular reabsorption of uric acid.
- Pegloticase is indicated as ULT for patients refractory to conventional treatment (eg, allopurinol, probenecid).

- Pegloticase lowers plasma uric acid by promoting uric acid breakdown. How? Pegloticase is an enzyme that converts uric acid to allantoin, a water-soluble compound that is readily excreted by the kidney.

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Drugs Affecting Calcium Levels and Bone Mineralization

Calcium Physiology

Calcium-Related Pathophysiology

Drugs for Disorders Involving Calcium

Calcium Salts

Vitamin D

Calcitonin-Salmon

Bisphosphonates

Raloxifene

Teriparatide

Denosumab

Cinacalcet

Drugs for Hypercalcemia

Osteoporosis

General Considerations

Treating Osteoporosis in Women

Treating Osteoporosis in Men

It is difficult to exaggerate the biologic importance of calcium, an element critical to blood coagulation and to the functional integrity of bone, nerve, muscle, and the heart. Because these calcium-dependent processes can be seriously disrupted by alterations in calcium availability, calcium levels must stay within narrow limits. To regulate calcium, the body employs three factors: parathyroid hormone, vitamin D, and calcitonin. When these regulatory mechanisms fail, hypercalcemia or hypocalcemia results.

Our discussion of calcium and related drugs has four parts. First, we review calcium physiology. Second, we discuss the syndromes produced by disruption of calcium metabolism. Third, we discuss the pharmacologic agents used to treat calcium-related disorders. And fourth, we consider osteoporosis, the most common calcium-related disorder.

CALCIUM PHYSIOLOGY

Functions, Sources, and Daily Requirements

Functions. Calcium is critical to the function of the skeletal system, nervous system, muscular system, and cardiovascular system. In the skeletal system, calcium is required for the structural integrity of bone. In the nervous system, calcium helps regulate axonal excitability and transmitter release. In the muscular system, calcium participates in excitation-contraction coupling and contraction itself. In the cardiovascular system, calcium plays a role in myocardial contraction, vascular contraction, and blood coagulation.

TABLE 75-1 ■ Daily Calcium Intake by Life-Stage Group

Life-Stage Group*	Calcium Intake (mg/day)		
	AI [†]	RDA	UL [‡]
0–6 months	200	—	1000
6–12 months	260	—	1500
1–3 years	—	700	2500
4–8 years	—	1000	2500
9–18 years	—	1300	3000
19–50 years	—	1000	2500
51–70 years			
Males	—	1000	2000
Females	—	1200	2500
Over 70 years	—	1200	2000

AI = Adequate Intake, RDA = Recommended Dietary Allowance, UL = Tolerable Upper Intake Level.

*All values apply to males and females, except in the 51 to 70 age group. Calcium requirements don't change during pregnancy or lactation.

[†]Values for Adequate Intake are derived through experimental or observational data that show a mean calcium intake that appears to sustain a desired indicator of health, such as calcium retention in bone, for most members of the population group. AI values are employed for young children because there are insufficient data to derive an RDA.

[‡]The Tolerable Upper Intake Level is defined as the maximum intake that is not likely to pose a risk of adverse health effects in almost all healthy individuals in a specified group. The UL is not intended to be a recommended level of intake. There is no established benefit to consuming calcium above the RDA. Data from the Institute of Medicine of the National Academies: *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press, 2010.

Dietary Sources. Dairy products are good sources of calcium. For example, we can get about 300 mg from 1 cup of milk, 8 ounces of yogurt, or 1.5 ounces of cheese. Other good sources include broccoli (180 mg/cup), cooked spinach (240 mg/cup), fortified orange juice (300 mg/8 oz), and fortified cereals (250 to 1000 mg/serving). Information on the calcium content of other foods is available online at www.ucsfhealth.org/education/calcium_content_of_selected_foods/index.html.

Daily Requirements. How much calcium do we need? In 2010, the Institute of Medicine (IOM) of the National Academies issued updated recommendations in a report titled *Dietary Reference Intakes for Calcium and Vitamin D*. As shown in Table 75-1, adolescents ages 9 through 18 need the most calcium: 1300 mg/day. Men and women ages 19 through

50 need 1000 mg/day. After age 50, women should increase their intake to 1200 mg/day, as should men after age 70.

Are North Americans taking in enough calcium? According to the IOM report, the answer is *Yes*: Most of us get sufficient calcium from our diets. However, there is concern that two groups—adolescent girls and postmenopausal women—may not get enough calcium from diet alone, and hence may need calcium supplements. How much supplemental calcium should be taken? Only enough to make up the *difference* between what the diet provides (about 600 to 900 mg/day) and the recommended dietary allowance (RDA). If dietary calcium plus calcium from supplements exceed the RDA, there is a risk of toxicity: Recent data indicate that taking too much supplemental calcium increases the risk of vascular calcification, myocardial infarction (heart attack), and stroke. In addition, consuming too much calcium can cause kidney stones, which we have known for years.

Body Stores

Calcium in Bone. The vast majority of calcium in the body (more than 98%) is present in bone, in the form of hydroxyapatite crystals. It is important to appreciate that bone—and the calcium it contains—is not static. Rather, bone undergoes continuous remodeling, a process in which old bone is resorbed, after which new bone is laid down (Fig. 75-1). The cells that resorb old bone are called *osteoclasts* and the cells that deposit new bone are called *osteoblasts*. Both cell types originate in the bone marrow. In adults, about 25% of trabecular bone (the honeycomb-like material in the center of bones) is replaced each year. In contrast, only 3% of cortical bone (the dense material that surrounds trabecular bone) is replaced each year.

Calcium in Blood. The normal value for total serum calcium is 10 mg/dL (2.5 mmol/L, 5 mEq/L). Of this total, about 50% is bound to proteins and other substances, and hence is unavailable for use. The remaining 50% is present as free, ionized calcium—the form that participates in physiologic processes.

Absorption and Excretion

Absorption. Absorption of calcium takes place in the small intestine. Under normal conditions, about one-third of ingested calcium is absorbed. Absorption is increased by parathyroid hormone (PTH) and vitamin D (see below). In contrast, glucocorticoids decrease calcium absorption. Also, a variety of foods (eg, spinach, whole-grain cereals, bran) contain compounds that can interfere with calcium absorption.

Excretion. Calcium excretion is primarily renal. The amount lost is determined by glomerular filtration and the degree of tubular reabsorption. Excretion can be reduced by PTH, vitamin D, and thiazide diuretics (eg, hydrochlorothiazide). Conversely, excretion can be increased by loop diuretics (eg, furosemide), calcitonin (see below), and loading with sodium. In addition to calcium lost in urine, substantial amounts can be lost in breast milk.

Physiologic Regulation of Calcium Levels

Blood levels of calcium are tightly controlled. Three processes are involved:

- Absorption of calcium from the intestine
- Excretion of calcium by the kidney
- Resorption or deposition of calcium in bone

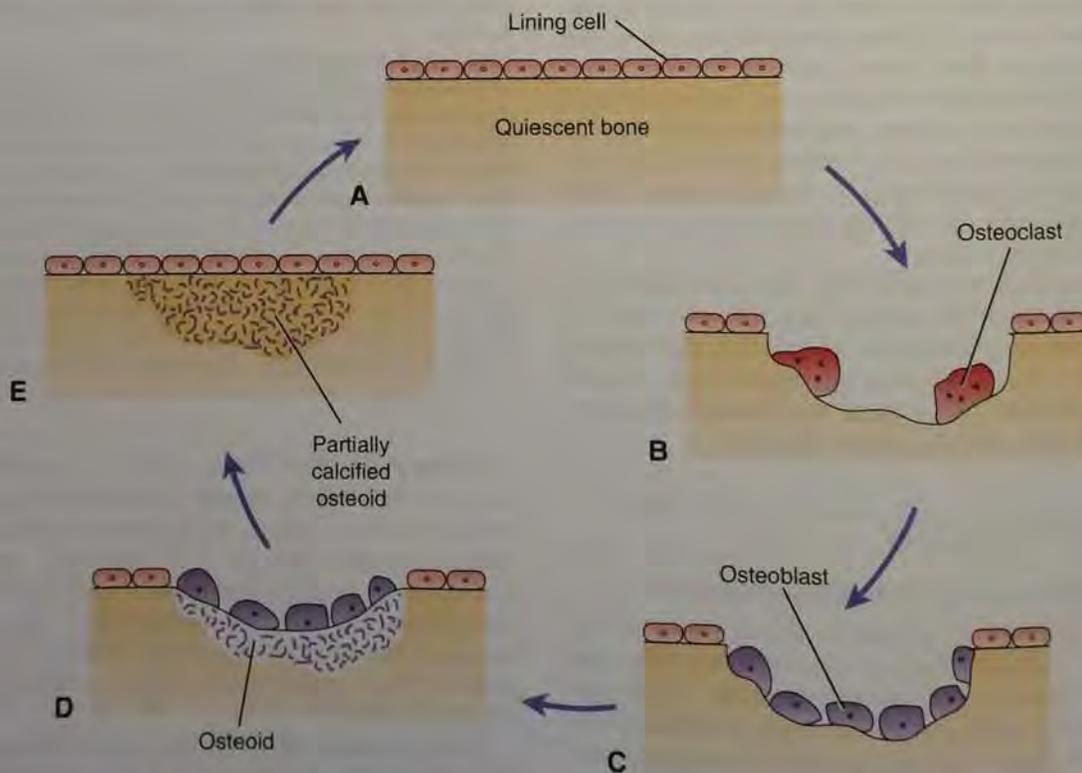


Figure 75-1 • Bone remodeling cycle.

A, Quiescent bone with lining cells covering the surface. **B,** Resorption of old bone by multinucleated osteoclasts. **C,** Osteoblasts migrate to the absorption site. **D,** Osteoblasts deposit osteoid, a matrix of collagen and other proteins. **E,** Osteoid undergoes calcification.

TABLE 75-2 • Effects of Parathyroid Hormone, Vitamin D, and Calcitonin on Calcium and Phosphate

	PTH	Vitamin D	Calcitonin
Calcium			
Plasma calcium level	Increase	Increase	Decrease
Intestinal calcium absorption	Increase	Increase	No effect
Renal calcium excretion	Decrease	Decrease	Increase
Calcium resorption from bone	Increase	Increase	Decrease
Phosphate			
Plasma phosphate level	Decrease	Increase	

PTH = parathyroid hormone.

Regulation of these processes is under the control of three factors: *parathyroid hormone*, *vitamin D*, and *calcitonin*, as summarized in Table 75-2. You should note that preservation of calcium levels in blood takes priority over preservation of calcium in bone. Hence, if serum calcium is low, calcium will be resorbed from bone and transferred to the blood—even if resorption compromises the structural integrity of bone.

Parathyroid Hormone. Release of PTH is regulated primarily by calcium, acting through calcium-sensing receptors on cells of the parathyroid gland. When calcium levels are *high*, activation of the calcium-sensing receptors is *increased*, causing secretion of PTH to be *suppressed*. Conversely, when calcium levels are low, receptor activation is reduced, causing PTH release to rise. PTH then restores calcium to normal levels by three mechanisms. Specifically, PTH

- Promotes calcium resorption from bone
- Promotes tubular reabsorption of calcium that had been filtered by the kidney glomerulus
- Promotes activation of vitamin D, and thereby promotes increased absorption of calcium from the intestine

In addition to its effects on calcium, PTH reduces plasma levels of phosphate.

Vitamin D. Vitamin D is similar to PTH in that both agents increase plasma calcium levels, and they do so by the same mechanisms: (1) increasing calcium resorption from bone, (2) decreasing calcium excretion by the kidney, and (3) increasing calcium absorption from the intestine. Vitamin D differs from PTH in that vitamin D elevates plasma levels of phosphate, whereas PTH reduces levels of phosphate. The actions of vitamin D are discussed further below.

Calcitonin. Calcitonin, a hormone produced by the thyroid gland, decreases plasma levels of calcium. Hence, calcitonin acts in opposition to PTH and vitamin D. Calcitonin is released from the thyroid gland when calcium levels in blood rise too high. Calcitonin lowers calcium levels by inhibiting the resorption of calcium from bone and increasing calcium excretion by the kidney. Unlike PTH and vitamin D, calcitonin does not influence calcium absorption.

CALCIUM-RELATED PATHOPHYSIOLOGY

Hypercalcemia

Clinical Presentation. Hypercalcemia is usually asymptomatic. When symptoms are present, they often involve the kidney (damage to tubules and collecting ducts, resulting in polyuria, nocturia, and polydipsia), GI tract (nausea, vomiting, and constipation), and central nervous system (lethargy and depression). Hypercalcemia may also result in dysrhythmias and deposition of calcium in soft tissues. As noted above, consuming too much supplemental calcium increases the risk of vascular calcification, myocardial infarction, and stroke.

Causes. Hypercalcemia may arise from a variety of causes. Life-threatening elevations in calcium are most often the result of cancer. Hyperparathyroidism is another common cause of severe hypercalcemia (see below). Additional causes include vitamin D intoxication, sarcoidosis, and use of thiazide diuretics.

Treatment. Calcium levels can be lowered with drugs that (1) promote urinary excretion of calcium, (2) decrease mobilization of calcium from bone, (3) decrease intestinal absorption of calcium, and (4) form complexes with free calcium in blood. For severe hypercalcemia, initial therapy consists of replacing lost fluid with IV saline, followed by diuresis using IV saline and a loop diuretic (eg, furosemide). Other agents for lowering calcium include inorganic phosphates (which promote calcium deposition in bone and reduce calcium absorption); edetate disodium (EDTA, which binds calcium and promotes its excretion); glucocorticoids (which reduce intestinal absorption of calcium); and a group of drugs—calcitonin, bisphosphonates (eg, pamidronate), inorganic phosphates, and gallium nitrate—that inhibit resorption of calcium from bone. Cinacalcet can be used for hypercalcemia associated with hyperparathyroidism.

Hypocalcemia

Clinical Presentation and Cause. Hypocalcemia increases neuromuscular excitability. As a result, tetany, convulsions, and spasm of the pharynx and other muscles may occur. Hypocalcemia is caused most often by a deficiency of either PTH, vitamin D, or dietary calcium.

Treatment. Severe hypocalcemia is corrected by infusing an IV calcium preparation, usually calcium gluconate. Once calcium levels have been restored, an oral calcium salt (eg, calcium citrate) can be given for maintenance. Vitamin D should be included in the regimen if there is a coexisting deficiency.

Rickets

Rickets is a disease of childhood brought on by either insufficient dietary vitamin D or limited exposure to sunlight. The disease is extremely rare in the United States. Rickets is characterized by defective bone growth and skeletal deformities. Bone abnormalities are caused as follows: (1) vitamin D deficiency results in reduced calcium absorption; (2) in response to hypocalcemia, PTH is released; (3) PTH restores serum calcium by promoting calcium resorption from bone, thereby causing bones to soften; and (4) stress on the softened bones caused by bearing weight results in deformity. Treatment consists of vitamin D replacement therapy.

Osteomalacia

Osteomalacia is the adult counterpart of rickets. Like rickets, this condition results from insufficient vitamin D. In the absence of vitamin D, mineralization of bone is impaired, resulting in bowing of the legs, fractures of the long bones, and kyphosis (“hunchback” curvature of the spine). In addition, patients may experience diffuse, dull, aching bone pain. Treatment consists of vitamin D replacement therapy.

Osteoporosis

Osteoporosis, the most common disorder of calcium metabolism, is characterized by low bone mass and increased bone fragility. Osteoporosis is discussed at length in a later section.

Paget's Disease of Bone

Clinical Presentation. Paget's disease of bone is a chronic condition seen most frequently in adults over age 40. After osteoporosis, Paget's disease is the most common disorder of bone in the United States. The disease is characterized by increased bone resorption and replacement of the resorbed bone with abnormal bone. Increased bone turnover causes elevation in serum alkaline phosphatase (reflecting increased bone deposition) and increased urinary hydroxyproline (reflecting increased bone resorption). It is important to note that alterations in bone homeostasis do not occur evenly throughout the skeleton. Rather, alterations occur locally, most often in the pelvis, femur, spine, skull, and tibia. Although most people with Paget's disease are asymptomatic,

about 10% experience bone pain and osteoarthritis. Skeletal deformity may also occur. Bone weakness may lead to fractures. Neurologic complications may occur secondary to compression of the spinal cord, spinal nerves, and cranial nerves. If bone associated with hearing is affected, deafness may result.

Treatment. Asymptomatic patients are usually not treated. Mild pain can be managed with analgesics and anti-inflammatory agents. When the disease is more severe, a bisphosphonate (eg, alendronate, pamidronate, zoledronate) is the treatment of choice. Benefits derive from suppressing bone resorption.

Hypoparathyroidism

Reductions in PTH usually result from inadvertent removal of the parathyroid glands during surgery on the thyroid gland. Lack of PTH causes hypocalcemia, which in turn may produce paresthesias, tetany, skeletal muscle spasm, laryngospasm, and convulsions. Symptoms can be relieved with calcium supplements (see *Hypocalcemia* above) and vitamin D.

Hyperparathyroidism

Primary Hyperparathyroidism. Primary hyperparathyroidism usually results from a benign parathyroid adenoma. The resulting increase in PTH secretion causes hypercalcemia and lowers serum phosphate. Hypercalcemia can cause skeletal muscle weakness, constipation (from decreased smooth muscle tone), and central nervous system (CNS) symptoms (lethargy, depression). Hypercalciuria and hyperphosphaturia are also present and may cause renal calculi. Mobilization of calcium and phosphate from bone may produce bone abnormalities. The only definitive treatment for primary hyperparathyroidism is surgical resection of the parathyroid glands. Hypercalcemia can be managed with calcium-lowering drugs, including cinacalcet [Sensipar], a drug that suppresses PTH secretion.

Secondary Hyperparathyroidism. Secondary hyperparathyroidism is a common complication of chronic kidney disease (CKD), occurring in nearly all patients undergoing dialysis. The disorder is characterized by high levels of PTH and disturbances of calcium and phosphorus homeostasis. Traditionally, the disorder has been managed with a vitamin D sterol (eg, paricalcitol) and calcium-containing phosphate-binding agents. However, these treatments frequently make mineral homeostasis worse. A relatively new drug—cinacalcet [Sensipar]—can reduce PTH levels while having a positive impact on calcium and phosphorus, and hence may become a treatment of choice.

DRUGS FOR DISORDERS INVOLVING CALCIUM

Calcium Salts

Calcium salts are available in oral and parenteral formulations for treating hypocalcemic states. These salts differ in their percentage of elemental calcium, which must be accounted for when determining dosage.

Oral Calcium Salts

Therapeutic Uses. Oral calcium preparations are used to treat *mild hypocalcemia*. In addition, calcium salts are taken as *dietary supplements*. People who may need supplementary

calcium include adolescents, the elderly, and postmenopausal women. As discussed in Chapter 61 (see Box 61-1), calcium supplements may have the added benefit of reducing symptoms of *premenstrual syndrome*. Also, recent data indicate that calcium supplements can produce a significant, albeit modest, reduction in recurrence of *colorectal adenomas*.

Adverse Effects. When calcium is taken chronically in high doses (3 to 4 gm/day), *hypercalcemia* can result. Hypercalcemia is most likely in patients who are also receiving large doses of vitamin D. Signs and symptoms include GI disturbances (nausea, vomiting, constipation), renal dysfunction (polyuria, nephrolithiasis), and CNS effects (lethargy, depression). In addition, hypercalcemia may cause cardiac dysrhythmias and deposition of calcium in soft tissue. Hypercalcemia can be minimized with frequent monitoring of plasma calcium content.

Drug Interactions. *Glucocorticoids* (eg, prednisone) reduce absorption of oral calcium. Calcium reduces absorption of *tetracyclines*, and hence these agents should be administered at least 1 hour apart. Similarly, calcium reduces absorption of *thyroid hormone*; to ensure adequate thyroid hormone absorption, these agents should be administered several hours apart. *Thiazide diuretics* decrease renal calcium excretion and may thereby cause hypercalcemia.

Food Interactions. Certain foods contain substances that can suppress calcium absorption. One such substance—oxalic acid—is found in spinach, rhubarb, Swiss chard, and beets. Phytic acid, another depressant of calcium absorption, is present in bran and whole-grain cereals. Oral calcium should not be administered with these foods.

Preparations and Dosage. The calcium salts available for oral administration are listed in Table 75-3. Note that the dosage required to provide a particular amount of elemental calcium differs among preparations. Calcium carbonate, for example, has the highest percentage of calcium. Chewable tablets are preferred to standard tablets because of more consistent bioavailability. Bioavailability of *calcium citrate* appears especially good, owing to high solubility. When calcium supplements are taken, total daily calcium intake (dietary plus supplemental) should equal the values in Table 75-1. To help ensure adequate absorption, no more than 600 mg should be consumed at one time.

Parenteral Calcium Salts

Therapeutic Use. Parenteral calcium salts are given to raise calcium levels rapidly in patients with symptoms of severe hypocalcemia (ie, hypocalcemic tetany). Only two parenteral preparations are available in the United States: *calcium chloride* and *calcium gluconate*. A third product—*calcium gluceptate*—has been withdrawn. Intravenous calcium gluconate is preferred to calcium chloride.

Adverse Effects. *Calcium chloride* is highly irritating. Intramuscular injection may cause necrosis and sloughing, and hence this route must never be used. When the drug is administered IV, care must be taken to avoid extravasation, because local infiltration can produce severe injury. Although less irritating than calcium chloride, *calcium gluconate* can produce pain, slough-

TABLE 75-3 • Oral Calcium Salts

Generic Name	Trade Name	Calcium Content	Dose Providing 1000 mg of Calcium
Calcium acetate	PhosLo, Calphron, Eliphos	25%	4 gm
Calcium carbonate	Tums, Rolaids, others	40%	2.6 gm
Calcium citrate	Citracal, Cal-Cee	21%	4.8 gm
Calcium glubionate	Calcionate, Calciquid	6.6%	15.2 gm
Calcium gluconate*	Cal-G	9%	11 gm
Calcium lactate	Cal-Lac	13%	7.6 gm
Tricalcium phosphate	Posture	39%	2.6 gm

*Also available in parenteral form (see Table 75-4).

TABLE 75-4 ■ Parenteral Calcium Salts

Generic Name	Dosage Form	Calcium per mL of Solution	Route	Usual Adult Dosage Range
Calcium chloride	10% solution	27 mg	IV	5–10 mL (135–270 mg Ca)
Calcium gluconate*	10% solution	9 mg	IV	5–20 mL (45–180 mg Ca)
Calcium gluceptate†	22% solution	18 mg	IV IM	5–20 mL (90–360 mg Ca) 2–5 mL (36–90 mg Ca)

*Also available in an oral formulation (see Table 75-3).

†No longer available in the United States.

mg, and abscess formation if administered IM. Overdose with either calcium salt can produce signs and symptoms of hypercalcemia (weakness, lethargy, nausea, vomiting, coma, and possibly death).

Drug Interactions. Parenteral calcium may cause severe bradycardia in patients taking *digoxin*. Accordingly, calcium infusions should be done slowly and cautiously in these patients. Several classes of compounds—*phosphates, carbonates, sulfates, and tartrates*—may cause calcium to precipitate, and hence should not be added to parenteral calcium solutions.

Dosage and Administration. Both parenteral calcium salts are given IV. Solutions of these salts should be warmed to body temperature prior to administration. Intravenous injections should be done slowly (0.5 to 2 mL/min). Dosage forms and dosages are summarized in Table 75-4.

Vitamin D

The term *vitamin D* refers to two compounds: *ergocalciferol* (vitamin D₂) and *cholecalciferol* (vitamin D₃). Vitamin D₃ is the form of vitamin D produced naturally in humans when our skin is exposed to sunlight. Vitamin D₂ is a form of vitamin D that occurs in plants. Vitamin D₂ is used as a prescription drug and to fortify foods. Both forms are used in over-the-counter supplements. It is important to note that both forms of vitamin D produce nearly identical biologic effects. Therefore, rather than distinguishing between them, we will use the term *vitamin D* to refer to vitamins D₂ and D₃ collectively.

Physiologic Actions

Vitamin D is an important regulator of calcium and phosphorus homeostasis. Vitamin D increases blood levels of both elements, primarily by increasing their absorption from the intestine and promoting their resorption from bone. In addition, vitamin D reduces renal excretion of calcium and phosphate (although the quantitative significance of this effect is not clear). With usual doses of vitamin D, there is no net loss of calcium from bone. However, vitamin D *can* promote bone decalcification if serum calcium concentrations cannot be maintained by increasing intestinal calcium absorption.

Health Benefits

Vitamin D is essential for bone health, owing to its effects on calcium utilization. Does vitamin D have other health benefits? Maybe. Maybe not. Studies suggest that vitamin D may protect against diabetes, arthritis, cardiovascular disease, autoimmune disorders, and cancers of the breast, colon, prostate, and ovary. However, according to the IOM report on calcium and vitamin D, the available data are insufficient to support health claims beyond bone health. Hence, until more definitive data are available, the possibility of additional benefits remains open, but not proved.

Sources and Daily Requirements

Sources. Vitamin D is obtained through the diet, supplements, and exposure to sunlight. With the exception of shiitake mushrooms and oily fish (eg, salmon, tuna), natural foods have very little vitamin D. Accordingly, dietary vitamin D is obtained mainly through vitamin D–fortified foods, especially cereals, milk, yogurt, margarine, cheese, and orange juice.

Requirements. In 2010, the IOM issued revised guidelines for vitamin D intake. They now recommend:

- For children under 1 year old, 400 international units (IU)/day
- For all people ages 1 through 70, 600 IU/day
- For adults age 71 and older, 800 IU/day

These recommendations are based on the assumption that people get very little of their vitamin D from exposure to sunlight.

According to the IOM report, most people in North America have blood levels of vitamin D in the range needed to support good bone health, and hence do not need vitamin D supplements. Whether taking supplements would confer other benefits remains to be proved.

Vitamin D Deficiency

Vitamin D deficiency is defined by a serum concentration of 25-hydroxyvitamin D (25OHD) below 20 ng/mL. (Levels above 20 ng/mL are sufficient to maintain bone health.) In actual practice, the target level of 25OHD is usually 30 to 60 ng/mL.

The classic manifestations of vitamin D deficiency are *rickets* (in children) and *osteomalacia* (in adults). Signs and symptoms are described above. Taking vitamin D can completely reverse the symptoms of both conditions, unless permanent deformity has already developed.

How much vitamin D is needed to *treat deficiency*? In 2011, the Endocrine Society made the following recommendations:

- For children under 1 year old, 2000 IU/day
- For children 1 to 18 years old, 4000 IU/day
- For adults age 19 and older, up to 10,000 IU/day

Much higher doses are needed for patients who are obese, and for those taking glucocorticoids and some other drugs.

Screening for vitamin D deficiency is recommended for patients at risk, including pregnant women, obese people, and people with dark skin (because, compared with light-skinned people, they make less vitamin D in response to sunlight).

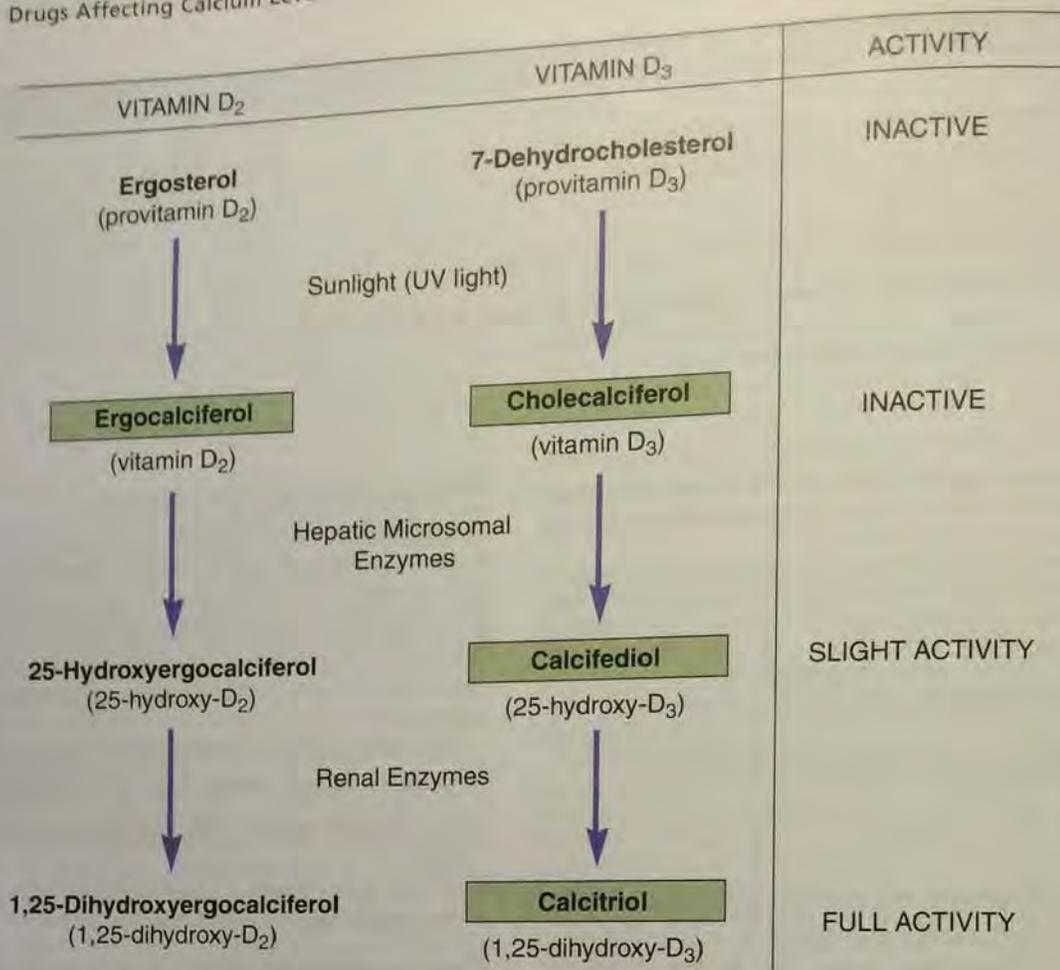


Figure 75-2 • Vitamin D activation.

Ergosterol is found in yeasts and fungi. 7-Dehydrocholesterol is present in the skin. Green boxes indicate forms of vitamin D used therapeutically.

Activation of Vitamin D

In order to affect calcium and phosphate metabolism, vitamin D must first undergo activation. The extent of activation is carefully regulated, and is determined by calcium availability: When plasma calcium falls, activation of vitamin D is increased. The pathways for activating vitamins D₂ and D₃ are shown in Figure 75-2.

Let's begin by focusing on vitamin D₃, the natural human vitamin. As shown in Figure 75-2, vitamin D₃ (cholecalciferol) is produced in the skin through the action of sunlight on provitamin D₃ (7-dehydrocholesterol). Neither provitamin D₃ nor vitamin D₃ itself possesses significant biologic activity. In the next reaction, enzymes in the liver convert cholecalciferol into calcifediol, which serves as a transport form of vitamin D₃ and possesses only slight biologic activity. In the final step, calcifediol is converted into the highly active calcitriol. This reaction occurs in the kidney and can be stimulated by (1) PTH, (2) a drop in dietary vitamin D, and (3) a fall in plasma levels of calcium.

Vitamin D₂ is activated by the same enzymes that activate vitamin D₃. As we saw with vitamin D₃, only the last compound in the series (in this case 1,25-dihydroxyergocalciferol) has significant biologic activity.

Pharmacokinetics

As a rule, vitamin D is administered orally and then absorbed from the small intestine. Bile is essential for absorption. In the absence of sufficient bile, IM dosing may be required. In the blood, vitamin D is transported complexed with vitamin D-binding protein. Storage of vitamin D occurs primarily in the liver. As discussed, vitamin D undergoes metabolic activation. Reactions that occur in the liver produce the major transport form of vitamin D. A later reaction (in the kidney) produces the fully active form. Excretion of vitamin D is via the bile. Very little leaves in the urine.

Viewing Vitamin D as a Hormone

Although referred to as a vitamin, vitamin D has all the characteristics of a hormone. With sufficient exposure to sunlight, the body can manufacture all the vitamin D it needs. Hence, under ideal conditions, external sources of vitamin D

appear unnecessary. Following its production in the skin, vitamin D travels to other locations (liver, kidney) for activation. Like other hormones, activated vitamin D then travels to various sites in the body (bone, intestine, kidney) to exert regulatory actions. Also like other hormones, vitamin D undergoes feedback regulation: as plasma levels of calcium fall, activation of vitamin D increases; when plasma levels of calcium return to normal, activation of vitamin D declines.

Toxicity (Hypervitaminosis D)

Serious vitamin D toxicity (hypervitaminosis D) can be produced by vitamin D doses that exceed 1000 IU/day (in infants) and 50,000 IU/day (in adults). Poisoning occurs most commonly in children; causes include accidental ingestion by the child and excessive dosing with vitamin D by parents. Doses of potentially toxic magnitude are also encountered clinically. When huge therapeutic doses are used, the margin of safety is small, and patients should be monitored closely for signs of poisoning.

Clinical Presentation. Most signs and symptoms of vitamin D toxicity occur secondary to hypercalcemia. Early responses include weakness, fatigue, nausea, vomiting, and constipation. With persistent hypercalcemia, kidney function is affected, resulting in polyuria, nocturia, and proteinuria. Calcium deposition in soft tissues can damage the heart, blood vessels, and lungs; calcium deposition in the kidneys can cause nephrolithiasis. Very large doses of vitamin D can cause decalcification of bone, resulting in osteoporosis; mobilization of bone calcium can occur despite the presence of high calcium concentrations in blood. In children, vitamin D poisoning can suppress growth for 6 months or longer.

Treatment. Treatment consists of stopping vitamin D intake, reducing calcium intake, and increasing fluid intake. Glucocorticoids may be given to suppress calcium absorption. If hypercalcemia is severe, renal excretion of calcium can be accelerated using a combination of IV saline and furosemide (a diuretic).

Therapeutic Uses

The primary indications for vitamin D are nutritional rickets, osteomalacia, and hypoparathyroidism. Other applications include vitamin D-resistant rickets, vitamin D-dependent rickets, and renal osteodystrophy.

Preparations, Dosage, and Administration

There are six preparations of vitamin D. Four of these—ergocalciferol, cholecalciferol, calcifediol, and calcitriol—are identical to forms of vitamin D that occur naturally. The other two—paricalcitol and doxercalciferol—are synthetic derivatives of natural vitamin D. (The naturally occurring preparations are highlighted in green boxes in Fig. 75-2.) Individual vitamin D preparations differ in their clinical applications (see below).

Two forms of vitamin D—vitamin D₃ (cholecalciferol) and vitamin D₂ (ergocalciferol)—are used routinely as *dietary supplements*. Of the two, vitamin D₃ is preferred. Why? Because vitamin D₃ is more effective than vitamin D₂ at raising blood levels of 25OHD, the active form of vitamin D in the body.

Vitamin D is almost always administered by mouth. One product—calcitriol—can also be given IV. Dosage is usually prescribed in international units. (One IU is equivalent to the biologic activity in 0.025 mcg of vitamin D₃.) Daily dosages of vitamin D range from 400 IU (for dietary supplementation) to as high as 500,000 IU (for vitamin D-resistant rickets).

Ergocalciferol (Vitamin D₂). Ergocalciferol [Calciferol Drops, Drisdol] is approved for hypoparathyroidism, vitamin D-resistant rickets, and familial hypophosphatemia. Ergocalciferol is supplied in capsules (50,000 IU) and an oral solution (8000 IU/mL). The dosage for vitamin D-resistant rickets ranges from 12,000 to 500,000 IU daily. The dosage for hypoparathyroidism ranges from 50,000 to 200,000 IU daily (together with 4 gm of calcium lactate 6 times/day).

Cholecalciferol (Vitamin D₃). Vitamin D₃ [Delta-D] is given as a dietary supplement and for prophylaxis and treatment of vitamin D deficiency. Compared with ergocalciferol (vitamin D₂), cholecalciferol (vitamin D₃) is more effective at raising blood levels of vitamin D. Cholecalciferol is available in tablets containing 400 and 1000 IU.

Calcifediol (25-Hydroxy-D₃). Calcifediol [Calderol] is indicated for the management of metabolic bone disease and hypocalcemia in patients undergoing chronic renal dialysis. Calcifediol is available in capsules (20 and 50 mcg) for oral use. The initial dosage is 300 to 350 mcg/wk (administered in divided doses on a daily or every-other-day schedule). For maintenance, daily doses of 50 to 100 mcg are usually adequate.

Calcitriol (1,25-Dihydroxy-D₃). Calcitriol [Rocaltrol, Calcijex] is indicated for treatment of hypoparathyroidism and management of hypocalcemia in patients undergoing chronic renal dialysis. The drug is supplied in capsules (0.25 and 0.5 mcg), oral solution (1 mcg/mL), and solution for injection (1 and 2 mcg/mL). For dialysis patients, daily doses of 0.5 to 1 mcg are usually adequate. The initial dosage for hypoparathyroidism is 0.25 mcg/day.

Doxercalciferol. Doxercalciferol [Hectorol] is indicated for prevention and treatment of secondary hyperparathyroidism in patients undergoing chronic renal dialysis. The drug is available in capsules (2.5 and 5 mcg) for oral dosing, and solution (2 mcg/mL) for IV dosing. Dosage must be carefully tailored to the patient. With oral administration, treatment begins with 10 mcg 3 times weekly administered at dialysis; dosage may be gradually increased to a maximum of 20 mcg 3 times a week. With IV administration, treatment begins with a 4-mcg IV bolus 3 times weekly at the end of each dialysis session.

Paricalcitol. Like doxercalciferol, paricalcitol [Zemlar] is indicated for prevention and treatment of secondary hyperparathyroidism in patients undergoing chronic renal dialysis. The drug is available in capsules (1, 2, and 4 mcg) for oral dosing, and in solution (5 mcg/mL) for dosing by IV bolus. With oral administration, two schedules may be used: (1) once daily and (2) 3 times a week. Treatment begins at 1 to 2 mcg/dose (with the once-daily schedule) or 2 to 4 mcg/dose (with the 3-times-weekly schedule). With IV administration, treatment begins with 0.04 to 0.1 mcg/kg given any time during dialysis—but no more frequently than every other day. Dosage may be gradually increased every 2 to 4 weeks. Doses as high as 0.24 mcg/kg have been used safely.

Calcitonin-Salmon

Calcitonin-salmon [Miacalcin, Fortical], a form of calcitonin derived from salmon, is similar in structure to calcitonin synthesized by the human thyroid. Salmon calcitonin produces the same metabolic effects as human calcitonin but has a longer half-life and greater milligram potency. The drug is usually given by nasal spray, but can also be given by injection. Both routes are extremely safe.

Actions

Calcitonin has two principal actions: It (1) inhibits the activity of osteoclasts, and thereby decreases bone resorption; and (2) inhibits tubular resorption of calcium, and thereby increases

calcium excretion. As a result of decreasing bone turnover, calcitonin decreases alkaline phosphatase in blood and increases hydroxyproline in urine.

Therapeutic Uses

Osteoporosis. Calcitonin-salmon, given by nasal spray or injection, is indicated for *treatment* of established postmenopausal osteoporosis—but not for prevention. Benefits derive from suppressing bone resorption. The treatment program should include supplemental calcium and adequate intake of vitamin D. Use of calcitonin for osteoporosis is discussed further under *Osteoporosis*.

Paget's Disease of Bone. Calcitonin is helpful in moderate to severe Paget's disease and is the drug of choice for rapid relief of pain associated with the disorder. Benefits occur secondary to inhibition of osteoclasts. Neurologic symptoms caused by spinal cord compression may be reduced.

Hypercalcemia. Calcitonin can lower plasma calcium levels in patients with hypercalcemia secondary to hyperparathyroidism, vitamin D toxicity, and cancer. Levels of calcium (and phosphorus) are reduced owing to inhibition of bone resorption and increased renal excretion of calcium. Although calcitonin is effective against hypercalcemia, it is not a preferred treatment.

Adverse Effects

Calcitonin is very safe. With intranasal dosing, nasal dryness and irritation are the most common complaints. Following parenteral (IM, subQ) administration, about 10% of patients experience nausea, which diminishes with time. An additional 10% have inflammatory reactions at the injection site. Flushing of the face and hands may also occur. When salmon calcitonin is taken for a year or longer, neutralizing antibodies often develop. In some patients, these antibodies bind enough calcitonin to prevent therapeutic effects.

Preparations, Dosage, and Administration

Intranasal Spray. Salmon calcitonin for intranasal use [Miacalcin, Fortical] is available in a metered-dose spray device that delivers 200 IU/activation. This formulation is approved only for *postmenopausal osteoporosis*. The dosage is 200 IU (1 spray) each day, alternating nostrils daily.

Parenteral. Salmon calcitonin for parenteral use [Miacalcin] is supplied in 2-mL vials containing 200 IU/mL. Administration is IM or subQ. Dosages are the same for both routes. Dosages for specific indications are

- *Postmenopausal osteoporosis*—100 IU/day
- *Paget's disease of bone*—100 IU/day initially, followed by 50 IU (daily or 3 times a week) for maintenance
- *Hypercalcemia*—the initial dosage is 4 IU/kg every 12 hours; the maximal dosage is 8 IU/kg every 6 hours

Bisphosphonates

Bisphosphonates are structural analogs of pyrophosphate (Fig. 75-3), a normal constituent of bone. These drugs undergo incorporation into bone, and then inhibit bone resorption by decreasing the activity of osteoclasts. Principal indications are postmenopausal osteoporosis, osteoporosis in men, glucocorticoid-induced osteoporosis, Paget's disease of bone, and hypercalcemia of malignancy. Bisphosphonates may also help prevent and treat bone metastases in patients with cancer (see Chapter 103). Although these drugs are generally very safe, serious adverse effects can occur, including ocular inflammation, osteonecrosis of the jaw, atypical femur fractures, and atrial fibrillation (primarily with IV zoledronate).

Bisphosphonates differ with respect to indications, routes, and dosing schedules. As indicated in Table 75-5, some bisphosphonates are given PO, some are given IV, and some are given by both routes. With oral dosing, absorption from the GI tract is extremely poor. Dosing schedules vary from as

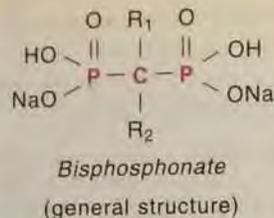
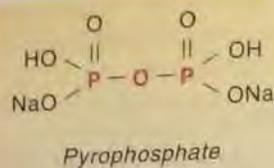


Figure 75-3 = Structure of pyrophosphate and general structure of bisphosphonates.

often as once a day (with oral agents) to as seldom as once every 2 years (with IV zoledronate).

Alendronate

Alendronate [Fosamax, Fosamax Plus D], the most widely used oral bisphosphonate, will serve as our prototype for the family. The drug is approved for postmenopausal osteoporosis, male osteoporosis, glucocorticoid-induced osteoporosis, and Paget’s disease of bone. Oral bioavailability is poor. Although alendronate is generally safe, esophageal ulceration has occurred in some patients.

Pharmacokinetics. Alendronate is administered orally, but bioavailability is very low (only 0.7%). If the drug is taken with solid food, essentially none is absorbed. Even coffee or orange juice can decrease absorption by 60%. Absorption is also decreased by bivalent cations—including calcium, magnesium, and iron—which bind with alendronate and all other bisphosphonates. Of the small fraction that undergoes absorp-

tion, about 50% is taken up rapidly by bone. The remaining 50% is excreted unchanged in the urine. Once alendronate has become incorporated into bone, it remains there for decades.

Mechanism of Action. Alendronate suppresses resorption of bone by decreasing both the number and activity of osteoclasts. Several mechanisms are involved. As osteoclasts begin to resorb alendronate-containing bone, they ingest some of the drug, which then acts on the osteoclasts to inhibit their activity. In addition, alendronate reduces the number of osteoclasts by (1) acting directly to decrease their recruitment and (2) acting on osteoblasts, which then produce an inhibitor of osteoclast formation.

Therapeutic Use. Osteoporosis in Postmenopausal Women. Alendronate is approved for both the prevention and treatment of osteoporosis in postmenopausal women. Benefits derive from decreasing bone resorption by osteoclasts. The use of alendronate for osteoporosis is discussed further under *Osteoporosis*, later in the chapter.

Osteoporosis in Men. Alendronate is approved for treating osteoporosis in men. In this group, the drug increases bone mineral density (BMD), reduces vertebral fractures, and decreases loss of height.

Glucocorticoid-Induced Osteoporosis. Alendronate is considered a first-choice drug for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP), a common complication of glucocorticoid therapy that leads to fractures in at least 50% of patients. Studies indicate that alendronate helps restore lost bone and may reduce the risk of fractures.

Paget’s Disease of Bone. Alendronate is a first-line treatment for Paget’s disease. Continuous daily therapy for 3 months produces a 50% decrease in serum alkaline phosphatase, indicating a substantial reduction in bone turnover. As in osteoporosis, benefits derive from inhibiting bone resorption by osteoclasts.

Adverse Effects. Alendronate is generally well tolerated. Esophagitis is the principal concern. Rarely, the drug causes musculoskeletal pain, ocular inflammation, atypical femur fractures, and osteonecrosis of the jaw. Whether alendronate can cause esophageal cancer is uncertain.

TABLE 75-5 = Bisphosphonates: Routes and Uses

Drug Name	Route	Major Uses*				
		Osteoporosis in Postmenopausal Women	Osteoporosis in Men	Paget’s Disease of Bone	Hypercalcemia of Malignancy	Glucocorticoid-Induced Bone Loss
Alendronate [Fosamax]	PO	A	A	A		A
Risedronate [Actonel, Atelvia]	PO	A	A	A		A
Tiludronate [Skelid]	PO			A		
Ibandronate [Boniva]	PO, IV	A				
Etidronate [Didronel] [†]	PO, IV			A		
Zoledronate [Reclast]	IV	A	A	A		I
Zoledronate [Zometa] [‡]	IV					A
Pamidronate [Aredia] [§]	IV	I		A	A	I

*A = FDA-approved indication, I = investigational use.
[†]Also approved for prevention and treatment of heterotopic ossification.
[‡]Also approved for multiple myeloma and bone metastases from solid tumors.
[§]Also approved for osteolytic bone metastases.

Esophagitis. Esophagitis, sometimes resulting in ulceration, is the most serious adverse effect. Fortunately, esophagitis is rare, occurring in only 1 of every 10,000 patients. The cause of injury is prolonged contact with the esophageal mucosa, which can occur if alendronate fails to pass completely through the esophagus. Reasons for incomplete passage include taking the drug with insufficient water, taking the drug in a supine position, lying down after taking the drug, and having a pre-existing esophageal disorder that impedes drug passage. To promote complete passage, and thereby minimize risk of esophagitis, alendronate should be administered according to established guidelines (see below). Patients should be instructed to discontinue alendronate and contact the prescriber if they experience symptoms of esophageal injury (difficulty swallowing, pain upon swallowing, or new or worsening heartburn). Because of the risk of esophagitis, alendronate is contraindicated for patients with esophageal disorders that could prevent successful swallowing and for patients who are unable to sit or stand for at least 30 minutes.

Atypical Femoral Fractures. Very rarely, alendronate and other bisphosphonates have been associated with atypical fractures of the femur, which occur with little or no trauma. Postmenopausal women taking bisphosphonates long term are most vulnerable. Why do these fractures occur? One explanation is that excessive suppression of bone turnover reduces bone remodeling, and, as a result, repair of microcracks is suppressed, and hence bone strength is reduced. Fortunately, the absolute risk of atypical fractures is low—about 5 additional cases for every 10,000 patient-years of bisphosphonate use. Risk increases with duration of treatment.

Do the benefits of preventing typical fractures (which are common) outweigh the risk of causing atypical fractures (which are rare)? The answer is clearly “Yes”—but only for women with osteoporosis deemed at high risk of a typical fracture. For women without osteoporosis who are at low risk for a typical fracture, the benefits of bisphosphonates may not justify the risks.

What can be done to reduce the risk of an atypical fracture? In 2010, a task force assembled by the American Society for Bone and Mineral Research recommended the following:

- Do not prescribe bisphosphonates for patients considered at low risk for osteoporosis-related fractures.
- Consider alternative treatments, such as raloxifene or teriparatide, for patients with osteoporosis of the spine and normal (or only moderately reduced) BMD of the femoral neck or hip.
- After 5 years of bisphosphonate use, the need for continued treatment should be evaluated annually.

Esophageal Cancer. Alendronate and other oral bisphosphonates may—or may not—increase the risk of esophageal cancer. Studies have reached conflicting conclusions. If the risk is real, it is small (about 1 additional case for every 1000 patients over age 60 treated for 5 years) and probably due to esophageal injury caused during oral dosing. Measures that might reduce risk include reducing the dosing frequency (ie, dosing weekly rather than daily), taking the drug with a full glass of water, and staying upright for 30 to 60 minutes after dosing.

Musculoskeletal Pain. Musculoskeletal pain, sometimes severe, has been reported during postmarketing surveillance. So far, a causal link with alendronate has not been established. Onset may occur shortly after the first dose or months later. Pain can be managed with analgesics, including opioids and ketorolac when pain is severe. In most cases, discomfort gradually resolves after stopping alendronate. Interestingly, among patients who resume alendronate use, only 11% experience a return of pain. If pain does return,

patients taking the drug for osteoporosis can switch to a different agent, such as raloxifene, calcitonin-salmon, or teriparatide.

Ocular Problems. Ocular problems are rare, but can be serious. Possible effects include conjunctivitis, scleritis, blurred vision, and eye pain. Drug-induced release of inflammatory cytokines may be the cause. Advise patients to report any vision changes or eye pain.

Osteonecrosis of the Jaw. Very rarely, patients have developed osteonecrosis of the jaw (ONJ), a potentially severe complication seen mostly with IV bisphosphonates (see discussion of zoledronate).

Hyperparathyroidism. In patients with Paget's disease, alendronate can induce hyperparathyroidism. How? By inhibiting accelerated bone resorption, alendronate causes blood levels of calcium to fall; in response, secretion of PTH is increased. To prevent hyperparathyroidism, patients should receive calcium supplements.

Atrial Fibrillation. Because an intravenous bisphosphonate (zoledronate) has been associated with rare cases of atrial fibrillation (AF), there is concern that oral alendronate may also cause the disorder. However, a Danish case-control study involving 13,586 patients found no evidence that either of two oral bisphosphonates—alendronate or etidronate—increased AF risk.

Administration. Proper administration is necessary to maximize bioavailability and minimize the risk of esophagitis (and possibly esophageal cancer). To maximize bioavailability, alendronate should be taken in the morning before breakfast (ie, on an empty stomach). No food, including orange juice or coffee, should be consumed for at least 30 minutes. To minimize the risk of esophagitis, patients should be instructed to

- Take alendronate with a full glass of water
- Remain upright (sitting or standing) for at least 30 minutes
- Avoid chewing or sucking alendronate tablets

Preparations and Dosage. Alendronate [Fosamax] is available alone in tablets (5, 10, 35, 40, and 70 mg) and an oral solution (70 mg in 75 mL). In addition, alendronate is available in a fixed-dose combination with vitamin D (cholecalciferol) under the trade name *Fosamax Plus D*. Dosing for osteoporosis in women or men may be done once daily (in the morning) or once weekly (on the same morning each week). Once-weekly dosing, which is just as effective as once-daily dosing, is possible because alendronate undergoes incorporation into bone, where it remains and acts for years. Bivalent cations—including calcium, iron, magnesium, and antacids that contain calcium, aluminum, or magnesium—can decrease alendronate absorption, and hence should not be taken for at least 30 minutes after taking alendronate. Dosages are as follows:

- **Osteoporosis in postmenopausal women**—for prevention, 5-mg tablet daily or 35 mg once weekly; for treatment, 10 mg once daily or 70 mg once weekly
- **Osteoporosis in men**—10 mg once daily or 70 mg once weekly
- **Paget's disease**—40 mg once daily for 6 months for men or women
- **Glucocorticoid-induced osteoporosis**—5 mg once daily (for men, premenopausal women, and postmenopausal women taking estrogen) or 10 mg once daily (for postmenopausal women not taking estrogen)

Risedronate

Actions and Uses. Risedronate [Actonel, Atelvia] is an oral bisphosphonate approved for postmenopausal osteoporosis, male osteoporosis, glucocorticoid-induced osteoporosis, and Paget's disease of bone. As with other bisphosphonates, benefits derive from inhibiting osteoclast-mediated resorption of bone. In postmenopausal women with osteoporosis, risedronate increases bone mineral density and reduces the risk of vertebral and nonvertebral fractures.

Pharmacokinetics. Like other oral bisphosphonates, risedronate is poorly absorbed from the GI tract. Absorption is only 1% under fasting conditions. The impact of food depends on the formulation used. With Actonel (an immediate-release [IR] formulation), food greatly reduces absorption. By contrast, with Atelvia (an enteric-coated, delayed-release [DR] formulation), food does not reduce absorption. In fact, Atelvia should be taken with food to reduce stomach pain. Following absorption, most of the drug becomes incorporated into bone. The rest is excreted unchanged in the urine. Risedronate in bone persists for years.

Adverse Effects. The most common adverse effects are arthralgia (32%), diarrhea (20%), headache (18%), rash (12%), nausea (10%), and a flu-like syndrome (10%). Like alendronate, risedronate poses a significant

risk of esophagitis, and a very small risk of atypical femoral fractures. Ocular problems, and musculoskeletal pain are rare. If risedronate poses a risk of esophageal cancer, ONJ, or AF, the risk is very small.

Preparations, Dosage, and Administration. Risedronate is supplied in IR tablets (5, 30, 35, 75, and 100 mg) sold as *Actonel*, and in 35-mg enteric-coated DR tablets sold as *Atelvia*. The IR tablets are approved for postmenopausal osteoporosis, male osteoporosis, glucocorticoid-induced osteoporosis, and Paget's disease of bone. The DR tablets are approved only for postmenopausal osteoporosis. With the IR tablets, each dose should be taken in the morning before ingesting the first food or fluids of the day (except for water). With the DR tablets, each dose should be taken in the morning after breakfast. (*Atelvia* is the only oral bisphosphonate that can be taken after eating, rather than before.) With both formulations, dosing should be done with a full glass of water. Also, the patient should be upright when swallowing, and should not lie down for at least 30 minutes. Because divalent cations—including calcium, iron, and magnesium—greatly reduce absorption, these should not be administered within 2 hours of administering either risedronate formulation. Dosages are as follows:

- *Postmenopausal osteoporosis.* for prevention or treatment (*Actonel* or *Atelvia*)—With *Actonel*, 5 mg once daily, 35 mg once weekly, 150 mg once a month, or 75 mg on 2 consecutive days each month. With *Atelvia*, 35 mg once weekly.
- *Osteoporosis in men* (*Actonel* only)—35 mg once a week
- *Glucocorticoid-induced osteoporosis in men or women, for prevention or treatment* (*Actonel* only)—5 mg once daily
- *Paget's disease in men or women* (*Actonel* only)—30 mg once daily for 2 months. If needed, a second 2-month course can be given, provided at least 2 months have elapsed since completing the first course.

Ibandronate

Actions and Uses. Ibandronate [*Boniva*], available in oral and IV formulations, is approved for prevention and treatment of *postmenopausal osteoporosis*. Dosing may be done once a day, once a month, or once every 3 months. As with other bisphosphonates, benefits derive from inhibiting osteoclast-mediated resorption of bone. In clinical trials, ibandronate increased BMD in the lumbar spine and other sites, and reduced the risk of vertebral fractures. Although comparative studies have not been done, the drug is probably as effective as alendronate and risedronate, the only other bisphosphonates approved for oral therapy of osteoporosis.

Pharmacokinetics. With oral dosing, bioavailability is extremely low—only 0.6%. Food decreases availability by another 90%. Following absorption, ibandronate undergoes rapid binding to bone or excretion in the urine. Metabolism, if any, is minimal. The half-life in blood is 10 to 60 hours. However, because of binding to bone, active drug remains in the body for years.

Adverse Effects and Interactions. With oral administration, ibandronate is generally well tolerated. Like other oral bisphosphonates, it can cause adverse GI effects, including esophagitis, dyspepsia, and abdominal pain. Ocular inflammation, atypical fractures, and ONJ are rare. Musculoskeletal pain has not been reported. Whether ibandronate increases the risk of esophageal cancer is unknown. As with other bisphosphonates, bivalent cations (eg, calcium, magnesium, iron) can greatly decrease absorption.

With IV administration, ibandronate and other bisphosphonates may cause renal damage, especially if administered too rapidly. Accordingly, ibandronate should be injected slowly—over an interval of 15 to 30 seconds. Intravenous ibandronate should not be used by patients taking other nephrotoxic drugs, or by those with severe renal impairment, defined as serum creatinine above 2.3 mg/dL or creatinine clearance less than 30 mL/min. In addition to causing renal damage, IV ibandronate may cause an acute reaction characterized by fever, joint pain, and myalgia, primarily with the first dose.

Preparations, Dosage, and Administration. *Oral.* Ibandronate [*Boniva*] for oral dosing is supplied in 150-mg tablets. The dosage for prevention and treatment of osteoporosis is 150 mg once a month, taken on the same day each month. Dosing is done on an empty stomach in the morning. Patients should swallow tablets whole with a full glass of water, while standing or sitting upright. For 60 minutes after dosing, patients must remain upright, and must not eat or drink anything, including medications and dietary supplements.

If a monthly dose is missed, and the next scheduled dose is at least 7 days away, then the missed dose should be taken in the morning, and the next dose should be taken as originally scheduled.

If the monthly dose is missed, and the next scheduled dose is less than 7 days away, then the missed dose should not be taken, and dosing should resume according to the original schedule.

Intravenous. Ibandronate [*Boniva*] for IV dosing is supplied in solution (1 mg/mL) in 5-mL, pre-filled syringes. For treatment of osteoporosis the dosage is 3 mg every 3 months, administered by slow IV push (over 15 to 30 seconds). Kidney function should be determined before each dose and, if severe renal impairment is detected, the dose should be withheld.

Tiludronate

Actions and Uses. Tiludronate [*Skelid*] is an oral bisphosphonate approved only for *Paget's disease of bone*. The drug decreases abnormal bone growth and, unlike etidronate, does so without interfering with bone mineralization. Like other bisphosphonates, tiludronate undergoes incorporation into bone. When osteoclasts resorb this bone, they ingest the drug, which then inhibits further osteoclast-mediated bone resorption.

Pharmacokinetics. Tiludronate is administered by mouth, and bioavailability is low. Food further decreases availability. In blood, about 90% of the drug is bound to serum proteins, mainly albumin. Tiludronate is eliminated largely unchanged in the urine.

Adverse Effects. The most common side effects are nausea (9.3%), diarrhea (9.3%), and dyspepsia (5.3%). These are usually mild and rarely require cessation of treatment. Like alendronate, tiludronate poses a risk of esophagitis, ocular problems, musculoskeletal pain, and possibly esophageal cancer. Other side effects include chest pain, edema, paresthesias, hyperparathyroidism, vomiting, and flatulence.

Preparations, Dosage, and Administration. Tiludronate [*Skelid*] is supplied in 200-mg tablets. The dosage is 400 mg once a day for 3 months. Patients should be instructed to take tiludronate with a full glass of water. Also, they should not eat for 2 hours before or after taking the drug. Because aspirin and bivalent cations (eg, calcium, iron, magnesium) greatly reduce tiludronate absorption, they should not be administered within 2 hours of administering tiludronate.

Etidronate

Actions, Uses, and Adverse Effects. Etidronate [*Didronel*] is approved for *Paget's disease* and for prevention and treatment of *heterotrophic ossification* (abnormal bone formation in extraskeletal soft tissue). The drug is also used for glucocorticoid-induced osteoporosis, although it is not approved for this disorder. In patients with highly active Paget's disease, etidronate can produce moderate clinical improvement. Unfortunately, when the drug is discontinued, relapse may occur rapidly. Side effects include abdominal cramps, diarrhea, nausea, and increased bone pain. In addition, etidronate causes defective mineralization of newly formed bone (osteomalacia), and can thereby increase the risk of fractures. Whether the drug causes esophageal cancer is uncertain.

Preparations, Dosage, and Administration. Etidronate [*Didronel*] is available in 200- and 400-mg tablets for oral dosing. As with all other oral bisphosphonates, bioavailability is low. To maximize absorption, patients should wait 2 hours before ingesting food, antacids high in metals (eg, calcium, iron, magnesium, aluminum), and vitamins that contain mineral supplements.

Patients with *Paget's disease* may be given either (1) 5 to 10 mg/kg/day (for no more than 6 months), or (2) 11 to 20 mg/kg/day (for no more than 3 months). Treatment can be repeated, but not until 90 days have elapsed since completing the prior course.

The dosage for preventing *heterotrophic ossification* in patients undergoing total hip replacement is 20 mg/kg every day for 1 month before surgery and for 3 months after.

Zoledronate

Actions and Uses. Zoledronate [*Reclast, Zometa*], also called zoledronic acid, is an IV bisphosphonate with five approved indications: *postmenopausal osteoporosis*, *osteoporosis in men*, *Paget's disease of bone*, *glucocorticoid-induced osteoporosis*, and *hypercalcemia of malignancy* (HCM). In addition, the drug is used off-label to prevent fractures and other skeletal-related events in patients with bone metastases from solid tumors. Like other bisphosphonates, zoledronate undergoes incorporation into bone, where it remains for years. When osteoclasts ingest the drug, it inhibits their activity, and thereby prevents bone resorption.

In patients with HCM, inhibition of bone resorption lowers calcium levels in blood. In one study, zoledronate normalized serum calcium in 88% of patients within 10 days of a single

infusion. Compared with pamidronate, another IV bisphosphonate for HCM, zoledronate has three advantages. Specifically, onset is faster, duration is longer, and, perhaps most importantly, infusion time is shorter (15 minutes vs. 2 to 4 hours), making dosing more convenient.

For management of postmenopausal osteoporosis, zoledronate differs from all other bisphosphonates, in that dosing is done just once a year or once every 2 years. Compared with placebo treatment, once-yearly zoledronate decreases the incidence of vertebral fractures by 70%, hip fractures by 41%, and nonvertebral fractures by 25%. In addition, zoledronate improves BMD and markers of bone metabolism.

Adverse Effects. The most common reaction is transient fever (44%), followed by nausea (29%), constipation (26%), dyspnea (22%), abdominal pain (16%), and bone and joint pain (12%). In addition, zoledronate can cause clinically significant reductions in serum levels of calcium, phosphorus, and magnesium. Accordingly, levels of these elements should be followed and corrected when indicated.

Zoledronate has been associated with bone injury, most often *osteonecrosis of the jaw* (ONJ), a condition characterized by local bone death and decreased bone strength. The underlying cause is impaired blood perfusion. (Bisphosphonates impair perfusion by inhibiting growth of blood vessels.) Among patients using zoledronate, most cases of ONJ developed after tooth extractions and other dental procedures, which can increase risk by promoting infection. Other risk factors include cancer, cancer chemotherapy, use of systemic glucocorticoids, and poor oral hygiene. To reduce ONJ risk, a dental exam with appropriate preventive dentistry should be conducted before giving zoledronate, especially in patients with ONJ risk factors. Patients should avoid elective dental work while using zoledronate.

Zoledronate can cause dose-dependent *kidney damage*, which can progress to acute renal failure and, rarely, to death. Risk is increased by:

- Chronic renal impairment
- Advanced age
- Dehydration (eg, secondary to fever, sepsis, diarrhea)
- Use of diuretics (which can cause dehydration)
- Use of nephrotoxic drugs
- Rapid infusion of zoledronate

Owing to the risk of renal failure, zoledronate is contraindicated in patients with significant renal impairment (creatinine clearance below 35 mL/min) or outright renal failure. To minimize risk, dosage should be kept low (5 mg or less per infusion) and the infusion should be slow (15 minutes or longer). In addition, the patient should be adequately hydrated before each infusion. To monitor for renal damage, creatinine clearance should be determined at baseline, prior to each dose, and periodically after each infusion. If renal impairment develops, zoledronate dosage should be reduced.

Rarely, zoledronate has been associated with serious *atrial fibrillation*, resulting in disability or hospitalization. In one trial, the incidence was 1.3%, compared with 0.5% in patients taking placebo. Most cases developed more than 30 days after zoledronate infusion.

Drug Interactions. Risk of renal failure is increased by diuretics (which can cause dehydration) and by other *nephrotoxic drugs*, including cyclosporine, amphotericin B, aminoglycoside antibiotics, and the nonsteroidal anti-inflammatory drugs (NSAIDs).

Preparations, Dosage, and Administration. Zoledronate is available in solution under two trade names: Reclast and Zometa. These solutions differ in concentration and indications.

Zometa, indicated for *hypercalcemia of malignancy*, is supplied as a concentrated solution (4 mg/5 mL) that must be diluted in 100 mL of 0.9% sodium chloride or 5% dextrose. The maximum recommended dose is 4 mg. In patients with renal impairment, dosage should be reduced. All doses must be given as a single IV infusion over *no less than 15 minutes*. If hypercalcemia does not resolve, or if it resolves and then returns, a second infusion can be given, but no sooner than 7 days after the first infusion, and only if kidney function is adequate.

Reclast is supplied as a *dilute solution* (5 mg/100 mL) in single-use vials. Indications and dosages are as follows:

- *Postmenopausal osteoporosis, treatment*—5 mg once a year, infused over 15 minutes or longer
- *Postmenopausal osteoporosis, prevention*—5 mg once every 2 years, infused over 15 minutes or longer
- *Osteoporosis in men*—5 mg once a year, infused over 15 minutes or longer
- *Glucocorticoid-induced osteoporosis*—5 mg once a year, infused over 15 minutes or longer
- *Paget's disease*—5 mg infused over 15 minutes or more. Just one dose produces extended remission. Specific re-treatment data are not available.

Pamidronate

Pamidronate [Aredia] is a bisphosphonate approved for IV therapy of *Paget's disease*, *hypercalcemia of malignancy*, and *osteolytic bone metastases*. Because of dose-related GI intolerance (eg, mucosal erosion in the esophagus and stomach), pamidronate is not given orally.

Therapeutic Use and Dosage. Hypercalcemia of Malignancy. Many cancer cells release factors that stimulate resorption of bone by osteoclasts. The result is hypercalcemia, increased risk of fractures, and bone pain. By inhibiting osteoclast activity, pamidronate can blunt cancer-mediated bone resorption, and can thereby reduce blood levels of calcium. The recommended dosage is 60 to 90 mg infused over 2 to 24 hours. Longer infusion times reduce the risk of renal injury.

Paget's Disease of Bone. Like other bisphosphonates, pamidronate can decrease bone resorption in patients with Paget's disease. The dosage is 30 mg infused slowly (over at least 4 hours) on 3 consecutive days. With this dosage, the mean duration of remission is 14 months.

Osteolytic Bone Metastases. For osteolytic bone lesions of *multiple myeloma*, the dosage is 90 mg infused over 4 hours once a month. For bone metastases of *breast cancer*, the dosage is 90 mg infused over 2 hours every 3 to 4 weeks.

Adverse Effects. Although IV pamidronate is generally safe, serious adverse effects can occur. Like zoledronate, pamidronate has been associated with ONJ, usually after an invasive dental procedure. In some patients, the first dose causes transient flu-like symptoms. If pamidronate is not infused with sufficient fluid, venous irritation can occur. In contrast to etidronate, pamidronate does not interfere with bone mineralization. Because pamidronate inhibits accelerated bone resorption of Paget's disease, blood levels of calcium will fall, thereby triggering increased release of PTH; to prevent hyperparathyroidism, patients should receive supplemental calcium.

Raloxifene

Raloxifene [Evista] belongs to a class of agents known as *selective estrogen receptor modulators* (SERMs)—drugs that exert estrogenic effects in some tissues and antiestrogenic effects in others. Like estrogen, raloxifene preserves BMD and reduces plasma levels of cholesterol. However, in contrast to estrogen, which promotes cancer of the breast and endometrium, raloxifene protects against these cancers. Because of its effects on bone, raloxifene is used to prevent and treat postmenopausal osteoporosis. Because of its effects on breast tissue, the drug is used to reduce the risk of breast cancer. Another SERM—tamoxifen—is used to *treat* breast cancer as well as prevent it (see Chapter 103).

Mechanism of Action

Raloxifene and other SERMs are structurally similar to estrogen, and hence can bind to estrogen receptors. However, unlike estrogen itself, which functions as an agonist in all tis-

sues, SERMs function as agonists in some tissues and antagonists in others. Hence, SERMs can either mimic or block the actions of estrogen, depending on the SERM and the tissue involved. Raloxifene mimics the effects of estrogen on bone, lipid metabolism, and blood clotting, and blocks estrogen effects in the breast and endometrium.

Pharmacokinetics

Raloxifene is administered by mouth, and 60% is absorbed. However, owing to extensive first-pass metabolism, absolute bioavailability is below 2%. Excretion is fecal. The drug's half-life is about 28 hours.

Therapeutic Uses

Raloxifene offers significant benefits regarding osteoporosis and breast cancer, but also poses a risk of serious thromboembolic events. Accordingly, women must carefully weigh the risks and benefits before choosing this drug.

Postmenopausal Osteoporosis. Raloxifene is used to prevent and treat osteoporosis in postmenopausal women. The drug can preserve or increase BMD, although not as effectively as estrogen. Raloxifene reduces the risk of *spinal* fractures by 55%, but does not reduce the risk of fractures at other sites. Use of raloxifene in osteoporosis is discussed further under *Osteoporosis*.

Breast Cancer. Raloxifene protects against estrogen receptor (ER)-positive breast cancer. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which enrolled 7705 postmenopausal women with osteoporosis, taking raloxifene for a median of 40 months reduced the risk of ER-positive breast cancer by 76%—but only in women with high levels of estrogen. There was no reduction in the risk of ER-negative breast cancer. Encouraged by these results, the National Cancer Institute funded a large 5-year trial, called the Study of Tamoxifen and Raloxifene (STAR). STAR enrolled 19,747 women at high risk of breast cancer, with the objective of comparing risk reduction conferred by raloxifene or tamoxifen, a SERM already proved to reduce risk by 50%. The results of STAR, released in 2007, showed that raloxifene is just as effective as tamoxifen and also safer, causing fewer cases of uterine cancer and blood clots. As a result of these studies, raloxifene is now approved for reducing the risk of invasive breast cancer in postmenopausal women who either (1) have osteoporosis or (2) are at high risk of breast cancer, even if they don't have osteoporosis.

Cardiovascular Disease. Preliminary data from the MORE trial indicate that, during the first 4 years of therapy, raloxifene reduces the risk of cardiovascular events (myocardial infarction [MI], unstable angina, coronary ischemia, and stroke) by 40% in women who are at high risk for such events, but not in women who are at low risk. In contrast to estrogen, raloxifene does not increase the risk of early cardiovascular events. Although these data suggest that raloxifene might be employed to protect against cardiovascular disease, more data are needed before the drug can be recommended for this use.

Adverse Effects and Interactions

Raloxifene is generally well tolerated, although it can cause thrombotic events and fetal injury. Raloxifene appears devoid of significant drug-drug and drug-food interactions.

Venous Thromboembolism. Like estrogen, raloxifene increases the risk of deep vein thrombosis (DVT), pulmonary embolism, and stroke. Because inactivity promotes DVT, patients should discontinue raloxifene at least 72 hours before prolonged immobilization (eg, postsurgical recovery, extended bed rest), and should not resume the drug until full mobility has been restored. Also, patients should minimize

periods of restricted activity, as can happen when traveling or revising a pharmacology text. Raloxifene is contraindicated for patients with a history of venous thrombotic events.

Fetal Harm. Raloxifene is classified in *Food and Drug Administration (FDA) Pregnancy Risk Category X: The potential for fetal harm outweighs any possible benefits of use during pregnancy*. In animal studies, doses below those used in humans have resulted in abortion, retarded fetal development, decreased neonatal survival, and anatomic abnormalities, including hydrocephaly and uterine hypoplasia. Accordingly, raloxifene is contraindicated for use by pregnant women. Although use during pregnancy is obviously no concern for postmenopausal patients, it can be a concern for younger women taking the drug to prevent breast cancer.

Hot Flushes. In contrast to estrogen, raloxifene does not reduce hot flushes (aka hot flashes) caused by estrogen deficiency after menopause. In fact, raloxifene may cause hot flushes in women who were previously asymptomatic.

Comparison with Estrogen

The SERMs were developed in hopes of creating a drug with all the benefits of estrogen and none of its drawbacks. Raloxifene partly fulfills this hope. Like estrogen, raloxifene increases BMD in postmenopausal women and reduces the risk of fractures. In contrast to estrogen, which increases the risk of breast cancer, raloxifene protects against breast cancer. Similarly, whereas estrogen stimulates endometrial growth, and thereby increases the risk of endometrial cancer, raloxifene does not stimulate endometrial growth, and may actually protect against endometrial cancer. Estrogen reduces plasma levels of low-density lipoprotein (LDL) cholesterol (bad cholesterol) and raises levels of high-density lipoprotein (HDL) cholesterol (good cholesterol). Like estrogen, raloxifene reduces LDL cholesterol, but it does not raise HDL cholesterol. Nonetheless, raloxifene may offer superior protection against cardiovascular events. In postmenopausal women, estrogen can cause breast pain and resumption of menstruation, effects that are unlikely to be greeted with cheers. In contrast, raloxifene does not cause breast pain, and rarely causes return of menstruation. On the other hand, estrogen can alleviate symptoms of estrogen deficiency (eg, hot flushes, vaginal drying and itching), whereas raloxifene cannot. Both drugs increase the risk of DVT and fetal harm. Table 75-6 summarizes the ways in which estrogen and raloxifene are alike and different.

Preparations, Dosage, and Administration

Raloxifene [Evista] is available in 60-mg oral tablets. The dosage for all indications is 60 mg once a day, taken with or without food. Women taking raloxifene to prevent or treat postmenopausal osteoporosis should ensure adequate intake of calcium and vitamin D.

Teriparatide

Teriparatide [Forteo] is a form of parathyroid hormone (PTH) produced by recombinant DNA technology. The drug has three indications:

- Treatment of osteoporosis in postmenopausal women
- Treatment of osteoporosis in men
- Treatment of glucocorticoid-induced osteoporosis

Teriparatide is the only drug for osteoporosis that increases bone formation. All others decrease bone resorption. In postmenopausal women with documented osteoporosis, daily

TABLE 75-6 ■ Comparison of Estrogen and Raloxifene

Drug Target	Estrogen	Raloxifene
Bone	Increases BMD and reduces fracture risk	Increases BMD (but not as much as estrogen) and reduces fracture risk
Breast	Increases risk of breast cancer; causes breast enlargement and pain	Protects against breast cancer; does <i>not</i> cause breast enlargement or pain
Endometrium	Increases risk of endometrial cancer	Does <i>not</i> promote endometrial cancer, and <i>may</i> offer protection
Plasma lipids	Lowers LDL cholesterol and raises HDL cholesterol	Lowers LDL cholesterol, but does not raise HDL cholesterol
Menopausal symptoms	Alleviates menopausal symptoms (eg, hot flashes, vaginal dryness and itching)	Does <i>not</i> alleviate menopausal symptoms, and may actually increase hot flashes
Menstruation	Causes bleeding in 45% of postmenopausal women	Causes bleeding in 3%–5% of postmenopausal women
Blood clotting	Increases risk of DVT and pulmonary embolism	Same as estrogen
Coronary heart disease	Increases risk of MI early in therapy	No increase in MI risk early in therapy; lowers risk of MI in women with MI risk factors
Developing fetus	Contraindicated during pregnancy because of possible fetal harm	Same as estrogen

subQ injections of teriparatide for 18 months increased BMD of the lumbar spine and femoral neck, and reduced the risk of vertebral fractures by 65%. Similar responses are seen in men. Teriparatide-induced increases in BMD are twice those seen with alendronate.

In early clinical trials, two dosages were used: 20 mcg once daily and 40 mcg once daily. The larger dose produced a greater increase in vertebral BMD (13.7% vs. 9.7%), but did not produce a greater reduction in fractures. Moreover, it *did* produce a greater incidence of side effects. Accordingly, the 20-mcg dose is recommended. With this dose, plasma levels peak about 20 minutes after subQ injection, and decline to undetectable within 3 hours.

How does PTH affect bone? The drug has two actions: it (1) increases bone resorption by osteoclasts, and (2) increases bone deposition by osteoblasts. The net effect—resorption or deposition—depends on how the drug is administered. When given by continuous IV infusion, which produces a *steady* elevation of serum PTH, teriparatide *decreases* BMD, primarily by accelerating calcium resorption by osteoclasts. In contrast, when given by daily subQ injections, which produce *transient* elevations in serum PTH, the drug *increases* BMD, primarily by increasing bone deposition by osteoblasts.

Teriparatide is generally well tolerated. In clinical trials, adverse effects included nausea, headache, back pain, and leg cramps. In addition, serum levels of calcium, magnesium, and uric acid rose early in treatment, but then returned to normal levels within 5 weeks. Initial doses may cause orthostatic hypotension and associated dizziness.

The side effect of greatest concern is *osteosarcoma* (bone cancer). Teriparatide has caused a rare form of bone cancer in rats, but not in monkeys. To date, cancer has not been detected in humans. Nonetheless, teriparatide should be avoided by patients with bone metastases or a history of skeletal cancer,

and by patients at increased risk for bone cancer, including those with open epiphyses, Paget's disease of bone, or prior irradiation of bone.

Preparations, Dosage, and Administration. Teriparatide [Forteo] is supplied in 3-mL, pre-filled pen injectors that contain 750 mcg of drug. For all indications, the recommended dosage is 20 mcg once daily by subQ injection into the anterior thigh or abdomen. Each pen can be used up to 28 days after the first injection, after which it should be discarded, even if some drug remains. Patients should store the pens cold—2°C to 8°C (36°F to 46°F)—but not frozen, and should take them out of the cold only to make an injection. Treatment costs over \$7600 a year.

Denosumab Therapeutic Uses

Denosumab [Prolia, Xgeva], approved in 2010, is a first-in-class RANKL inhibitor with two indications: (1) treatment of osteoporosis in postmenopausal women at high risk for fractures, and (2) prevention of skeletal-related events (see below) in patients with bone metastases from solid tumors. Dosage is much higher in patients with bone metastases than in patients with osteoporosis, and hence side effects are more severe in patients with bone metastases.

Denosumab is marketed under two trade names: Prolia and Xgeva. Prolia is used for postmenopausal osteoporosis. Xgeva is used for bone metastases.

Clinical Trials

Osteoporosis in Postmenopausal Women. Denosumab was tested in a 3-year study that enrolled 7868 postmenopausal women with osteoporosis. Half the women received denosumab (60 mg injected subQ every 6 months), and the other half received placebo injections. All subjects also received at least 1000 mg of calcium daily and at least 400 IU of vitamin D daily. The result? Compared with the women

who got placebo injections, those who got denosumab had 68% fewer vertebral fractures, 40% fewer hip fractures, and 20% fewer fractures at other sites (wrist, leg, or shoulder). In a separate 12-month study, denosumab (60 mg subQ every 6 months) increased BMD at multiple sites (lumbar spine, femoral neck, trochanter, radius) more effectively than oral alendronate (70 mg once a week). Taken together, these data suggest that denosumab is equal to bisphosphates for treating menopausal osteoporosis.

Prevention of Skeletal-Related Events in Patients with Bone Metastases. In cancer patients, denosumab is used to prevent (delay) skeletal-related events (SREs)—bone fracture, spinal cord compression, bone pain requiring radiation—after cells from a solid tumor have metastasized to bone. Efficacy was evaluated by comparing denosumab with zoledronate (a bisphosphonate) in three double-blind trials that enrolled 5723 patients. One trial enrolled patients with breast cancer, one enrolled patients with prostate cancer, and one enrolled patients with other cancers, including multiple myeloma, kidney cancer, small cell lung cancer, and non-small cell lung cancer. Patients received either denosumab (120 mg subQ every 4 weeks) or zoledronate (4 mg IV every 4 weeks). The results? In patients with breast cancer or prostate cancer, denosumab was *superior* to zoledronate at delaying SREs. In patients with other cancers, denosumab was *equal* to zoledronate at delaying SREs. Use of denosumab in cancer is discussed further in Chapter 103.

Mechanism of Action

Denosumab is a monoclonal antibody that decreases the formation and function of osteoclasts, and thereby decreases bone resorption and increases BMD and bone strength. What's the underlying mechanism? Denosumab prevents the activation of a receptor known as RANK, found on the surface of osteoclasts and their precursor cells. Under normal conditions, RANK is activated by binding with an endogenous compound known as the *RANK ligand*, or simply RANKL. When activated by RANKL, RANK stimulates the formation and activity of osteoclasts. Where does denosumab fit in? It binds with RANKL, and thereby prevents RANKL from activating RANK.

Pharmacokinetics

Administration is subQ. Blood levels peak 10 days after a single injection. With monthly injections (as used for cancer patients), denosumab levels reach plateau in 6 months. The elimination half-life is 28 days. Renal impairment does not affect denosumab kinetics. The effect of hepatic impairment has not been studied.

Adverse Effects

In postmenopausal women with osteoporosis, the most common adverse effects are back pain, pain in the extremities, musculoskeletal pain, hypercholesterolemia, and urinary bladder infection. In cancer patients with bone metastases, the most common adverse effects are fatigue, hypophosphatemia, and nausea. In all patients, suppression of bone turnover may delay fracture healing and increase the risk of new fractures and ONJ. The most serious adverse effects—hypocalcemia, infections, skin reactions, and ONJ—are discussed below.

Hypocalcemia. Denosumab can exacerbate pre-existing hypocalcemia, presumably by reducing osteoclast activity. If

hypocalcemia is present, it must be corrected before starting denosumab. The risk of hypocalcemia is elevated in patients with impaired renal function (including those on dialysis) and patients with other risk factors (eg, a history of hypoparathyroidism, thyroid surgery, malabsorption syndromes, or excision of the small intestine). The manufacturer recommends monitoring levels of calcium, magnesium, and phosphorus in this at-risk group. To help prevent hypocalcemia, all patients should take 1000 mg of calcium every day and at least 400 IU of vitamin D every day.

Serious Infections. Denosumab increases the risk of serious infections, although the absolute risk is low. In clinical trials, some patients developed endocarditis, serious skin infections, and infections of the abdomen, urinary tract, and ear. Patients who develop signs of severe infection should seek immediate medical attention. Infection risk is increased in patients who are immunocompromised (eg, owing to HIV infection or treatment with immunosuppressant drugs).

Dermatologic Reactions. Denosumab increases the risk of dermatitis, eczema, rashes, and other skin reactions. Of note, these are not limited to the injection site. If a severe reaction occurs, discontinuation of denosumab should be considered.

Osteonecrosis of the Jaw. Like the bisphosphonates, denosumab increases the risk of ONJ. Risk is further increased by invasive dental procedures (eg, tooth extractions, dental implants, oral surgery), and hence these should be conducted before starting denosumab. Patients who develop ONJ should be under the care of a dentist or oral surgeon. Maintaining good oral hygiene reduces ONJ risk.

Preparations, Dosage, and Administration

Denosumab is available in solution under two trade names: Prolia and Xgeva. These products differ in concentration, indications, and dosage.

Prolia: Dosage and Administration. Prolia is indicated for osteoporosis in postmenopausal women at risk for fractures. The drug is supplied in (1) single-use vials containing 1 mL of a 60-mg/mL solution, and (2) single-use, pre-filled syringes containing 1 mL of a 60-mg/mL solution. The recommended dosage is 60 mg every 6 months, injected subQ into the upper arm, upper thigh, or abdomen. If a dose is missed, it should be given as soon as possible. Subsequent doses should be given every 6 months thereafter. To prevent hypocalcemia, patients should take 1000 mg of calcium daily plus at least 400 IU of vitamin D daily.

Xgeva: Dosage and Administration. Xgeva is indicated for preventing skeletal-related events in patients with bone metastases from solid tumors. The drug is supplied in single-use vials that contain 120 mg denosumab/1.7 mL. The recommended dosage is 120 mg every 4 weeks, injected subQ into the upper arm, upper thigh, or abdomen. As with Prolia, patients should take calcium and vitamin D to prevent hypocalcemia.

Prolia and Xgeva: Storage, Warming, and Inspection. Solutions should be stored under refrigeration, and then warmed before use (by standing at room temperature for 15 to 30 minutes). All preparations should be clear and colorless (or pale yellow). Preparations that have particles, or are cloudy or discolored, should not be used.

Cinacalcet

Actions and Therapeutic Use. Cinacalcet [Sensipar] is a "calcimimetic" drug approved for primary hyperparathyroidism (caused by parathyroid carcinoma) as well as secondary hyperparathyroidism (caused by chronic kidney disease [CKD]). In both cases, benefits derive from decreasing secretion of parathyroid hormone (PTH). How is secretion suppressed? Recall that extracellular calcium regulates PTH se-

cretion by binding with calcium-sensing receptors on cells of the parathyroid gland, thereby signaling those cells to reduce PTH secretion. All that cinacalcet does is (somehow) increase the sensitivity of the calcium-sensing receptors to activation by extracellular calcium. As a result, the ability of calcium to suppress PTH release is amplified.

Clinical trials have shown that, in patients with hyperparathyroidism secondary to CKD, cinacalcet decreases serum PTH by 23% to 46%, and improves calcium and phosphorus homeostasis. Similarly, in patients with primary hyperparathyroidism, the drug decreases serum PTH and normalizes serum calcium.

Pharmacokinetics. Dosing is oral, and absorption is increased by food. In the blood, cinacalcet is highly bound (93% to 97%) to plasma proteins. Cinacalcet undergoes extensive hepatic metabolism, followed by excretion in the urine (80%) and feces (15%). The drug's half-life is 30 to 40 hours.

Adverse Effects. The most common adverse effects are nausea (31%), vomiting (27%), and diarrhea (21%). Because cinacalcet lowers calcium levels, hypocalcemia is an obvious concern. Accordingly, calcium levels should be monitored (see below), and patients should be informed about possible manifestations of hypocalcemia (eg, cramping, convulsions, myalgias, paresthesias, tetany) and instructed to report them.

Drug Interactions. Cinacalcet is metabolized in part by cytochrome P450 isozyme 3A4, and hence inhibitors of this enzyme (eg, ketoconazole, itraconazole, erythromycin) can raise cinacalcet levels. If cinacalcet is used with one of these drugs, cinacalcet dosage may need an adjustment.

Monitoring. In patients with *parathyroid carcinoma*, measure serum calcium within 1 week of the first dose and each dosage change. Once a maintenance dosage has been established, measure serum calcium every 1 month.

In patients with *secondary hyperparathyroidism*, measure serum calcium and phosphorus within 1 week of the first dose and each dosage change, and measure PTH within 4 weeks of the first dose and each dosage change. Once a maintenance dosage has been established, measure calcium and phosphorus monthly, and PTH every 1 to 3 months.

Preparations, Dosage, and Administration. Cinacalcet [Sensipar] is available in tablets (30, 60, and 90 mg) for oral use. To enhance absorption, the drug should be taken with a meal or shortly after.

In patients with *parathyroid carcinoma*, the initial dosage is 30 mg twice daily. Then, every 2 to 4 weeks, dosage is increased as follows—60 mg twice daily, 90 mg twice daily, 90 mg 3 times/day, 90 mg 4 times a day—until the dosing goal (normalization of serum calcium) is achieved.

In patients with *secondary hyperparathyroidism*, the initial dosage is 90 mg once daily. Then, every 2 to 4 weeks, dosage is increased as follows—60 mg once daily, 90 mg once daily, 120 mg once daily, 180 mg once daily—until the dosing goal (PTH level between 150 and 300 pg/mL) is achieved.

Drugs for Hypercalcemia

Furosemide. Furosemide, a loop diuretic, promotes renal excretion of calcium. This action is useful for treating hypercalcemic emergencies. In managing such emergencies, isotonic saline (IV) must be given prior to furosemide. The dosage of furosemide for adults is 80 to 100 mg every 1 to 2 hours as needed, infused no faster than 4 mg/min. To avoid fluid and electrolyte imbalance, urinary losses must be measured and replaced. The basic pharmacology of furosemide is discussed in Chapter 41 (Diuretics).

Glucocorticoids. Glucocorticoids reduce intestinal absorption of calcium, and can thereby reduce hypercalcemia. For severe hypercalcemia, parenteral glucocorticoid therapy is indicated (eg, 100 to 500 mg hydrocortisone sodium succinate IV daily). Because glucocorticoids can produce serious adverse effects when taken chronically, the risks of long-term treatment must be carefully weighed against the benefits. The basic pharmacology of the glucocorticoids is discussed in Chapter 72 (Glucocorticoids in Nonendocrine Disorders).

Gallium Nitrate. Gallium nitrate [Ganite] is used to treat hypercalcemia of malignancy. In addition, the drug is used investigationaly for Paget's disease of bone and postmenopausal osteoporosis. Gallium reduces calcium levels by preventing bone resorption. It may also increase bone formation.

Gallium is highly nephrotoxic and must not be used with other nephrotoxic drugs, such as amphotericin B and the aminoglycosides. To minimize kidney damage, the patient must be hydrated with IV fluids before treatment. Renal function must be monitored. The usual single dose is 100 to 200 mg/m². This dose is diluted in 1 L of 5% dextrose or 0.9% sodium chloride and infused over 24 hours. Dosing is repeated daily for 5 days.

Bisphosphonates. Pamidronate, etidronate, and zoledronate are approved for hypercalcemia of malignancy. The mechanism is suppression of bone resorption by osteoclasts. The pharmacology of these agents is discussed above.

Inorganic Phosphates. Phosphates reduce plasma levels of calcium, and hence can be used to treat hypercalcemia. Suggested mechanisms for reducing plasma calcium include (1) decreased bone resorption, (2) increased bone formation, and (3) decreased intestinal absorption of calcium (secondary to decreased renal activation of vitamin D). Intravenous use of phosphates is hazardous and limited to patients with life-threatening hypercalcemia. Oral administration is considerably safer.

Oral phosphates are used for mild to moderate hypercalcemia. These agents should not be given to patients with renal impairment or elevated serum phosphate. Oral phosphates should not be combined with antacids that contain aluminum, magnesium, or calcium—agents that bind phosphate and thereby prevent its absorption. Initial treatment should provide 1 to 2 gm of phosphorus/day. Doses are reduced when serum calcium levels normalize.

Edetate Disodium. EDTA [Endrate] is a chelating agent that binds calcium in the blood. As a result, it can rapidly reduce plasma levels of free calcium. The EDTA-calcium complex is filtered by the glomerulus but not reabsorbed by kidney tubules, and hence renal excretion of calcium is increased. Although EDTA is highly effective at reducing hypercalcemia, it can be dangerous: EDTA can cause profound hypocalcemia, resulting in tetany, convulsions, dysrhythmias, and possibly death. Severe nephrotoxicity can also occur. Because of its toxicity, EDTA is used only for life-threatening hypercalcemic crisis. The usual adult dose is 40 mg/kg infused over 4 to 6 hours. The total daily dose must not exceed 3 gm.

OSTEOPOROSIS

General Considerations

Osteoporosis is a serious medical problem characterized by low bone mass, altered bone architecture, and increased bone fragility. Because of bone fragility, patients are susceptible to fractures from minor traumatic events, such as coughing, rolling over in bed, or falling from a standing position.

Osteoporosis is the most common bone disease in humans. More than 10 million Americans have osteoporosis—80% of them older women—and another 34 million have reduced bone mass, a risk factor for osteoporosis. Every year, osteoporosis leads to 1.5 million fractures. The most common fracture sites are the vertebrae (spine), distal forearm (wrist), and femoral neck (hip). Vertebral fractures can result in loss of height, spinal deformity, chronic back pain, and impaired breathing. Complications from hip fractures are a significant cause of mortality: Of the 300,000 Americans who get hip fractures each year, about 50,000 die from complications.

The economic burden of osteoporosis is high. Each year in the United States, osteoporosis-related fractures lead to more than 432,000 hospital admissions, nearly 2.5 million medical office visits, and about 180,000 admissions to nursing homes—at an estimated cost of \$17 billion, or \$47 million a day.

Bone Mass

In men and women, bone mass changes across the life span. Bone mass peaks in the third decade, remains stable to age 50, and then slowly declines—at a rate that is usually less than

1% a year. In addition to this slow, aging-related decline, women go through a phase of *accelerated* bone loss (2% to 3% a year) that begins after menopause and continues for several years. In both the slow and accelerated phases of decline, bone is lost because resorption of old bone outpaces deposition of new bone.

Primary Prevention: Calcium, Vitamin D, and Lifestyle

The risk of osteoporosis can be reduced by lifelong implementation of measures that can help maximize bone strength. Specifically, we need to ensure sufficient intake of calcium and vitamin D, and we need to adopt a lifestyle that promotes bone health. Calcium is needed to maximize bone growth early in life and to maintain bone integrity later in life. Vitamin D is needed to ensure calcium absorption. The amount of calcium needed for optimal bone health is indicated in Table 75-1. Note that calcium requirements are greatest for adolescents and teens (1300 mg/day), then drop for younger adults (1000 mg/day), and then rise for older adults (1200 mg/day). If diet alone cannot meet calcium needs, supplements should be employed. Lifestyle measures that promote bone health are

- Performing regular weight-bearing exercise (walking, jogging, dancing, racquet sports, team sports, stair climbing)
- Avoiding excessive alcohol
- Avoiding smoking

Diagnosing Osteoporosis and Assessing Fracture Risk

Osteoporosis is diagnosed by measuring bone mineral density (BMD), an important predictor of fracture risk. Both the National Osteoporosis Foundation (NOF) and the U.S. Preventive Services Task Force (USPSTF) recommend routine BMD testing for *all women* beginning at age 65, and for *younger postmenopausal women* deemed at increased risk for osteoporotic fractures. In addition, the NOF recommends testing of *all men* age 70 and older. (The USPSTF makes no recommendation regarding men.) BMD testing is not recommended for children or adolescents, nor is routine testing indicated for premenopausal women or healthy young men.

The standard technique for measuring BMD is *dual-energy x-ray absorptiometry* (DEXA). DEXA scans only take a few minutes, and exposure to radiation is minimal—about one-tenth that of a standard chest x-ray. Results of DEXA scans are reported in terms of *standard deviations* (SD) below mean BMD values in young adults. A BMD value that is 1 SD below the mean indicates 10% bone loss, a value that is 2 SD below the mean indicates 20% bone loss, and so forth. Using this system, the World Health Organization (WHO) has defined *normal* BMD for women as being no more than 1 SD below the mean for young adults. BMD values between 1 SD below the mean and 2.5 SD below the mean define *low bone mass* (also known as *osteopenia*). BMD values 2.5 SD or greater below the mean define *osteoporosis*. To simplify communication, we can talk about DEXA results in terms of a *T-score*, rather than using the phrase *SD above (or below) the mean*. For example, instead of saying that a BMD reading was 2.5 SD below the mean, we can simply say the T-score was -2.5 .

Although loss of bone at one site (eg, wrist) can predict the risk of fractures at other sites (eg, hip, spine), it is preferable to measure BMD at specific sites to predict the risk for those sites. Accordingly, a thorough evaluation would include BMD measurements in the wrist, spine, and hip—the sites at which osteoporotic fractures occur most often.

Although we use BMD values to diagnose osteoporosis, it is important to understand that low BMD is not the only predictor of fractures. Other important predictors include a family history of hip fractures, a personal history of fractures, low body mass index, and use of oral glucocorticoids. To account for these risk factors, the WHO developed an important tool, called FRAX, which can assess an *individual's* 10-year risk of experiencing a fracture. This web-based, interactive program, released in 2008, is available online at www.shef.ac.uk/FRAX/. Individual risk is calculated after entering the following data:

- Age
- Gender
- Weight
- Height
- Previous fracture
- Hip fracture in a parent
- Secondary osteoporosis (ie, malnutrition, hyperthyroidism, diabetes, and other disorders associated with osteoporosis)
- Rheumatoid arthritis
- Glucocorticoid use
- Current smoking
- Alcohol consumption
- Hip BMD

Of note, FRAX is tailored to specific countries, and, for the United States, to four specific subgroups: African Americans, Hispanics, Caucasians, and Asians.

Who Should Be Treated?

An updated guideline—*Clinician's Guide to Prevention and Treatment of Osteoporosis*—was released by the NOF in 2010. According to this document, postmenopausal women and men age 50 and older should be considered for treatment if they present with

- A hip fracture or vertebral fracture
- Osteoporosis (T-score of -2.5 or less at the femoral neck or spine)
- Low bone mass (T-score between -1 and -2.5 at the femoral neck or spine) *plus either* a 10-year probability of a hip fracture of 3% or more *or* a 10-year probability of another major osteoporosis-related fracture of 20% or more, based on a U.S.-adapted FRAX calculation.

Treating Osteoporosis in Women

The objective of treatment is to reduce the occurrence of fractures. How? By maintaining or increasing bone strength. Two types of drugs can be used: (1) agents that decrease bone resorption and (2) agents that promote bone formation. Antiresorptive drugs—estrogen, raloxifene, bisphosphonates, calcitonin, and denosumab—are used most often. These agents do a good job of preventing bone loss, but are not very good at restoring bone mass once it is gone. Accordingly, antiresorp-

tive drugs are most beneficial when used early—before substantial loss has occurred. At this time, teriparatide [Forteo] is the only drug that effectively promotes bone formation. Of the drugs employed for osteoporosis, three agents—teriparatide, denosumab, and zoledronate (a bisphosphonate)—are most likely to reduce fractures.

Antiresorptive Therapy

Bone resorption can be reduced with estrogen, raloxifene, bisphosphonates (eg, alendronate), calcitonin, and denosumab, all of which reduce osteoclast activity. These antiresorptive agents can retard bone loss, but are largely unable to reverse loss that has already occurred. When these agents are used, bone density may increase slightly during the first year or two, but then levels off. With all antiresorptive drugs, success requires a sufficiency of calcium and vitamin D.

Estrogen. The basic pharmacology of estrogen as well as postmenopausal estrogen therapy are discussed at length in Chapter 61. Discussion here focuses on the role of estrogen in osteoporosis. *Because of new insight into the benefits and risks of estrogen, prolonged replacement is no longer considered appropriate for most women* (see below and Chapter 61).

Estrogen acts indirectly to suppress osteoclast proliferation, and thereby maintains a brake on bone resorption. Consequently, when estrogen levels decline, either because of natural menopause or surgical removal of the ovaries, osteoclasts increase in number, causing bone resorption to increase dramatically. Estrogen replacement can restore the brake on osteoclast proliferation, and can thereby suppress resorption.

Estrogen is approved for preventing and treating bone loss following menopause or surgical removal of the ovaries. Treatment reduces the overall risk of fractures by 24%. Estrogen is most effective when initiated immediately after menopause. However, treatment begun at age 60 and even later can still offer significant protection. If estrogen is discontinued, a period of accelerated bone loss will ensue.

The standard dosage for estrogen therapy is 0.625 mg/day of conjugated equine estrogens [Premarin] or its equivalent. However, less estrogen (eg, 0.3 mg/day) may be nearly as effective in osteoporosis, while causing fewer side effects (vaginal bleeding, breast tenderness, headache, nausea) and, in all probability, posing a lower risk of breast cancer.

As discussed in Chapter 61, women with an intact uterus should also receive a progestin (eg, medroxyprogesterone) in order to minimize the risk of estrogen-induced endometrial cancer. For women without a uterus, the progestin is unnecessary.

For years, hormone therapy* (HT)—estrogen with or without a progestin—had been considered the treatment of choice for preventing postmenopausal bone loss. Today, however, the benefits no longer appear to outweigh the risks. As discussed in Chapter 61, data from recent trials, including the first reports from the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS), indicate that HT offers fewer benefits than previously thought, and carries greater risks. Yes, HT does

*In the past, postmenopausal estrogen/progestin therapy was usually referred to as hormone replacement therapy (HRT). However, the term hormone therapy is generally preferred today.

reduce bone loss and the risk of osteoporotic fractures. However, HT increases the risk of breast cancer, cholecystitis, myocardial infarction, and stroke. Accordingly, in the fall of 2002, the U.S. Preventive Services Task Force recommended against using combination HT (estrogen plus a progestin) to prevent osteoporosis or any other chronic disorder. (Using HT short term to manage menopausal symptoms is still considered appropriate.) Fortunately, for prevention and treatment of osteoporosis, we have effective alternatives: raloxifene, bisphosphonates, calcitonin, and teriparatide. Women currently using HT for osteoporosis are encouraged to consider a switch. For a more detailed discussion of the pros and cons of HT, refer to Chapter 61.

Raloxifene. Raloxifene [Evista] is approved for prevention and treatment of postmenopausal osteoporosis. The drug reduces bone turnover, and thereby increases BMD, although not as well as estrogen. For maximal benefits, treatment must be accompanied by adequate intake of calcium and vitamin D. Raloxifene is somewhat less effective than estrogen, but safer. Raloxifene is less effective than bisphosphonates. The basic pharmacology of raloxifene is discussed above.

In the MORE trial, treatment with raloxifene (60 or 120 mg once daily) for 36 months increased BMD and reduced fracture risk. The increase in BMD was 2.3% in the femoral neck and 2.7% in the spine. Increased BMD was associated with a reduced risk of spinal fractures: After 36 months, at least one new spinal fracture was seen in 10.1% of women taking placebo, compared with 6.6% of those taking 60 mg of raloxifene, and 5.4% of those taking 120 mg of raloxifene. This represents a 52% decrease in risk with raloxifene. However, although raloxifene reduced the risk of *spinal* fractures, it failed to reduce fractures at *non-spinal* sites (eg, wrist, hip).

Bisphosphonates. At this time, four bisphosphonates—alendronate, risedronate, ibandronate, and zoledronate—are approved for prevention and treatment of osteoporosis in postmenopausal women. However, although other bisphosphonates are not approved, it is reasonable to assume they would also be effective.

Alendronate. Alendronate [Fosamax] was the first bisphosphonate approved for postmenopausal osteoporosis. The drug is safe and helps prevent fractures. Alendronate was approved initially only for *treating* existing osteoporosis, and was later approved for *prevention*. In both cases, benefits derive from inhibiting bone resorption by osteoclasts. To be effective, alendronate must be accompanied by adequate intake of calcium and vitamin D. The basic pharmacology of alendronate is discussed above.

When studied in osteoporotic postmenopausal women (average age 65), alendronate produced a modest increase in BMD in the hip and spine. More importantly, treatment decreased the rate of new fractures: Compared with patients taking placebo, those taking alendronate experienced 51% fewer fractures of the hip, 47% fewer fractures of the spine, and 48% fewer fractures of the wrist. Furthermore, when spinal fractures did occur, loss of height was less than in women who got spinal fractures while taking placebo. The dosage for treatment of osteoporosis is 10 mg once a day or 70 mg once a week.

When given to *prevent* osteoporosis in postmenopausal women (ages 44 to 50), alendronate produced a small increase in BMD of the spine and hip. In contrast, women taking pla-

cebo lost BMD at both sites. The response to alendronate was basically the same as the response to estrogen. The dosage for prevention of osteoporosis is 5 mg once a day or 35 mg once a week—half the dosage used to treat osteoporosis.

Risedronate, Ibandronate, and Zoledronate. Like alendronate, risedronate [Actonel, Atelvia], ibandronate [Boniva], and zoledronate [Reclast] are approved for prevention and treatment of osteoporosis in postmenopausal women. In clinical trials, these drugs increased BMD and reduced the incidence of fractures. With risedronate, the dosage for prevention or treatment is 5 mg once daily, 35 mg once weekly, 75 mg on 2 consecutive days each month, or 150 mg once a month. With ibandronate, the oral dosage for prevention or treatment is 150 mg once a month, and the intravenous dosage is 3 mg every 3 months. With zoledronate (given by slow IV push), the dosage for treatment is 5 mg once a year, and the dosage for prevention is 5 mg every 2 years.

Calcitonin-Salmon. Salmon calcitonin—either intranasal [Miacalcin, Fortical] or subQ [Miacalcin]—is used to treat established osteoporosis, but not to prevent osteoporosis. Benefits derive from inhibiting osteoclastic bone resorption. By doing so, the drug decreases bone loss and the risk of fractures. In women ages 68 to 72, two years of treatment with calcitonin increased BMD in the spine by 3%. In contrast, spinal BMD decreased by 1% in women taking placebo. In younger postmenopausal women (mean age 53), calcitonin increased average BMD by 2%, whereas average BMD decreased by 7% in women taking placebo. Not only is calcitonin moderately effective, it is very safe: The drug has been used for over 20 years with no long-term adverse effects. For management of osteoporosis, the intranasal dosage is 1 spray (200 IU) a day (into alternating nostrils daily), and the subQ dosage is 100 IU/day. The pharmacology of calcitonin-salmon is discussed above.

Denosumab. Denosumab, when sold as *Prolia*,* is used to treat osteoporosis in postmenopausal women considered at high risk for fractures. However, the drug is not approved for osteoporosis prevention. Denosumab reduces the formation and activity of osteoclasts, and thereby helps preserve (or improve) bone strength. Compared with alendronate, denosumab is more effective at increasing BMD. And compared with placebo, denosumab is more effective at reducing fractures of the hip, spine, wrist, leg, and shoulder. Denosumab has a long half-life, and hence dosing is infrequent (60 mg subQ every 6 months). The pharmacology of denosumab is discussed above.

Bone-Forming Therapy: Teriparatide

Teriparatide [Forteo], a recombinant form of PTH, promotes bone formation by increasing the activity of osteoblasts. In clinical trials, the drug increased BMD of the lumbar spine, femoral neck, and total body, and significantly reduced the

risk of vertebral fractures. Teriparatide is the first and only drug for osteoporosis that works by increasing bone formation, rather than by decreasing bone resorption. As a rule, teriparatide should be reserved for patients at high risk of fractures. Why? Because the drug is expensive, inconvenient (it requires subQ injection), and potentially dangerous (it may promote bone cancer). The pharmacology of teriparatide is discussed above.

Treating Osteoporosis in Men

In the United States, about 2 million men have aging-related osteoporosis, and another 3 million are at risk. Hip fractures occur in 80,000 American men annually, compared with 269,000 American women. Of the men who get a hip fracture, 36% die within a year. Although rates of osteoporosis and fractures in men are significant, they are still much lower than in women. As discussed, bone mass in men peaks in the third decade, and begins progressive decline around age 50. The rate of decline in men is about equal to that in women—except that in men, there is no counterpart to the accelerated phase of bone loss that occurs following menopause. If men and women lose bone mass at similar rates, why do men experience less osteoporosis? The main reason is that bones in men, at their peak, are larger and stronger than bones in women. Hence, once decline begins, male bones can tolerate more loss before fractures are likely. Factors that contribute to the risk of osteoporosis in men include low testosterone, prolonged use of glucocorticoids, white race, calcium deficiency, vitamin D deficiency, smoking, excessive alcohol consumption, and insufficient exercise. As in women, 10-year fracture risk can be assessed using the FRAX calculator developed by the WHO.

Treatment of male osteoporosis is confounded by a paucity of research. (Osteoporosis is one of the few areas of therapeutics in which research in women has greatly exceeded research in men.) At this time, only four drugs—alendronate [Fosamax], risedronate [Actonel],* zoledronate [Reclast], and teriparatide [Forteo]—are approved for osteoporosis in men. In one study, 2 years of alendronate increased BMD of the lumbar spine and hip, and significantly decreased the incidence of vertebral fractures. Benefits with risedronate, zoledronate, and teriparatide are similar. For alendronate, zoledronate, and teriparatide, dosages are the same as those used in women. For risedronate, the only approved dosage is 35 mg once a week. Calcitonin has been tried in men, but proof of efficacy is lacking. If testosterone deficiency underlies osteoporosis, testosterone replacement therapy is indicated, unless the patient has testicular cancer or some other disorder that contraindicates testosterone use. All men should ensure adequate intake of calcium and vitamin D.

*Denosumab is sold under two trade names: *Prolia* and *Xgeva*. Only *Prolia* is used for osteoporosis.

*The delayed-release formulation of risedronate, sold as *Atelvia*, is not approved for osteoporosis in men, although it is approved for osteoporosis in women.

KEY POINTS

- Calcium is critical to the function of the skeletal, nervous, muscular, and cardiovascular systems.
- More than 98% of calcium in the body is present in bone.
- Bone undergoes continuous remodeling, a process in which osteoclasts resorb old bone and osteoblasts lay down new bone.
- The body maintains calcium levels by adjusting the rates of calcium resorption from bone, calcium absorption from the intestine, and calcium excretion by the kidney. These processes are regulated by parathyroid hormone (PTH), vitamin D, and calcitonin.
- PTH elevates serum calcium by promoting resorption of calcium from bone, enhancing renal tubular resorption of calcium, and activating vitamin D, which then promotes absorption of calcium from the intestine.
- Like PTH, vitamin D increases serum calcium by increasing calcium resorption from bone, decreasing calcium excretion by the kidney, and increasing calcium absorption from the intestine.
- Calcitonin lowers calcium levels by inhibiting calcium resorption from bone and increasing calcium excretion by the kidney.
- The RDA for calcium is highest for adolescents ages 9 to 18 (1300 mg/day). Women over the age of 50 and all people over the age of 70 also need relatively high amounts (1200 mg/day).
- If the RDA cannot be met with diet alone, calcium supplements can be taken to make up the difference. However, be aware that too much supplemental calcium increases the risk of vascular calcification, myocardial infarction, and stroke.
- The various calcium salts used for therapy differ widely in their percentage of calcium.
- Vitamin D is obtained through the diet and by exposure to sunlight.
- Vitamin D deficiency causes rickets in children and osteomalacia in adults. Deficiency may also contribute to certain autoimmune disorders and cancers, although convincing evidence is lacking.
- Calcitonin-salmon has the same metabolic effects as human calcitonin, but has a longer half-life and greater milligram potency.
- Calcitonin-salmon is used primarily for osteoporosis. Benefits derive from inhibiting bone resorption by osteoclasts.
- Calcitonin-salmon is very safe.
- Alendronate, our prototype for the bisphosphonates, has four approved indications: prevention and treatment of osteoporosis in postmenopausal women, treatment of osteoporosis in men, treatment of Paget's disease of bone in men and women, and treatment of glucocorticoid-induced osteoporosis in men and women.
- Bioavailability of alendronate is very low in the absence of food, and essentially zero in the presence of food. Accordingly, nothing should be eaten for at least 30 minutes after taking the drug.
- Following absorption, alendronate undergoes incorporation into bone, where it can remain for decades.
- Alendronate suppresses bone resorption by decreasing both the number and activity of osteoclasts.
- Alendronate can cause severe esophagitis if it stays in contact with the esophageal mucosa. Accordingly, patients should take the drug with a full glass of water and then remain upright for at least 30 minutes.
- Rarely, alendronate has been associated with musculoskeletal pain, ocular inflammation, osteonecrosis of the jaw, and atypical fractures of the femur.
- Denosumab is a first-in-class RANKL inhibitor indicated for postmenopausal osteoporosis and prevention of skeletal-related events in patients with bone metastases from solid tumors.
- By inhibiting RANKL, denosumab prevents RANKL from activating RANK receptors, and thereby reduces the formation and function of osteoclasts.
- Denosumab has four serious side effects: hypocalcemia, infections, skin reactions, and ONJ.
- Raloxifene belongs to the family of SERMs, drugs that are estrogenic in some tissues and antiestrogenic in others.
- Raloxifene mimics the effects of estrogen on bone, lipid metabolism, and blood clotting, and blocks the effects of estrogen in the breast and endometrium.
- Raloxifene is indicated for preventing and treating postmenopausal osteoporosis, and for reducing the risk of breast cancer in postmenopausal women.
- Raloxifene can cause DVT and fetal harm.
- Teriparatide is the first and only drug for osteoporosis that works by increasing bone formation. (All the others decrease bone resorption.)
- Teriparatide may increase the risk of bone cancer.
- Osteoporosis is characterized by low bone mass and increased bone fragility, which renders patients vulnerable to fractures from minor trauma.
- The most common sites of osteoporotic fractures are the vertebrae (spine), distal forearm (wrist), and femoral neck (hip).
- Osteoporosis occurs mainly in the elderly. Why? Because after age 50, men and women experience aging-related bone loss that is slow but relentless. In addition, women experience several years of accelerated bone loss following menopause. In both cases, bone is lost because bone resorption by osteoclasts outpaces bone deposition by osteoblasts.
- To maximize bone strength, and thereby minimize the risk of osteoporosis, we all need to (1) ensure lifelong sufficiency of calcium and vitamin D and (2) adopt lifestyle measures that promote bone health: regular weight-bearing exercise and avoidance of smoking and excessive alcohol.
- Osteoporosis is diagnosed by measuring BMD, which is done most commonly using dual-energy x-ray absorptiometry (DEXA).
- The World Health Organization's diagnostic criterion for osteoporosis is BMD that is more than 2.5 standard deviations below the mean BMD for young adults.
- The objective of osteoporosis therapy is to reduce fractures.

- Fracture risk, which can be calculated using the FRAX tool developed by the WHO, is based on BMD and other factors, including age, use of glucocorticoids, and a personal or family history of fractures.
- With currently available drugs, we are more able to prevent bone loss (using antiresorptive agents) than to rebuild bone that is already gone (using bone-forming agents).
- Antiresorptive drugs—estrogen, raloxifene, bisphosphonates (eg, alendronate), and calcitonin—decrease bone loss by inhibiting the activity of osteoclasts.
- Estrogen increases BMD and reduces fracture risk.

- In the past, estrogen was considered a treatment of choice for prevention and treatment of postmenopausal osteoporosis. Today, however, there is strong evidence that benefits in osteoporosis do not outweigh the risks (breast cancer, myocardial infarction, stroke, cholecystitis).
- Calcitonin is the safest drug for osteoporosis, but is less effective than estrogen or alendronate. Comparisons with raloxifene are not available.

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Summary of Major Nursing Implications*

VITAMIN D

Calcifediol
Calcitriol
Cholecalciferol
Doxercalciferol
Ergocalciferol
Paricalcitol

Preadministration Assessment

Therapeutic Goal

Treatment of rickets, osteomalacia, and hypoparathyroidism, and prevention of vitamin D deficiency.

Baseline Data

The prescriber may order serum levels of vitamin D, calcium, phosphorus, and alkaline phosphatase as well as a 24-hour urinary calcium determination.

Assess dietary vitamin D and calcium content.

Identifying High-Risk Patients

Vitamin D is *contraindicated* in patients with hypercalcemia, hypervitaminosis D, and malabsorption syndrome.

Exercise *caution* in patients taking digoxin.

Implementation: Administration

Routes

Oral, IM.

Administration

Instruct the patient to swallow oral preparations intact, without crushing or chewing.

Therapeutic responses to vitamin D require adequate calcium intake. Assess dietary calcium content and adjust to ensure calcium sufficiency.

Ongoing Evaluation and Interventions

Monitoring Summary

Monitor serum calcium, serum phosphorus, and urinary calcium.

Minimizing Adverse Interactions

Digoxin. Vitamin D–induced hypercalcemia can cause dysrhythmias in patients taking digoxin. Monitor serum calcium and make certain it remains normal.

Management of Toxicity

Large therapeutic doses may cause hypervitaminosis D, a syndrome characterized by hypercalcemia, hypercalciuria, decalcification of bone, and deposition of calcium in soft tissues. Monitor serum calcium content; levels should stay below 10 mg/dL. Monitor serum phosphorus and urinary calcium as well. **If vitamin D toxicity develops, instruct the patient to discontinue vitamin D immediately, increase fluid intake, and institute a low-calcium diet.** In severe cases, calcium excretion can be accelerated with IV saline plus furosemide.

ORAL CALCIUM SALTS

Calcium acetate
Calcium carbonate
Calcium citrate
Calcium glubionate
Calcium gluconate
Calcium lactate
Tricalcium phosphate

Preadministration Assessment

Therapeutic Goal

Treatment of mild hypocalcemia and supplementation of dietary calcium.

Baseline Data

Obtain a serum calcium level.

Identifying High-Risk Patients

Calcium salts are *contraindicated* for patients with hypercalcemia, renal calculi, and hypophosphatemia.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Implementation: Administration

Route

Oral.

Dosage

Individual calcium salts differ with respect to percentage of elemental calcium. As a result, the dose required to provide a specific amount of calcium differs among the salts. **Advise patients against switching to a different preparation.**

Administration

Advise patients to take oral calcium salts with a large glass of water; dosing with or after meals promotes absorption. Advise patients to avoid taking calcium with foods that can suppress calcium absorption (eg, spinach, Swiss chard, beets, bran, whole-grain cereals).

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Prolonged therapy can cause hypercalcemia. **Inform patients about signs of hypercalcemia (nausea, vomiting, constipation, frequent urination, lethargy, and depression), and instruct them to notify the prescriber if these occur.** Hypercalcemia can be minimized with frequent monitoring of serum calcium.

Minimizing Adverse Interactions

Glucocorticoids. These drugs reduce calcium absorption; increased calcium dosage may be required.

Tetracyclines. Calcium binds to tetracyclines, thereby reducing tetracycline absorption. **Instruct patients to separate administration of these agents by at least 1 hour.**

Thyroid Hormone. Calcium interferes with absorption of thyroid hormone. **Instruct patients to separate administration of these agents by several hours.**

Thiazide Diuretics. Thiazides decrease renal excretion of calcium. A reduction in calcium dosage may be needed to avoid hypercalcemia.

PARENTERAL CALCIUM SALTS

Calcium chloride
Calcium gluconate

Preadministration Assessment

Therapeutic Goal

Reversal of clinical manifestations of hypocalcemia.

Baseline Data

Assess for signs and symptoms of hypocalcemia (tetany, convulsions, laryngospasm, spasm of other muscles). Obtain measurement of serum calcium.

Identifying High-Risk Patients

Parenteral calcium is *contraindicated* for patients with hypercalcemia or ventricular fibrillation.

Use with *extreme caution* in patients taking digoxin.

Implementation: Administration

Route

Intravenous.

Administration

Warm solutions to body temperature prior to IV dosing. Perform IV injections slowly (0.5 to 2 mL/min).

Drugs that contain phosphate, carbonate, sulfate, and tartrate groups can precipitate calcium; do not mix these drugs with parenteral calcium solutions.

Calcium chloride may cause necrosis and sloughing if solutions become extravasated. Monitor the infusion closely.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Evaluate the patient for reductions in tetany, muscle spasm, laryngospasm, paresthesias, and other symptoms of severe hypocalcemia.

Minimizing Adverse Effects

Hypercalcemia. Overdose can produce acute hypercalcemia, resulting in nausea, vomiting, weakness, lethargy, coma, and possibly death. Avoid hypercalcemia through careful control of dosage.

Minimizing Adverse Interactions

Digoxin. Parenteral calcium may cause severe bradycardia in patients taking digoxin. Infuse calcium slowly and cautiously in these patients.

CALCITONIN-SALMON

Preadministration Assessment

Therapeutic Goal

Treatment of postmenopausal osteoporosis, Paget's disease of bone, and hypercalcemia.

Baseline Data

The prescriber may order measurements of serum alkaline phosphatase, calcium, and phosphorus, as well as a 24-hour urinary hydroxyproline.

Identifying High-Risk Patients

Salmon calcitonin is *contraindicated* for patients allergic to this preparation.

Implementation: Administration

Routes

Intranasal. For osteoporosis only.

Parenteral (IM, subQ). For osteoporosis, Paget's disease, and hypercalcemia.

Administration

Intranasal. Instruct patients using Miacalcin to activate the metered-dose pump by holding the bottle upright and depressing the two white sidearms toward the bottle 6 times, which should produce a faint initial spray. The drug

*Patient education information is highlighted as **blue text**.

Summary of Major Nursing Implications*—cont'd

is then administered by placing the nozzle in the nostril and depressing the pump handle.

Subcutaneous. Teach patients how to inject calcitonin subQ, and instruct them to rotate sites of injection.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Postmenopausal Osteoporosis. Measurement of BMD should indicate retardation of bone loss (and perhaps a small increase in BMD).

Paget's Disease of Bone. Monitor for reductions in bone pain, serum alkaline phosphatase levels, and 24-hour urinary hydroxyproline value.

Hypercalcemia. Monitor for reductions in serum calcium and phosphorus levels.

BISPHOSPHONATES USED FOR OSTEOPOROSIS

Alendronate
Ibandronate
Risedronate
Zoledronate

Preadministration Assessment

Therapeutic Goal

Prevention and treatment of osteoporosis.

Baseline Data

Obtain baseline values for BMD in the hip, spine, and wrist. For patients receiving zoledronate, obtain a baseline value for creatinine clearance and assess for adequate hydration.

Identifying High-Risk Patients

Oral bisphosphonates are *contraindicated* for patients with esophageal disorders that can impede swallowing, and for patients who cannot sit or stand for at least 30 minutes (60 minutes with ibandronate).

Zoledronate, an IV bisphosphonate, is *contraindicated* for patients with acute renal failure or creatinine clearance below 35 mL/min, and should be used with *caution* in patients who are elderly or dehydrated, and in those with chronic renal impairment and those taking other nephrotoxic drugs.

Implementation: Administration

Route

Oral. Alendronate, risedronate, ibandronate.

Intravenous. Zoledronate.

Dosing Schedule

Alendronate. Daily or weekly.

Risedronate. Daily, weekly, or monthly.

Ibandronate. Daily, monthly, or every 3 months.

Zoledronate. Yearly, or every 2 years.

Administration

Oral. Proper administration is needed to maximize absorption and minimize the risk of esophagitis. Accordingly, instruct patients to

- Administer in the morning before eating or drinking anything. This applies to all oral bisphosphonates except the Atelvia brand of risedronate, which can and should be administered after eating.
- Administer with a full glass of water.
- Administer while upright, either sitting or standing.
- Avoid chewing or sucking the tablet.
- After dosing, remain sitting or standing for at least 30 minutes (60 minutes with ibandronate).
- After dosing, postpone ingesting anything—including orange juice, coffee, antacids, and calcium, iron, or magnesium supplements—for at least 30 minutes (60 minutes with ibandronate).

Intravenous. Infuse zoledronate over a span of 15 minutes or longer.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Obtain periodic determinations of BMD. If BMD increases, or at least remains constant, treatment is a success. Conversely, a significant decline in BMD indicates failure.

Minimizing Adverse Effects

Esophagitis. Oral bisphosphonates can cause severe esophagitis, sometimes resulting in ulceration. To minimize risk, **instruct patients to (1) administer the drug in accord with the guidelines described above, (2) avoid lying down after dosing, and (3) discontinue the drug and contact the prescriber if they experience symptoms of esophageal injury (difficulty swallowing, pain upon swallowing, new or worsening heartburn).** Avoid these drugs in patients with esophageal disorders that could impede swallowing and in patients who are unable to sit or stand for 30 minutes (60 minutes with ibandronate).

Atypical Femoral Fractures. Very rarely, long-term bisphosphonate therapy has been associated with atypical fractures of the femur. To reduce risk, prescribers should

- Use these drugs only when needed (ie, avoid bisphosphonates in patients considered at low risk for osteoporosis-related fractures)
- Consider alternative treatments, such as raloxifene or teriparatide, for patients with osteoporosis of the spine and normal (or only moderately reduced) BMD of the femoral neck or hip
- Perform an annual re-evaluation of the need for continued therapy in patients who have taken bisphosphonates for 5 years

Esophageal Cancer. Oral bisphosphonates may (or may not) increase the risk of *esophageal cancer*. Measures that might reduce risk include reducing the dosing frequency (eg,

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

dosing monthly or weekly rather than daily), taking the drug with a full glass of water, and staying upright for 30 to 60 minutes after dosing.

Musculoskeletal Pain. Rarely, bisphosphonates cause muscle, bone, and joint pain. Severe pain may require an opioid or ketorolac for relief. As a rule, pain gradually diminishes when bisphosphonates are withdrawn. In most cases, pain does not return when bisphosphonates are resumed. If it does resume, osteoporosis should be managed with a different drug (eg, calcitonin-salmon, teriparatide, raloxifene).

Ocular Problems. Rarely, bisphosphonates cause conjunctivitis, scleritis, blurred vision, eye pain, and other ocular problems. **Inform patients about these effects and instruct them to report any vision changes or eye pain.**

Osteonecrosis of the Jaw. ONJ occurs primarily with IV bisphosphonates (pamidronate, zoledronate), not with oral bisphosphonates. To reduce ONJ risk, a dental exam with appropriate preventive dentistry should be conducted before giving IV bisphosphonates. Patients should avoid elective dental work while using these drugs.

Renal Toxicity. Intravenous zoledronate can damage the kidney, leading to acute renal failure, and possibly death. Exercise caution in patients at increased risk (owing to advanced age, chronic renal impairment, dehydration, or use of diuretics or nephrotoxic drugs). Prior to dosing, ensure that hydration is adequate and that kidney function is adequate too (creatinine clearance above 35 mL/min). To reduce risk, infuse zoledronate slowly (over 15 minutes or more). Monitor renal function by determining creatinine clearance at baseline, prior to each dose, and periodically after each infusion. If renal impairment develops, zoledronate dosage should be reduced.

Minimizing Adverse Interactions

Interactions with Zoledronate. Risk of renal failure with zoledronate is increased by use of *diuretics* (which can cause dehydration) and by use of other *nephrotoxic drugs*, including cyclosporine, amphotericin, aminoglycoside antibiotics, and the nonsteroidal anti-inflammatory drugs (NSAIDs). Exercise caution in patients using these agents.

RALOXIFENE

Preadministration Assessment

Therapeutic Goals

Prevention and treatment of postmenopausal osteoporosis, and reducing the risk of invasive breast cancer in postmenopausal women who have osteoporosis and/or a high risk for breast cancer.

Baseline Data

Obtain baseline values for BMD in the hip, vertebrae, and forearm.

Identifying High-Risk Patients

Raloxifene is *contraindicated* for use by patients who are pregnant or have a history of venous thrombotic events.

Implementation: Administration

Route

Oral.

Administration

Take once daily without regard to meals.

Ongoing Evaluation and Interventions

Promoting Therapeutic Effects

Advise women taking raloxifene for osteoporosis to ensure adequate intake of calcium and vitamin D.

Evaluating Therapeutic Effects

For women taking raloxifene to prevent or treat osteoporosis, obtain periodic determinations of BMD. If BMD increases, or at least remains constant, treatment is a success. Conversely, a significant decline in BMD indicates failure.

Minimizing Adverse Effects

Venous Thromboembolism. Raloxifene increases the risk of DVT, pulmonary embolism, and thrombotic stroke. **Advise patients to discontinue raloxifene at least 72 hours prior to prolonged immobilization (eg, postsurgical recovery, extended bed rest), and to resume treatment only after full mobility has been restored. Advise patients to avoid extended periods of restricted activity, as can happen when traveling.** Do not give raloxifene to patients with a history of venous thrombotic events.

Fetal Harm. Raloxifene can cause fetal harm, and must not be used during pregnancy.

ESTROGEN

Nursing implications for estrogen are summarized in Chapter 61.

*Patient education information is highlighted as **blue text**.

BASIC CONSIDERATIONS

Pathophysiology of Asthma
 Overview of Drugs for Asthma
 Administering Drugs by Inhalation

ANTI-INFLAMMATORY DRUGS

Glucocorticoids

Leukotriene Modifiers

Zileuton

Zafirlukast

Montelukast

Cromolyn

Omalizumab

BRONCHODILATORS

Beta₂-Adrenergic Agonists

Methylxanthines

Theophylline

Other Methylxanthines

Anticholinergic Drugs

Ipratropium

Tiotropium

GLUCOCORTICOID/LABA COMBINATIONS**MANAGEMENT OF ASTHMA**

Measuring Lung Function

Classification of Asthma Severity

Treatment Goals

Chronic Drug Therapy

Drugs for Acute Severe Exacerbations

Drugs for Exercise-Induced Bronchospasm

Reducing Exposure to Allergens and Triggers

si Box 76-1. Chronic Obstructive Pulmonary Disease

BASIC CONSIDERATIONS

Asthma is a common, chronic disorder that occurs in children and adults. In the United States, nearly 25 million people have the disease. Characteristic signs and symptoms are a sense of breathlessness and tightness in the chest, together with wheezing, dyspnea, and cough. The underlying cause is immune-mediated airway inflammation. In 2007, asthma led to nearly 14 million physician office visits and 1.75 million outpatient department visits. Each year, the disease kills about 3500 Americans. However, despite these

sobering statistics, with proper treatment, most patients can lead full lives with no limitations.

PATHOPHYSIOLOGY OF ASTHMA

Asthma is a *chronic inflammatory* disorder of the airways. In about 50% of children with asthma and in some adults, airway inflammation results from an immune response to known allergens. In the remaining children and in most adults, the cause of airway inflammation is unknown—although as-yet unidentified allergens are suspected.

Figure 76-1 depicts the events that lead to inflammation and bronchoconstriction in patients whose asthma is caused by specific allergens. Although this model may not apply completely to all asthma patients, it nonetheless provides a basis for understanding the drugs used for treatment. The inflammatory process begins with binding of allergen molecules (eg, house dust mite feces) to immunoglobulin E (IgE) antibodies on mast cells. This causes mast cells to release an assortment of mediators, including histamine, leukotrienes, prostaglandins, and interleukins. These mediators have two effects. They act immediately to cause *bronchoconstriction*. In addition, they promote infiltration and activation of inflammatory cells (eosinophils, leukocytes, macrophages). These inflammatory cells then release mediators of their own. The end result is *airway inflammation*, characterized by edema, mucus plugging, and smooth muscle hypertrophy, all of which obstruct airflow. In addition, inflammation produces a state of *bronchial hyperreactivity*. Because of this state, mild trigger factors (eg, cold air, exercise, tobacco smoke) are able to cause intense bronchoconstriction.

From a therapeutic perspective, the important message here is that symptoms of asthma result from a combination of inflammation and bronchoconstriction. Accordingly, treatment must address both components.

OVERVIEW OF DRUGS FOR ASTHMA

The major drugs for asthma are listed in Table 76-1. As indicated, they fall into two main pharmacologic classes: *anti-inflammatory agents* and *bronchodilators*. The principal anti-inflammatory drugs are the *glucocorticoids*. The principal bronchodilators are the *beta₂ agonists*. For chronic asthma, glucocorticoids are administered on a fixed schedule, almost always by inhalation. Beta₂ agonists may be administered on a fixed schedule (for long-term control) or PRN (to manage an acute attack). Like the glucocorticoids, beta₂ agonists are usually inhaled. As discussed in Box 76-1, the drugs we use

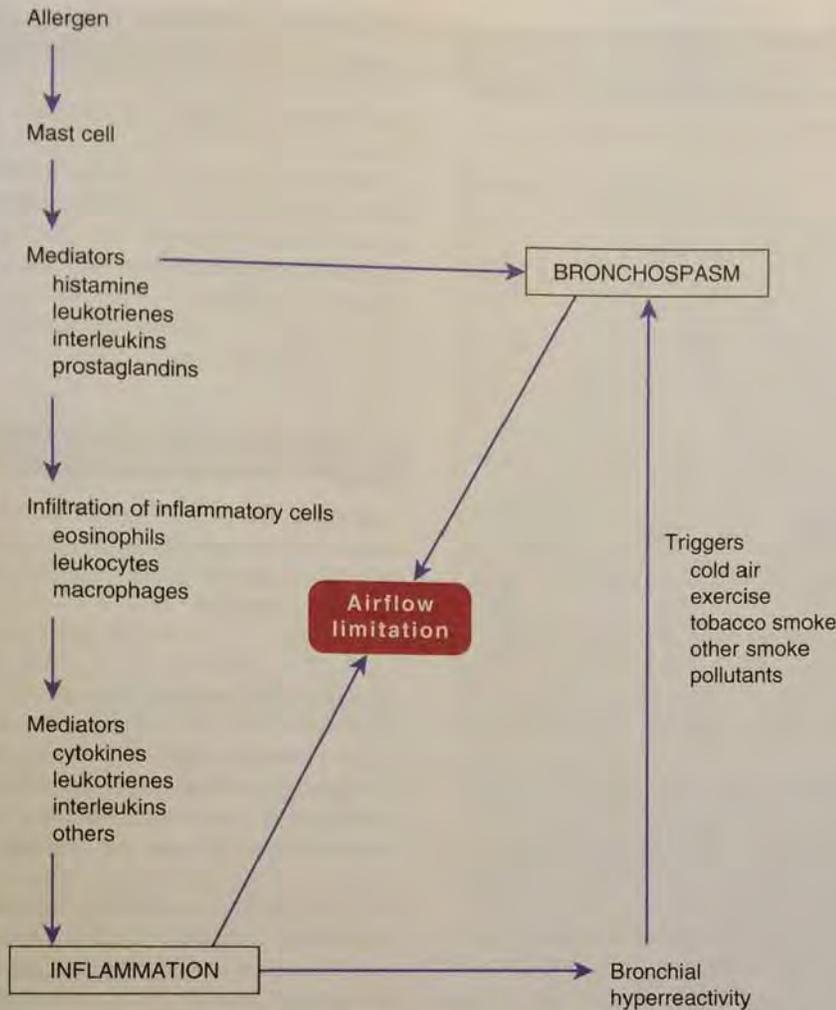


Figure 76-1 ■ Allergen-induced inflammation and bronchospasm in asthma.

for asthma are also used for chronic obstructive pulmonary disease (COPD).

ADMINISTERING DRUGS BY INHALATION

Most antiasthma drugs can be administered by inhalation, a route with three advantages: (1) therapeutic effects are enhanced (by delivering drugs directly to their site of action), (2) systemic effects are minimized, and (3) relief of acute attacks is rapid. Three types of inhalation devices are employed: metered-dose inhalers, dry-powder inhalers, and nebulizers.

Metered-Dose Inhalers

Metered-dose inhalers (MDIs) are small, hand-held, pressurized devices that deliver a measured dose of drug with each actuation. Dosing is usually accomplished with 1 or 2 puffs. When 2 puffs are needed, an interval of at least 1 minute should separate the first puff from the second. When using most MDIs, the patient must begin to inhale prior to activating the device. Hence, hand-lung coordination is required. MDIs can be difficult to use correctly. Accordingly, patients will need a demonstration as well as written and verbal instruction. Even with optimal use, only about 10% of the dose reaches the lungs.

About 80% impacts the oropharynx and is swallowed, and the remaining 10% is left in the device or exhaled.

Several kinds of *spacers* are available for use with MDIs. All of these devices, which attach directly to the MDI, serve to increase delivery of drug to the lungs and decrease deposition of drug on the oropharyngeal mucosa (Fig. 76-2). Some spacers contain a one-way valve that activates upon inhalation, thereby obviating the need for good hand-lung coordination. Some spacers also contain an alarm whistle that sounds off when inhalation is too rapid.

In the past, MDIs employed two kinds of propellants: *hydrofluoroalkane* (HFA) and *chlorofluorocarbons* (CFCs). Today, however, nearly all MDIs use HFA. Most MDIs made with CFCs have been discontinued. And the two that remain—*albuterol/ipratropium* [Combivent Inhalation Aerosol] and *pirbuterol* [Maxair Autohaler]—will be phased out by December 31, 2013. Why are CFCs being phased out? Because they can deplete the Earth's ozone layer, which protects us from ultraviolet radiation. HFA does not affect ozone.

Dry-Powder Inhalers

Dry-powder inhalers (DPIs) are used to deliver drugs in the form of a dry, micronized powder directly to the lungs. No propellant is employed. Hence, DPIs pose no environmental

TABLE 76-1 ■ Overview of Major Drugs for Asthma

ANTI-INFLAMMATORY DRUGS

Glucocorticoids

Inhaled

Beclomethasone dipropionate [QVAR]
 Budesonide [Pulmicort Flexhaler, Pulmicort Respules]
 Ciclesonide [Alvesco]
 Flunisolide [AeroSpan]
 Fluticasone propionate [Flovent HFA, Flovent Diskus]
 Mometasone furoate [Asmanex Twisthaler]

Oral

Prednisolone
 Prednisone

Leukotriene Modifiers

Montelukast, oral [Singulair]
 Zafirlukast, oral [Accolate]
 Zileuton, oral [Zyflo, Zyflo CR]

Cromolyn

Cromolyn, inhaled [Intal]

IgE Antagonist

Omalizumab, subQ [Xolair]

BRONCHODILATORS

Beta₂-Adrenergic Agonists

Inhaled: Short Acting

Albuterol [AccuNeb, ProAir HFA, Proventil HFA, Ventolin HFA]
 Levalbuterol [Xopenex, Xopenex HFA]
 Pirbuterol [Maxair Autohaler]*,†

Inhaled: Long Acting‡

Arformoterol [Brovana][‡]
 Formoterol [Foradil Aerolizer, Perforomist][‡]
 Indacaterol [Arcapta Neohaler][‡]
 Salmeterol [Serevent Diskus][‡]

Oral

Albuterol [VoSpire ER]
 Terbutaline (generic only)

Methylxanthines

Theophylline, oral [Theo-24, Theochron, Elixophyllin]

Anticholinergics

Ipratropium, inhaled [Atrovent HFA]
 Tiotropium, inhaled [Spiriva]

ANTI-INFLAMMATORY/BRONCHODILATOR COMBINATIONS

Budesonide/formoterol, inhaled [Symbicort]
 Fluticasone/salmeterol, inhaled [Advair Diskus, Advair HFA]
 Mometasone/formoterol, inhaled [Dulera]

*This formulation of pirbuterol will be phased out by December 31, 2013. A replacement formulation is in development.

†Approved only for chronic obstructive pulmonary disease, not asthma.

‡For treatment of asthma, must always be combined with an inhaled glucocorticoid.

risk. Unlike MDIs, DPIs are breath activated. As a result, DPIs don't require the hand-lung coordination needed with MDIs, and hence DPIs are much easier to use. Compared with MDIs, DPIs deliver more drug to the lungs (20% of the total released vs. 10%) and less to the oropharynx. Also, spacers are not used with DPIs.

Nebulizers

A nebulizer is a small machine used to convert a drug solution into a mist. The droplets in the mist are much finer than those produced by inhalers. Inhalation of the nebulized mist can be done through a face mask or through a mouthpiece held between the teeth. Nebulizers take several minutes to deliver the same amount of drug contained in 1 puff from an inhaler. For some patients, a nebulizer may be more effective than an inhaler. Although nebulizers are usually used at home or in a hospital, these devices, which weigh under 10 pounds, are sufficiently portable for use in other locations.

ANTI-INFLAMMATORY DRUGS

Anti-inflammatory drugs—especially inhaled glucocorticoids—are the foundation of asthma therapy. These drugs are taken daily for long-term control. Most people with asthma should receive one.

GLUCOCORTICIDS

Glucocorticoids (eg, budesonide, fluticasone) are the most effective antiasthma drugs available. Administration is usually by inhalation, but may also be IV or oral. Adverse reactions to inhaled glucocorticoids are generally minor, as are reactions to systemic glucocorticoids taken *acutely*. However, when *systemic* glucocorticoids are used *long term*, severe adverse effects are likely. The basic pharmacology of the glucocorticoids is presented in Chapter 72. Discussion here is limited to their use in asthma.

Mechanism of Antiasthma Action

Glucocorticoids reduce asthma symptoms by *suppressing inflammation*. Specific anti-inflammatory effects include

- Decreased synthesis and release of inflammatory mediators (eg, leukotrienes, histamine, prostaglandins)
- Decreased infiltration and activity of inflammatory cells (eg, eosinophils, leukocytes)
- Decreased edema of the airway mucosa (secondary to a decrease in vascular permeability)

By suppressing inflammation, glucocorticoids reduce bronchial hyperreactivity. In addition to reducing inflammation, glucocorticoids decrease airway mucus production and increase the number of bronchial beta₂ receptors as well as their responsiveness to beta₂ agonists.

Use in Asthma

Glucocorticoids are used for *prophylaxis* of chronic asthma. Accordingly, dosing must be done on a fixed schedule—not PRN. Because beneficial effects develop slowly, these drugs cannot be used to abort an ongoing attack. Glucocorticoids do not alter the natural course of asthma, even when used in young children.

Inhalation Use. Inhaled glucocorticoids are first-line therapy for asthma. All patients with moderate to severe asthma should use these drugs daily. Inhaled glucocorticoids are very effective and very safe.

BOX 76-1 ■ SPECIAL INTEREST TOPIC

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a progressive, largely irreversible disorder that restricts airflow in the lungs. Smoking cigarettes is usually the cause. Symptoms include chronic cough, excessive sputum production, wheezing, dyspnea, and poor exercise tolerance. In the United States, COPD affects about 24 million people, and is the *fourth leading cause of death*. COPD is treated with the same drugs we use for asthma. Unfortunately, although these drugs are highly effective in asthma, benefits in COPD are minimal, being limited to a small improvement in symptoms. Drug therapy does not slow disease progression, reduce hospitalizations, or prolong life.

Symptoms of COPD result largely from two pathologic processes: *chronic bronchitis* and *emphysema*. In most cases, both processes are caused by an exaggerated inflammatory reaction to cigarette smoke. Chronic bronchitis—defined by chronic cough and excessive sputum production—results from hypertrophy of mucus-secreting glands in the epithelium of the larger airways. Emphysema is defined as enlargement of the air space within the bronchioles and alveoli brought on by deterioration of the walls of these air spaces. Among individuals with COPD, the relative contribution of these two processes can vary. That is, some patients may suffer primarily from chronic bronchitis, some primarily from emphysema, and some from both disease processes.

Diagnosis and treatment of COPD was addressed in two clinical guidelines released in 2007. The first guideline—*Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*—was issued by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The second guideline—*Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease*—was issued by the American College of Physicians (ACP). The GOLD guideline is large and comprehensive. The ACP guideline, which is much smaller, was written as a practical guide for primary care clinicians. The recommendations below reflect those in the ACP guideline.

Diagnosis Based on Symptoms and Spirometry. Patients who have symptoms of COPD—especially dyspnea—should be tested with a *spirometer* to measure the degree of airway obstruction. As noted in our discussion of asthma management, a spirometer measures *forced expiratory volume* (FEV). Test results are expressed as a percent of the FEV that would be predicted for a healthy person of the same age, sex, height, and weight. To diagnose COPD, we need a value for FEV₁, that is, the FEV measured during the first second of ex-

halation into the spirometer. According to the ACP guidelines, treatment of stable COPD should be reserved for patients with an FEV₁ that is below 60% of the predicted value. However, it is important to note that diagnosis is not based on spirometry alone. Rather, the patient must have respiratory symptoms as well. In fact, in the absence of COPD symptoms, the guidelines recommend against using spirometry in the first place.

Initial Monotherapy. Symptomatic patients with an FEV₁ less than 60% of predicted should receive maintenance therapy with *one* of the following: (1) a long-acting inhaled beta₂ agonist (eg, salmeterol), (2) tiotropium (a long-acting inhaled anticholinergic drug), or (3) an inhaled glucocorticoid (eg, budesonide). Drugs in all three classes can reduce exacerbations. Evidence is insufficient to recommend one class over the other.*

Combination Therapy. Prescribers *may* consider combination inhaled therapies for symptomatic patients with an FEV₁ less than 60% of predicted. However, research on combination therapy has not shown a consistent benefit over monotherapy.

Use of Oxygen. Supplemental oxygen given 15 or more hours a day can improve survival in patients with resting hypoxemia (PaO₂ of 55 mm Hg or less) and severe airway obstruction (FEV₁ less than 30% of predicted). Accordingly, oxygen should be prescribed for these people.

Pulmonary Rehabilitation. For symptomatic patients with an FEV₁ less than 50% of predicted, pulmonary rehabilitation (eg, exercise therapy) can reduce hospitalizations, improve health status, and increase exercise capacity. Accordingly, a program of pulmonary rehabilitation may be considered for these patients. Benefits are not clear for patients with an FEV₁ that is above 50% of predicted.

Reducing Exacerbations. In patients with severe, chronic COPD, the risk of exacerbations may be reduced with *roflumilast* [Daliresp], an oral agent approved in 2011. The drug reduces inflammation, cough, and excessive mucus production by raising levels of cyclic adenosine monophosphate (cAMP) in lung cells. (Roflumilast is a selective inhibitor of phosphodiesterase type 4, an enzyme that inactivates cAMP.) Adverse effects include diarrhea, reduced appetite, weight loss, nausea, headache, back pain, insomnia, and depression. Safety in pregnancy has not been established. The dosage is 500 mcg once a day, taken with or without food. Roflumilast should be used in combination with tiotropium, a long-acting inhaled beta₂ agonist, or an inhaled glucocorticoid.

*Other drugs for COPD, which are not addressed in the guidelines, include albuterol (a short-acting inhaled beta₂ agonist), theophylline (a methylxanthine), and systemic glucocorticoids (eg, prednisone).

Oral Use. Oral glucocorticoids are reserved for patients with severe asthma. Because of their potential for toxicity, these drugs are prescribed only when symptoms cannot be controlled with safer medications (inhaled glucocorticoids, inhaled beta₂ agonists). Because the risk of toxicity increases with duration of use, treatment should be as brief as possible.

Adverse Effects

Inhaled Glucocorticoids. These preparations are largely devoid of serious toxicity, even when used in high doses. The most serious concern is adrenal suppression.

The most common adverse effects are *oropharyngeal candidiasis* and *dysphonia* (hoarseness, speaking difficulty). Both

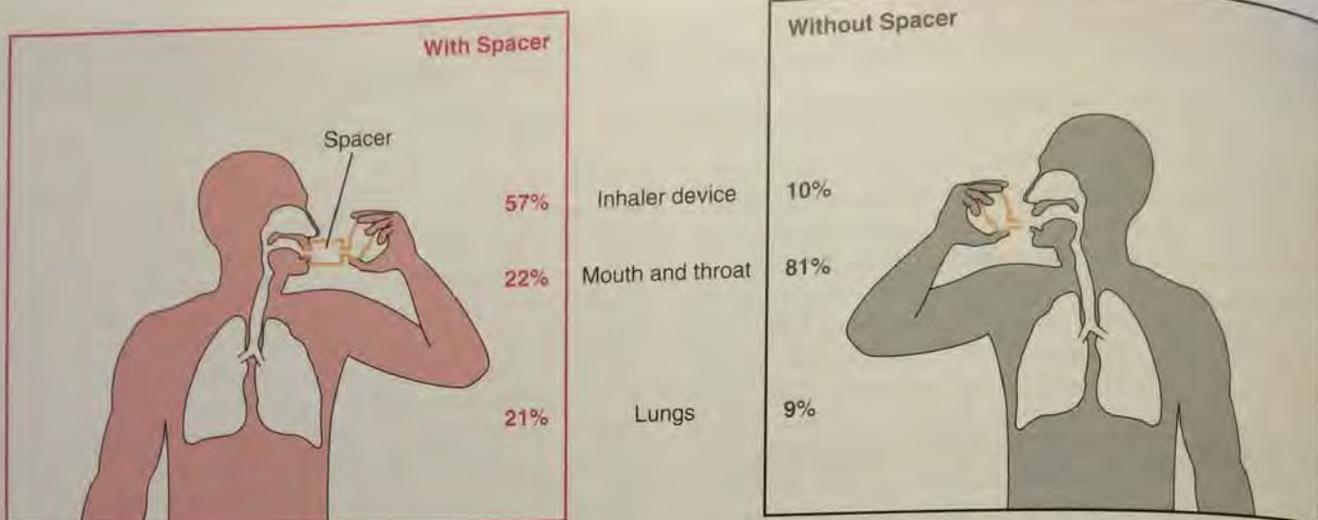


Figure 76-2 • Impact of a spacer device on the distribution of inhaled medication. Note that, when a spacer is used, more medication reaches its site of action in the lungs, and less is deposited in the mouth and throat.

effects result from local deposition of inhaled glucocorticoids. To minimize these effects, patients should gargle after each administration. Using a spacer device can help too. If candidiasis develops, it can be treated with an antifungal drug.

With long-term, high-dose therapy, some *adrenal suppression* may develop, although the degree of suppression is generally low. In contrast, with prolonged use of *oral* glucocorticoids, adrenal suppression can be profound. As noted below, *patients who have been switched from oral glucocorticoids to inhaled glucocorticoids must be given supplemental oral or IV doses at times of stress.* (At times of stress, inhaled glucocorticoids can control symptoms of asthma, but cannot replace the glucocorticoids required to support life.)

Glucocorticoids can *slow* growth in children and adolescents—but these drugs do *not* decrease adult height. *Short-term* studies have shown that inhaled glucocorticoids retard growth. However, *long-term* studies indicate that adult height is not reduced. Two studies reported in the October 12, 2000, issue of the *New England Journal of Medicine* demonstrated that inhaled budesonide does indeed slow growth in children—but only temporarily. Despite continued budesonide use, growth rate returns to normal within a year, and children eventually achieve their expected adult height. Moreover, adult height is not affected by either the duration of budesonide use or the total cumulative dose. Unfortunately, these studies focused only on *skeletal* growth, and hence we still don't know if glucocorticoids suppress growth and development of the brain, lungs, and other organs. Until more is known about how glucocorticoids affect organs, it would seem prudent to reserve these drugs for older children and for young children whose asthma is relatively severe; young children whose asthma is very mild, and hence can be treated effectively without glucocorticoids, should probably not receive these drugs.

Like oral glucocorticoids, inhaled glucocorticoids can promote *bone loss*—at least in premenopausal women. Fortunately, the amount of loss is much lower than the amount caused by oral glucocorticoids. To minimize bone loss, patients should (1) use the lowest dose possible, (2) ensure ad-

equate intake of calcium and vitamin D, and (3) participate in weight-bearing exercise.

There has been concern that prolonged therapy might increase the risk of *cataracts* and *glaucoma*. However, a study reported in 2011 showed no increase in the incidence of cataracts or elevated intraocular pressure in young adults who had been treated with inhaled budesonide for 16 years.

Oral Glucocorticoids. When used acutely (less than 10 days), even in very high doses, oral glucocorticoids do not cause significant adverse effects. However, prolonged therapy, even in moderate doses, can be hazardous. Potential adverse effects include *adrenal suppression*, *osteoporosis*, *hyperglycemia*, *peptic ulcer disease*, and, in young patients, *suppression of growth*.

Adrenal suppression is of particular concern. As discussed in Chapter 72, prolonged glucocorticoid use can decrease the ability of the adrenal cortex to produce glucocorticoids of its own. Because high levels of glucocorticoids are required to survive severe stress (eg, surgery, trauma, infection), and because adrenal suppression prevents production of endogenous glucocorticoids, *patients must be given increased doses of oral or IV glucocorticoids at times of stress. Failure to do so can prove fatal!* Following withdrawal of oral glucocorticoids (or transfer to inhaled glucocorticoids), several months are required for recovery of adrenocortical function. Throughout this time, all patients—including those switched to inhaled glucocorticoids—must be given supplemental oral or IV glucocorticoids at times of severe stress.

A complete list of contraindications to oral glucocorticoids is presented in the *Summary of Major Nursing Implications* at the end of this chapter.

Preparations, Dosage, and Administration

Inhaled Glucocorticoids. Six glucocorticoids are available for inhalation (Table 76-2). Four are available in MDIs, three are available in DPIs, and one is available in suspension for nebulization. Inhaled glucocorticoids are administered on a regular schedule—not PRN. Pediatric and adult dosages are summarized in Table 76-2. In all cases, the dosage should be

TABLE 76-2 • Inhaled Glucocorticoids: Formulations and Dosages

Drug	Formulation	Dosage	
		Adults	Children
Beclomethasone dipropionate [QVAR]	MDI: 40 or 80 mcg/puff	40–320 mcg twice daily	40–80 mcg twice daily (5–11 yr)
Budesonide [Pulmicort Flexhaler] [Pulmicort Respules]	DPI: 90 or 180 mcg/inhalation Suspension for nebulization	360–720 mcg twice daily 250–500 mcg once or twice daily or 1000 mcg once daily	180–360 mcg twice daily (6–17 yr) 500–1000 mcg/day (1–8 yr)
Ciclesonide [Alvesco]	MDI: 80 or 160 mcg/puff	80–320 mcg twice daily	80–320 mcg twice daily (12 yr and up)
Flunisolide [AeroSpan]	MDI: 80 mcg/puff	160–320 mcg twice daily	80–320 mcg twice daily (6–11 yr)
Fluticasone propionate [Flovent HFA] [Flovent Diskus]	MDI: 44, 110, or 220 mcg/puff DPI: 50, 100, or 250 mcg/puff	88–440 mcg twice daily 100–1000 mcg twice daily	88 mcg twice daily (4–11 yr) 50–100 mcg twice daily (4–11 yr)
Mometasone furoate [Asmanex Twisthaler]	DPI: 110 or 220 mcg/puff	220–440 mcg once or twice daily	110 mcg once daily (4–11 yr)

DPI = dry-powder inhaler, MDI = metered-dose inhaler.

kept as low as possible to minimize adrenal suppression, possible bone loss, and other adverse effects.

Glucocorticoids in MDIs. All of the glucocorticoid MDIs now on the market employ HFA as a propellant. All MDIs that employed a CFC propellant have been withdrawn. With the CFC-powered MDIs, patients needed to use a *spacer device* to increase drug delivery to the lungs. With the HFA-powered MDIs, no spacer is needed. Why? Because HFA produces smaller droplets than CFCs, and hence delivery of drugs to the lungs is greatly improved. Nonetheless, even with HFA-powered MDIs, drug delivery can be increased by inhaling a short-acting β_2 agonist 5 minutes prior to inhaling the glucocorticoid.

Nebulized Budesonide. Budesonide suspension [Pulmicort Respules] is the first inhaled glucocorticoid formulated for nebulized dosing. The product is approved for maintenance therapy of persistent asthma in children 1 to 8 years old—that is, children too young to use an MDI or DPI. Improvement should begin in 2 to 8 days; maximal benefits may take 4 to 6 weeks to develop. Budesonide suspension is available in 2-mL ampules containing 250 or 500 mcg of the drug. Administration is done with a jet nebulizer equipped with a mouthpiece or face mask; ultrasonic nebulizers should not be used. Administration takes 5 to 10 minutes. For children who are *not* taking an oral glucocorticoid, the initial dosage is 500 mcg/day in one or two doses. For children who *are* taking an oral glucocorticoid, the initial dosage is 1000 mcg/day in one or two doses. After 1 week, dosage of the oral glucocorticoid should be tapered off.

Oral Glucocorticoids. Prednisone and prednisolone are preferred glucocorticoids for oral therapy of asthma. For acute therapy, the usual adult dosage for either drug is 30 to 40 mg twice daily for 5 to 7 days.

For long-term treatment, *alternate-day dosing* is recommended (to minimize adrenal suppression). The *initial adult* dosage is 40 to 60 mg (of prednisone or prednisolone) administered every other morning. The *initial pediatric* dosage is 20 to 40 mg every other morning. After symptoms have been controlled for a month, dosages should be reduced by 5 to 10 mg every 2 weeks to establish the lowest dosage that can keep the patient free of symptoms. As discussed above, supplemental doses are required at times of stress.

LEUKOTRIENE MODIFIERS

When they were introduced in the late 1990s, the leukotriene modifiers were the first new drugs for asthma in over 20 years. All of these agents suppress the effects of leukotrienes, compounds that promote bronchoconstriction as well as

eosinophil infiltration, mucus production, and airway edema. In patients with asthma, these drugs can decrease inflammation, bronchoconstriction, edema, mucus secretion, and recruitment of eosinophils and other inflammatory cells.

Three leukotriene modifiers are currently available; zileuton, zafirlukast, and montelukast. Zileuton blocks leukotriene synthesis; zafirlukast and montelukast block leukotriene receptors. All three drugs are dosed orally. Current guidelines recommend using these agents as second-line therapy (if an inhaled glucocorticoid cannot be used), and as add-on therapy when an inhaled glucocorticoid alone is inadequate. Although generally well tolerated, all of the leukotriene modifiers can cause adverse neuropsychiatric effects, including depression, suicidal thinking, and suicidal behavior.

Zileuton

Zileuton [Zyflo, Zyflo CR], an inhibitor of leukotriene synthesis, is approved for asthma prophylaxis and maintenance therapy in adults and children age 12 years and older. Benefits derive from inhibiting 5-lipoxygenase, the enzyme that converts arachidonic acid into leukotrienes. Symptomatic improvement can be seen within 1 to 2 hours of dosing. Because effects are not immediate, zileuton cannot be used to abort an ongoing attack. Zileuton is less effective than an inhaled glucocorticoid alone, and appears to be less effective than a long-acting inhaled β_2 agonist as adjunctive therapy in patients not adequately controlled with an inhaled glucocorticoid.

Zileuton is given orally and undergoes rapid absorption, both in the presence and absence of food. Plasma levels peak 2 to 3 hours after dosing. Zileuton is rapidly metabolized by the liver, and the metabolites are excreted in the urine. Its plasma half-life is 2.5 hours.

Zileuton can injure the liver, as evidenced by increased plasma levels of alanine aminotransferase (ALT) activity. A few patients have developed symptomatic hepatitis, which reversed following drug withdrawal. To reduce the risk of serious liver injury, ALT activity should be monitored. The recommended schedule is once a month for 3 months, then every 2 to 3 months for the remainder of the first year, and periodically thereafter.

Postmarketing reports indicate that zileuton and the other leukotriene modifiers can cause adverse neuropsychiatric effects, including depression, anxiety, agitation, abnormal dreams, hallucinations, insomnia, irritability, restlessness, and suicidal thinking and behavior. If these develop, switching to a different medication should be considered.

Zileuton is metabolized by cytochrome P450, and hence can compete with other drugs for metabolism, thereby increasing their levels. Combined use with theophylline can markedly increase theophylline levels. Accordingly, dosage of theophylline should be reduced. Zileuton can also increase levels of warfarin and propranolol.

Zileuton is available in 600-mg immediate-release (IR) tablets, sold as Zyflo, and 600-mg extended-release (ER) tablets sold as Zyflo CR. With the

IR tablets, the recommended dosage is 600 mg 4 times a day. With the ER tablets, the recommended dosage is 600 mg twice a day, taken within 1 hour of the morning and evening meals.

Zafirlukast

Zafirlukast [Accolate], approved in 1996, was the first representative of a unique group of anti-inflammatory agents, the *leukotriene receptor antagonists*. The drug is approved for maintenance therapy of chronic asthma in adults and children 5 years of age and older. Benefits derive in part from reduced infiltration of inflammatory cells and decreased bronchoconstriction. According to a recent trial reported in the *New England Journal of Medicine* (May 21, 2011), zafirlukast, when used *short term* (2 months), is equivalent to an inhaled glucocorticoid as first-line therapy of asthma, and equivalent to an inhaled long-acting beta₂ agonist as add-on therapy in patients not controlled adequately with an inhaled glucocorticoid alone. However, benefits with long-term use (2 years) are less impressive.

Zafirlukast is administered orally, and absorption is rapid. Food reduces absorption by 40%. Hence, the drug should be administered at least 1 hour before meals or 2 hours after. Zafirlukast undergoes hepatic metabolism followed by fecal excretion. The half-life is about 10 hours, but may be as long as 20 hours in the elderly.

Zafirlukast causes few adverse effects—although there is concern about neuropsychiatric effects, liver injury, and Churg-Strauss syndrome. The most common side effects are headache and GI disturbances, both of which are infrequent. Arthralgia and myalgia may also occur. Like zileuton, zafirlukast can cause depression, suicidal thinking, hallucinations, and other neuropsychiatric effects. A few patients have developed Churg-Strauss syndrome, a potentially fatal disorder characterized by weight loss, flu-like symptoms, and pulmonary vasculitis (blood vessel inflammation). However, in all cases, symptoms developed when glucocorticoids were being withdrawn, suggesting that glucocorticoid withdrawal—and not zafirlukast—may be the underlying cause.

Rarely, patients develop clinical signs of liver injury (eg, abdominal pain, jaundice, fatigue). If these occur, zafirlukast should be discontinued, and liver function tests (especially serum ALT) should be performed immediately. If test results are consistent with liver injury, zafirlukast should not be resumed. Curiously, signs of liver injury have developed mainly in females.

Zafirlukast inhibits two isozymes of cytochrome P450, and hence can suppress metabolism of other drugs, thereby causing their levels to rise. Concurrent use can raise serum theophylline to toxic levels. Accordingly, serum theophylline should be closely monitored, especially when zafirlukast is started or stopped. Zafirlukast can also raise levels of warfarin (an anticoagulant), and may thereby cause bleeding.

Zafirlukast is available in 10- and 20-mg tablets. The dosage for adults and children age 12 and older is 20 mg twice a day. The dosage for children 5 to 11 years old is 10 mg twice a day. Zafirlukast should not be administered with food.

Montelukast

Montelukast [Singulair], a leukotriene receptor blocker, is the most commonly used leukotriene modulator. The drug has three approved indications: (1) prophylaxis and maintenance therapy of asthma in patients at least 1 year old; (2) prevention of exercise-induced bronchospasm (EIB) in patients at least 15 years old; and (3) relief of allergic rhinitis (see Chapter 77). Montelukast cannot be used for quick relief of an asthma attack because effects develop too slowly. For prophylaxis and maintenance therapy of asthma, maximal effects develop within 24 hours of the first dose, and are maintained with once-daily dosing in the evening. In clinical trials, montelukast decreased asthma-related nocturnal awakening, improved morning lung function, and decreased the need for a short-acting inhaled beta₂ agonist throughout the day. In the trial cited in the section on Zafirlukast above, montelukast, when used short-term, was equivalent to an inhaled glucocorticoid as first-line therapy, and equivalent to an inhaled long-acting beta₂ agonist as add-on therapy (in patients not adequately controlled with an inhaled glucocorticoid alone). Although montelukast is approved for preventing EIB, a short-acting beta₂ agonist is preferred.

Montelukast is rapidly absorbed following oral administration. Bioavailability is about 64%. Blood levels peak 3 to 4 hours after ingestion. The drug is highly bound (over 99%) to plasma proteins. Montelukast undergoes extensive metabolism by hepatic P450 enzymes followed by excretion in the bile. The plasma half-life ranges from 2.7 to 5.5 hours.

Montelukast is generally well tolerated. In clinical trials, adverse effects were equivalent to those of placebo. In contrast to zileuton and zafirlukast, montelukast does not seem to cause liver injury. As with zafirlukast, Churg-

Strauss syndrome has occurred when glucocorticoid dosage was reduced. Postmarketing reports suggest a link between montelukast and neuropsychiatric effects, especially mood changes and suicidality. Fortunately, these effects are rare.

Montelukast appears devoid of serious drug interactions. Unlike zileuton and zafirlukast, it does not increase levels of theophylline or warfarin. Concurrent use of phenytoin (an anticonvulsant that induces P450 enzymes) can decrease levels of montelukast.

Montelukast is available in three formulations: standard tablets (10 mg), chewable tablets (4 and 5 mg), and oral granules (4 mg/packet). The oral granules may be put directly in the mouth or may be mixed with one spoonful of either applesauce, carrots, rice, or ice cream. For prophylaxis or chronic treatment of asthma, dosing is done once a day in the evening, with or without food. Dosage is based on patient age as follows:

- Age 15 years and older—one 10-mg tablet daily
- Age 6 to 14 years—one 5-mg chewable tablet daily
- Age 2 to 5 years—one 4-mg chewable tablet or 4 mg of oral granules daily
- Age 12 to 23 months—4 mg of oral granules daily

To prevent EIB, patients should take one 10-mg tablet at least 2 hours before exercising. No additional dose should be taken for at least 24 hours. Patients already taking montelukast daily should not take any more to prevent EIB.

CROMOLYN

Cromolyn [Intal] is an inhalational agent that suppresses bronchial inflammation. The drug is used for *prophylaxis*—not quick relief—in patients with mild to moderate asthma. Anti-inflammatory effects are less than with glucocorticoids.

Effects on the Lung. Cromolyn suppresses inflammation; it does not cause bronchodilation. The drug acts in part by stabilizing the cytoplasmic membrane of mast cells, thereby preventing release of histamine and other mediators. In addition, cromolyn inhibits eosinophils, macrophages, and other inflammatory cells.

Pharmacokinetics. Cromolyn is administered by inhalation. The fraction absorbed from the lungs is small (about 8%) and produces no systemic effects. Absorbed cromolyn is excreted unchanged in the urine.

Therapeutic Uses. Chronic Asthma. Cromolyn is an alternative to inhaled glucocorticoids for prophylactic therapy of mild persistent asthma. The drug produces adequate control in 60% to 70% of patients. When administered on a fixed schedule, cromolyn reduces both the frequency and intensity of attacks. No tolerance to effects is seen with long-term use. To be of benefit, cromolyn must be administered *prior* to the onset of an attack; the drug is without benefit if taken after an episode has begun. In patients with chronic asthma, maximal effects may take several weeks to develop. Cromolyn is especially effective for prophylaxis of seasonal allergic attacks and for acute prophylaxis immediately prior to allergen exposure (eg, before mowing the lawn).

Exercise-Induced Bronchospasm. Cromolyn can prevent bronchospasm in patients at risk for EIB. For best results, cromolyn should be administered 15 minutes prior to anticipated exertion.

Allergic Rhinitis. Intranasal cromolyn [NasalCrom] can relieve symptoms of allergic rhinitis, as discussed in Chapter 77.

Adverse Effects. Cromolyn is the safest of all antiasthma medications. Significant adverse effects occur in fewer than 1 of every 10,000 patients. Occasionally, cough or bronchospasm occurs in response to cromolyn inhalation.

Preparations, Dosage, and Administration. Cromolyn for inhalation [Intal] can be administered with two devices: (1) a power-driven nebulizer and (2) an MDI. Patients will need instruction on using both. With the nebulizer, the *initial* dosage for adults and children is 20 mg 4 times a day. With the MDI, the *initial* dosage for adults and children is 2 to 4 puffs (1.6 to 3.2 mg) 4 times a day. For *maintenance* therapy with either device, the lowest effective dosage should be established. For therapy of chronic asthma, cromolyn must be administered on a fixed schedule.

OMALIZUMAB

Omalizumab [Xolair] is a monoclonal antibody with a unique mechanism of action: antagonism of IgE. The drug is a second-line agent indicated only for allergy-related asthma and only when preferred options have failed. Omalizumab offers modest benefits and has significant drawbacks: The drug poses a small risk of anaphylaxis and cancer, must be given subQ, and costs over \$10,000 a year. Furthermore, its long-term safety is unknown. Use of oma-

lizumab for seasonal allergic rhinitis and other allergic disorders is under investigation.

Mechanism of Action. Omalizumab forms complexes with free IgE in the blood and thereby reduces the amount of IgE available to bind with its receptors on mast cells. This greatly reduces the number of IgE molecules on the mast cell surface, and hence limits the ability of allergens to trigger release of histamine, leukotrienes, and other mediators that promote bronchospasm and airway inflammation. At recommended doses, omalizumab decreases free IgE in serum by 96%. When treatment stops, about 1 year is required for free IgE to return to its pretreatment level.

Therapeutic Use. Omalizumab is approved only for patients age 12 years and older with moderate to severe asthma that (1) is allergy related and that (2) cannot be controlled with an inhaled glucocorticoid. In clinical trials, the drug produced a modest decrease in the number of exacerbations, and often permitted a reduction in glucocorticoid use. Because of its mechanism of action, omalizumab can only help patients whose asthma is caused by a specific allergen (eg, pet dander, dust mite feces). Accordingly, a skin test or blood test proving allergen reactivity is required. Unless instructed otherwise, patients should continue all asthma medications they were using prior to starting omalizumab.

Pharmacokinetics. Omalizumab is administered subQ, and absorption is slow, producing peak plasma levels in 7 to 8 days. Degradation occurs in the liver. The drug's half-life is prolonged, about 26 days.

Adverse Effects. Omalizumab can cause a variety of adverse effects. The most common are injection-site reactions (45%), viral infection (23%), upper respiratory infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). Interim data from an ongoing trial indicate a risk of cardiovascular events, including ischemic heart disease, dysrhythmias, heart failure, pulmonary hypertension, cerebrovascular disorders, and thromboembolic events. Malignancy may also be a risk: During clinical trials, malignancy was seen in 0.5% of omalizumab recipients, compared with 0.2% of controls. Possible adverse consequences of long-term IgE suppression are unknown.

Life-threatening *anaphylaxis*—characterized by urticaria and edema of the throat and/or tongue—has occurred rarely (in less than 0.1% of patients). Anaphylaxis is most likely with the first dose, but can also occur after receiving repeated doses with no apparent sensitivity. To minimize injury from anaphylaxis, patients should be observed for 2 hours after the first three doses, and for 30 minutes after all subsequent doses. Facilities for managing anaphylaxis should be immediately available. Patients who experience a severe reaction should not be given omalizumab again.

Preparations, Dosage, and Administration. Omalizumab [Xolair] is available as a powder (202.5 mg) in single-use vials for reconstitution with 1.4 mL of sterile water. Dissolving the powder, which can take 20 minutes or longer, yields a final solution of 150 mg/1.2 mL. Administration is by subQ injection, which may take 5 to 10 seconds (because the solution is somewhat viscous). The reconstituted solution should be used within 4 hours (if stored at room temperature) or within 8 hours (if stored cold). Omalizumab powder should be stored cold.

The size of each dose and the dosing interval are determined by body weight and total serum IgE, measured at baseline. Dosages range from 150 to 300 mg every 4 weeks to 225 to 375 mg every 2 weeks. No more than 150 mg should be injected at any site. If a dose exceeds 150 mg, it should be divided among two or more sites.

BRONCHODILATORS

Bronchodilators provide symptomatic relief in patients with asthma, but do not alter the underlying disease process (inflammation). Accordingly, in almost all cases, patients taking a bronchodilator should be taking an inhaled glucocorticoid for long-term suppression of inflammation. Monotherapy with a bronchodilator is appropriate only when asthma is very mild and attacks are infrequent.

BETA₂-ADRENERGIC AGONISTS

Beta₂ agonists, given by inhalation, are the most effective drugs available for relieving acute bronchospasm and preventing exercise-induced bronchospasm (EIB). In addition, long-

acting formulations (given orally or by inhalation) can protect against bronchospasm over an extended time. Because of these beneficial effects, virtually all patients with asthma use these drugs. Keep in mind, however, that their use is not without risk. Specifically, there is evidence that *long-acting inhaled* beta₂ agonists can increase the risk of asthma-related death—but only when used *alone*. The basic pharmacology of the beta₂ agonists is presented in Chapter 17. Discussion here is limited to their use in asthma.

Mechanism of Antiasthma Action

The beta₂ agonists are sympathomimetic drugs that produce “selective” activation of beta₂-adrenergic receptors. By activating beta₂ receptors in smooth muscle of the lung, these drugs promote *bronchodilation*, and thereby relieve bronchospasm. In addition, beta₂ agonists suppress histamine release in the lung and increase ciliary motility. The beta₂-selective agents have replaced older, less selective sympathomimetics (eg, epinephrine, isoproterenol) for asthma therapy.

Classification by Route and Time Course

Beta₂ agonists may be administered orally or by inhalation, and their effects may be brief or prolonged. All of the oral agents are long acting. Among the inhaled agents, some are short acting and some are long acting. With the short-acting inhaled preparations, effects begin almost immediately, peak in 30 to 60 minutes, and persist for 3 to 5 hours. Because of this time course, the short-acting beta₂ agonists (SABAs) can be used to abort an ongoing attack, but cannot be used for prolonged prophylaxis. With the inhaled long-acting beta₂ agonists (LABAs), onset depends on the drug: With formoterol and arformoterol, onset is relatively rapid, whereas with salmeterol, onset is delayed. However, since these drugs are used on a fixed schedule for long-term control, the difference in onset is not very important.

Use in Asthma

Beta₂ agonists are employed for quick relief and long-term control. Drug selection depends on the goal.

Short-Acting Inhaled Beta₂ Agonists. Virtually all patients with asthma use these drugs. They are taken PRN to relieve an ongoing attack. And, in patients with EIB, they are taken before exercise to prevent an attack from occurring. For patients undergoing a severe acute attack, a nebulized SABA is the traditional treatment of choice. However, delivery with an MDI may be equally effective.

Long-Acting Inhaled Beta₂ Agonists. Patients who experience frequent attacks can inhale a LABA for long-term control. Dosing is done on a fixed schedule, not PRN. Please note that, in patients with asthma, LABAs are not first-line therapy, and they must always be *combined with a glucocorticoid*. In fact, their use *alone* in asthma is now *contraindicated*.^{*} For combined LABA/glucocorticoid therapy, the Food and Drug Administration (FDA) recommends using a product that contains both drugs in the same inhaler.

Oral Beta₂ Agonists. These drugs are used only for long-term control. Onset is too slow to abort an ongoing attack. Like the long-acting inhaled beta₂ agonists, the oral agents are not first-line therapy, and should not be used alone.

^{*}Although using a LABA alone is contraindicated for patients with asthma, LABAs can still be used alone in patients with COPD.

TABLE 76-3 • Beta₂-Adrenergic Agonists Used in Asthma

Drug [Trade Name]	Formulation	Initial Dosage	
		Adults	Children
Inhaled Agents: Short Acting			
Albuterol [ProAir HFA, Proventil HFA, Ventolin HFA] [Proventil, AccuNeb]	MDI (90 mcg/puff) Solution for nebulization	2 puffs every 4–6 hr PRN 1.25–5 mg every 4–8 hr PRN	2 puffs every 4–6 hr PRN 0.63–2.5 mg/kg every 4–6 hr PRN
Levalbuterol [Xopenex HFA] [Xopenex]	MDI (45 mcg/puff) Solution for nebulization	2 puffs every 4–6 hr PRN 0.63 mg every 6–8 hr PRN	2 puffs every 4–6 hr PRN 0.31–1.25 mg every 4–6 hr PRN
Pirbuterol [Maxair Autohaler]*	BA-MDI (200 mcg/puff)	2 puffs every 4–6 hr PRN	2 puffs every 4–6 hr PRN
Inhaled Agents: Long Acting†			
Arformoterol ^{†‡} [Brovana]	Solution for nebulization	15 mcg every 12 hr	Safety and efficacy not established
Formoterol* [Foradil Aerolizer] [Perforomist] [†]	DPI (12 mcg/puff) Solution for nebulization	1 puff every 12 hr 20 mcg every 12 hr	1 puff every 12 hr Safety and efficacy not established
Indacaterol [‡] [Arcapta Neohaler]	DPI (75 mcg/inhalation)	1 inhalation every 24 hr	
Salmeterol [†] [Serevent Diskus]	DPI (50 mcg/inhalation)	1 inhalation every 12 hr	1 inhalation every 12 hr
Oral Agents			
Albuterol Generic [VoSpire ER]	Tablets, syrup Tablets (extended release)	2 or 4 mg 3–4 times/day 8 mg every 12 hr	2 mg 3–4 times/day 4 mg every 12 hr
Terbutaline Generic	Tablets	5 mg 3 times/day	2.5 mg 3 times/day

BA-MDI = breath-activated metered-dose inhaler, DPI = dry-powder inhaler, HFA = hydrofluoroalkane propellant, MDI = metered-dose inhaler.

*Formulated with a CFC propellant and will be phased out by December 31, 2013. A new formulation is in development.

†When used to treat asthma, must always be combined with an inhaled glucocorticoid.

‡Approved only for chronic obstructive pulmonary disease, not asthma.

Adverse Effects

Inhaled Preparations: Short Acting. Inhaled SABAs are well tolerated. Systemic effects—tachycardia, angina, and tremor—can occur, but are usually minimal.

Inhaled Preparations: Long Acting. Inhaled LABAs may increase the risk of severe asthma and asthma-related death—but only when used incorrectly (ie, as monotherapy for long-term control). When used as recommended, they are very safe. The potential danger of these drugs was documented in the Salmeterol Multicenter Asthma Research Trial (SMART), which showed that, compared with patients taking a placebo, patients taking salmeterol for 28 weeks experienced more serious adverse events, including severe asthma attacks and asthma-related death. However, although the increase was statistically significant, it was also small. Furthermore, the increase was seen only in patients who were not taking a recommended first-line control drug (almost always an inhaled glucocorticoid). To minimize risk, LABAs should be used only in patients taking a recommended medication for long-term control, and only if that medication has been inadequate by itself. LABAs should never be used as first-line therapy for prolonged control, and should never be used alone.

Oral Preparations. The selectivity of the beta₂-adrenergic agonists is only relative, not absolute. Accordingly, when these drugs are administered orally, they are likely to produce some activation of beta₁ receptors in the heart. If dosage is excessive, stimulation of cardiac beta₁ receptors can cause *angina pectoris* and *tachydysrhythmias*. Patients should be instructed to report chest pain or changes in heart rate or rhythm.

Oral beta₂ agonists often cause *tremor* by activating beta₂ receptors in skeletal muscle. Tremor can be reduced by lowering the dosage. With continued drug use, tremor declines spontaneously.

Preparations, Dosage, and Administration

Nine selective beta₂ agonists are available (Table 76-3). Some are used for quick relief, and some for long-term control.

Inhaled Preparations for Quick Relief. To provide quick relief, beta₂ agonists must be administered by inhalation. Three types of devices may be used: MDIs, DPIs, and nebulizers.

For drugs administered with an MDI or DPI, the usual dosing schedule is 1 or 2 puffs 3 or 4 times a day. When 2 puffs

are needed, an interval of 1 minute or longer should separate them. During this interval, some bronchodilation develops, thereby facilitating penetration of the second puff.

For certain patients, nebulizers may be superior to inhalers. Experience has shown that some patients who have become unresponsive to a β_2 agonist delivered with an inhaler may respond to the same drug when it is given with a nebulizer. Why? Because the nebulizer delivers the dose slowly (over several minutes); as the bronchi gradually dilate, the drug gains deeper and deeper access to the lungs.

Inhaled Preparations for Long-Term Control. Three inhaled LABAs are approved for treatment of asthma: salmeterol [Serevent Diskus], formoterol [Foradil Aerolizer], and arformoterol [Brovana], the (*R,R*)-enantiomer of formoterol. All three drugs have a long duration of action, and hence are suited for long-term control. Dosing is done every 12 hours. If supplemental bronchodilation is needed between doses, a SABA should be employed. As discussed above, LABAs are not first-choice agents for long-term control, and they should not be used alone. Rather, they should always be combined with an inhaled glucocorticoid, preferably in the same inhaler device.

Although salmeterol is usually inhaled twice daily (every 12 hours), with continuous use, more frequent dosing may be needed. Why? Because benefits seem to persist for a shorter time as the duration of treatment increases.

Oral Preparations for Long-Term Control. Two oral β_2 agonists—albuterol and terbutaline—are approved for long-term control of asthma. Dosing is done 3 or 4 times a day.

METHYLXANTHINES

We first encountered the methylxanthines (theophylline, caffeine, others) in Chapter 36 (Central Nervous System Stimulants and Attention-Deficit/Hyperactivity Disorder). As discussed there, the most prominent actions of these drugs are (1) central nervous system (CNS) excitation and (2) bronchodilation. Other actions include cardiac stimulation, vasodilation, and diuresis.

Theophylline

Theophylline [Theo-24, Theochron, Elixophyllin] is the principal methylxanthine employed in asthma. Benefits derive primarily from bronchodilation. Theophylline has a narrow therapeutic range, and hence dosage must be carefully controlled. The drug is usually administered by mouth. Theophylline is not effective when inhaled.

In the past, theophylline was a first-line drug for asthma and nearly all patients with chronic asthma took it. However, use of theophylline has declined sharply, largely because we now have safer and more effective medications (eg, inhaled glucocorticoids, inhaled β_2 agonists).

Mechanism of Action

Theophylline produces bronchodilation by relaxing smooth muscle of the bronchi. Although the mechanism of bronchodilation has not been firmly established, the most probable is blockade of receptors for adenosine.

One frequently discussed mechanism suggests that methylxanthines act by inhibiting an enzyme called phosphodiesterase, and thereby elevate intracellular levels of cyclic AMP. This mechanism was proposed based on the ability of methylxanthines, in high concentrations, to inhibit phosphodiesterase in the test tube. However, since these high concentrations are not achieved in the body, it seems unlikely that phosphodiesterase inhibition underlies the clinical effects of methylxanthines.

Use in Asthma

Oral theophylline is used for maintenance therapy of chronic stable asthma. Although less effective than β_2 agonists, theophylline has a longer duration of action (when administered in a sustained-release formulation). With regular use, theophylline can decrease the frequency and severity of asthma attacks. Because its effects are prolonged, theophylline may be most appropriate for patients who experience nocturnal attacks.

Intravenous theophylline has been employed in emergencies. However, the drug is no more effective than β_2 agonists and glucocorticoids, and is clearly more dangerous.

Pharmacokinetics

Absorption. Oral theophylline is available in sustained-release formulations only. Immediate-release products have been discontinued. Absorption from sustained-release preparations is slow, but the resulting plasma levels are stable, being free of the wide fluctuations associated with the immediate-release products. Absorption from some sustained-release preparations can be affected by food.

Metabolism. Theophylline is metabolized in the liver. Rates of metabolism are affected by multiple factors—age, disease, drugs—and show wide individual variation. As a result, the plasma half-life of theophylline varies considerably among patients. For example, while the average half-life in nonsmoking adults is about 8 hours, the half-life can be as short as 2 hours in some adults and as long as 15 hours in others. Smoking cigarettes* (one to two packs a day) accelerates metabolism and decreases the half-life by about 50%. The average half-life in children is 4 hours. Metabolism is slowed in patients with certain pathologies (eg, heart disease, liver disease, prolonged fever). Some drugs (eg, cimetidine, fluoroquinolone antibiotics) decrease theophylline metabolism. Other drugs (eg, phenobarbital) accelerate metabolism. Because of these variations in metabolism, dosage must be individualized.

Drug Levels. Safe and effective therapy requires periodic measurement of theophylline blood levels. Traditionally, dosage has been adjusted to produce theophylline levels between 10 and 20 mcg/mL. However, many patients respond well at 5 mcg/mL, and, as a rule, there is little benefit to increasing levels above 15 mcg/mL. Hence, levels between 5 and 15 mcg/mL are appropriate for most patients. At levels above 20 mcg/mL, the risk of significant adverse effects is high.

Toxicity

Symptoms. Toxicity is related to theophylline levels. Adverse effects are uncommon at plasma levels below 20 mcg/mL. At 20 to 25 mcg/mL, relatively mild reactions occur (eg, nausea, vomiting, diarrhea, insomnia, restlessness). Serious adverse effects are most likely at levels above 30 mcg/mL. These reactions include severe dysrhythmias (eg, ventricular fibrillation) and convulsions that can be highly resistant to treatment. Death may result from cardiorespiratory collapse.

Treatment. At the first indication of toxicity, dosing with theophylline should stop. Absorption can be decreased by administering activated charcoal together with a cathartic. Ventricular dysrhythmias respond to lidocaine. Intravenous diazepam may help control seizures.

Drug Interactions

Caffeine. Caffeine is a methylxanthine with pharmacologic properties like those of theophylline (see Chapter 36). Accordingly, caffeine can intensify the adverse effects of theophylline on the CNS and heart. In addition, caffeine can compete with theophylline for drug-metabolizing enzymes, thereby causing theophylline levels to rise. Because of these interactions, individuals taking theophylline should avoid caffeine-containing beverages (eg, coffee, many soft drinks) and other sources of caffeine.

Drugs That Reduce Theophylline Levels. Several agents—including phenobarbital, phenytoin, and rifampin—can lower theophylline levels by inducing hepatic drug-metabolizing enzymes. Concurrent use of these agents may necessitate an increase in theophylline dosage.

Drugs That Increase Theophylline Levels. Several drugs—including cimetidine and the fluoroquinolone antibiotics (eg, ciprofloxacin)—can elevate plasma levels of theophylline, primarily by inhibiting hepatic metabolism. To avoid theophylline toxicity, the dosage of theophylline should be reduced when the drug is combined with these agents.

Oral Formulations

Oral theophylline is available as an elixir (80 mg/15 mL), sold as Elixophyllin, and in the following sustained-release formulations:

- 12-hour extended-release tablets (100, 200, and 300 mg) sold as Theochron
- 12-hour extended-release capsules (125, 200, and 300 mg) sold generically
- 24-hour controlled-release capsules (100, 200, 300, and 400 mg) sold as Theo-24

Unlike the elixir, the sustained-release tablets and capsules produce drug levels that are relatively stable. Accordingly, the sustained-release formulations are preferred for routine therapy.

Dosage and Administration

Oral. Dosage must be individualized. Traditionally, dosage has been adjusted to maintain plasma theophylline levels between 10 and 20 mcg/mL. However, levels between 5 and 15 mcg/mL are appropriate for most patients. To minimize chances of toxicity, doses should be low initially and then gradually increased. If a dose is missed, the following dose should *not* be doubled, because doing so could produce toxicity. Smokers require higher than average doses. Conversely, patients with heart disease, liver dysfunction, or prolonged fever are likely to require lower doses. Patients should be instructed not to chew the sustained-release tablets or capsules. Product information should be consulted for compatibility with food.

The initial dosage is based on the age and weight of the patient, and on the presence or absence of factors that can impair theophylline elimination. For specific initial dosages, consult the package insert. As noted above, maintenance doses should be adjusted to produce drug levels in the therapeutic range—typically 5 to 15 mcg/mL.

Intravenous. Intravenous theophylline is reserved for emergencies. Administration must be done slowly, because rapid injection can cause fatal cardiovascular reactions. Intravenous theophylline is incompatible with many other drugs. Accordingly, compatibility should be verified prior to mixing theophylline with other IV agents. For specific IV dosages, refer to the discussion of *aminophylline* below.

Other Methylxanthines

Aminophylline

Aminophylline is a theophylline salt that is considerably more soluble than theophylline itself. In solution, each molecule of aminophylline dissociates to yield two molecules of theophylline. Hence, the pharmacologic properties of aminophylline and theophylline are identical. Aminophylline is available in formulations for oral and IV dosing. Intravenous administration is employed most often.

Administration and Dosage. Intravenous. Because of its relatively high solubility, aminophylline is the preferred form of theophylline for IV use. Infusions should be done *slowly* (no faster than 25 mg/min), because rapid injection can produce severe hypotension and death. The usual loading dose is 6 mg/kg. The maintenance infusion rate should be adjusted to provide plasma levels of theophylline that are within the therapeutic range (10 to 20 mcg/mL). Aminophylline solutions are incompatible with a number of other drugs. Accordingly, compatibility must be verified before mixing aminophylline with other IV agents.

Oral. Aminophylline is available in 100- and 200-mg tablets. Dosing guidelines are the same as for theophylline.

Dyphylline

Although structurally similar to theophylline, dyphylline [Dylix, Lufyllin] is nonetheless a completely distinct compound, and is not converted to theophylline in the body. The drug has a half-life of 2 hours and is eliminated unchanged in the urine. Dyphylline is available in tablets (200 and 400 mg) and an elixir (100 mg/15 mL) for oral dosing. The usual adult dosage is 15 mg/kg every 6 hours.

ANTICHOLINERGIC DRUGS

Anticholinergic drugs improve lung function by blocking muscarinic receptors in the bronchi, thereby causing bronchial dilation. Two agents are available: ipratropium and tiotropium. These drugs are approved only for chronic obstructive pulmonary disease (COPD), but are used off-label for asthma. Both drugs are administered by inhalation. The principal difference between the two is pharmacokinetic: Tiotropium has a much longer duration of action, and hence can be dosed less often. With both drugs, systemic effects are minimal.

Ipratropium

Actions and Use in Asthma. Ipratropium [Atrovent HFA] is an atropine derivative administered by inhalation to relieve bronchospasm. The drug is approved only for bronchospasm associated with COPD, but is used for asthma nonetheless. Like atropine, ipratropium is a muscarinic antagonist. By blocking muscarinic cholinergic receptors in the bronchi, ipratropium promotes *bronchodilation*. Therapeutic effects begin within 30 seconds, reach 50% of their maximum in 3 minutes, and persist about 6 hours. Ipratropium is effective against allergen-induced asthma and exercise-induced

bronchospasm, but is less effective than the beta₂ agonists. However, because ipratropium and the beta₂-adrenergic agonists promote bronchodilation by different mechanisms, their beneficial effects are additive, hence combined use makes sense.

Adverse Effects. Systemic effects are minimal. Ipratropium is a quaternary ammonium compound, and therefore always carries a positive charge. As a result, the drug is not readily absorbed from the lungs or from the digestive tract. Hence, systemic effects are rare. The most common adverse reactions are dry mouth and irritation of the pharynx. If systemic absorption is sufficient, the drug may raise intraocular pressure in patients with glaucoma. Ipratropium has been associated with adverse cardiovascular events (heart attack, stroke, death). However, since absorption is minimal, it seems unlikely that ipratropium is the cause.

Patients with peanut allergy should avoid *Combivent* (ipratropium/albuterol), which contains soya lecithin as a carrier. Soya is in the same plant family as peanuts, and about 10% of people with peanut allergy are cross-allergic to soya. As a result, if these people are exposed to soya proteins, they are at risk of a life-threatening anaphylactic reaction.

Preparations, Dosage, and Administration. Ipratropium is available alone as Atrovent HFA and in combination with albuterol as Combivent and DuoNeb.

Ipratropium by itself is supplied in (1) solution (500 mcg/vial) and (2) MDIs that deliver 17 mcg per actuation. For patients using an MDI, the usual dosage is 2 inhalations 4 times a day, and the maximum dosage is 12 inhalations in 24 hours. For patients using the solution, the usual dosage is 500 mcg 3 or 4 times a day, administered by oral inhalation using a nebulizer.

Ipratropium plus albuterol is available in two formulations: solution for nebulization [DuoNeb] and an MDI [Combivent]. DuoNeb solution contains 500 mcg of ipratropium and 2500 mcg of albuterol in 3-mL, single-use vials. The recommended dosage is 3 mL administered 4 times a day by oral inhalation using a nebulizer. The Combivent MDI delivers 18 mcg of ipratropium and 90 mcg of albuterol with each actuation. The recommended dosage is 2 inhalations 4 times a day. This MDI uses a CFC propellant, and will be phased out by December 31, 2013.

Tiotropium

Actions and Therapeutic Use. Tiotropium [Spiriva] is a long-acting, inhaled anticholinergic agent approved for maintenance therapy of bronchospasm associated with COPD. The drug is not approved for asthma, but has been used off-label for patients who have not responded to other medications. Like ipratropium, tiotropium relieves bronchospasm by blocking muscarinic receptors in the lung. Therapeutic effects begin about 30 minutes after inhalation, peak in 3 hours, and persist about 24 hours. With subsequent doses, bronchodilation gets better and better, reaching a plateau after eight consecutive doses (8 days). Compared with ipratropium, tiotropium is more effective and its dosing schedule is more convenient (once daily vs. 4 times daily). Benefits of tiotropium and inhaled salmeterol (a long-acting beta₂ agonist) appear about equal. Inform patients that tiotropium is indicated only for long-term maintenance. For rapid relief of ongoing bronchospasm, they should inhale a short-acting beta₂ agonist.

Adverse Effects. The most common adverse effect is *dry mouth*, which develops in 16% of patients. Fortunately, this response is generally mild and diminishes over time. Patients can suck on sugarless candy for relief.

Systemic anticholinergic effects (eg, constipation, urinary retention, tachycardia, blurred vision) are minimal. Why? Because, like ipratropium, tiotropium is a quaternary ammonium compound, and hence absorption into the systemic circulation is very limited. Like ipratropium, tiotropium has been associated with adverse cardiovascular events. However, since absorption is low, tiotropium is not likely to be the cause.

Preparations, Dosage, and Administration. Tiotropium [Spiriva] is supplied in 18-mcg capsules along with a *Handihaler* DPI device. Administration is by inhalation only. The capsules should not be swallowed. The dosage is 18 mcg once a day.

GLUCOCORTICOID/LABA COMBINATIONS

Fluticasone/salmeterol [Advair Diskus, Advair HFA], *budesonide/formoterol* [Symbicort], and *mometasone/formoterol* [Dulera] are available in fixed-dose combina-

tions for inhalational therapy of asthma. The glucocorticoids (fluticasone, budesonide, and mometasone) provide anti-inflammatory benefits and the LABAs (salmeterol and formoterol) provide bronchodilation. All three products are indicated for long-term maintenance in adults and children. These combinations are more convenient than taking a glucocorticoid and LABA separately, but have the disadvantage of restricting dosage flexibility. These products are not recommended for initial therapy. Rather, they should be reserved for patients whose asthma has not been adequately controlled with an inhaled glucocorticoid alone. All three products carry a black box warning about possible increased risk of asthma severity or asthma-related death (from the LABA in the combination). However, because the LABA is combined with a glucocorticoid, risk should be minimal. The three combination products have not been directly compared. Nonetheless, when used in equivalent dosages, they are likely to be equally effective.

Fluticasone/Salmeterol

Fluticasone and salmeterol are available in a DPI sold as *Advair Diskus* and an MDI sold as *Advair HFA*. *Advair Diskus* is approved for patients age 4 years and older, whereas *Advair HFA* is approved for patients age 12 years and older.

Advair Diskus is available in three strengths that deliver the following doses of salmeterol/fluticasone per inhalation: 50/100 mcg, 50/250 mcg, and 50/500 mcg. Dosing consists of 1 inhalation every morning and evening. The dose of fluticasone selected should be equivalent to the dose of the glucocorticoid already in use.

Advair HFA is available in three strengths that deliver the following doses of salmeterol/fluticasone per inhalation: 21/45 mcg, 21/115 mcg, and 21/230 mcg. Dosing consists of 2 inhalations every morning and evening. As with *Advair Diskus*, the fluticasone dosage should be equivalent to the dosage of glucocorticoid in current use.

Budesonide/Formoterol

Budesonide/formoterol [*Symbicort*] is supplied in an MDI for use by patients age 12 years and older. *Symbicort* is available in two strengths that deliver either 80/4.5 mcg or 160/4.5 mcg of budesonide/formoterol per inhalation. Dosing consists of 2 inhalations every morning and evening. Patients currently taking low to medium glucocorticoid doses should start with the 80/4.5-mcg formulation. Patients taking medium to high glucocorticoid doses should start with the 160/4.5-mcg formulation.

Mometasone/Formoterol

Mometasone/formoterol [*Dulera*] is supplied in an MDI for use by patients age 12 years and older. *Dulera* is available in two strengths that deliver either 100/5 mcg or 200/5 mcg of mometasone/formoterol per inhalation. Dosing consists of 2 inhalations every morning and evening. Patients currently taking low to medium glucocorticoid doses should start with the 100/5-mcg formulation. Patients taking medium to high glucocorticoid doses should start with the 160/5-mcg formulation.

MANAGEMENT OF ASTHMA

In 2007, the National Asthma Education and Prevention Program (NAEPP) of the National Heart, Lung, and Blood Institute issued revised guidelines for asthma management. These guidelines—*Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma*—update the EPR-2 guidelines issued in 1997 (as well as the selected updates to EPR-2 issued in 2002). The discussion below reflects recommendations in EPR-3, which is available online at www.nhlbi.nih.gov/guidelines/asthma.

In EPR-3, management recommendations are made for three age groups: 0 to 4 years, 5 to 11 years, and 12 years and older. Recommendations for all three groups are similar, al-

though there are some important differences. *Discussion here is limited to the oldest group*, consisting of adults and older children. For recommendations that apply to younger patients, please consult EPR-3.

Measuring Lung Function

Before considering asthma therapy, we need to address tests of lung function. Three tests are described below.

Forced expiratory volume in 1 second (FEV₁) is the single most useful test of lung function. Unfortunately, the instrument required—a *spirometer*—is both expensive and cumbersome, and therefore not suited for use at home. To determine FEV₁, the patient inhales completely, and then exhales as completely and forcefully as possible into the spirometer. The spirometer measures how much air was expelled during the first second of exhalation. Results are then compared to a “predicted normal value” for a healthy person of similar age, sex, height, and weight. Hence, for a patient with asthma, the FEV₁ might be 75% of the predicted value.

Forced vital capacity (FVC), also measured with a spirometer, is defined as the total volume of air the patient can exhale following a full inhalation.

FEV₁/FVC (ie, FEV₁ divided by FVC) is the fraction (percentage) of vital capacity exhaled during the first second of forced expiration. Normal values for FEV₁/FVC range from 85% (for people 8 to 19 years old) down to 70% (for people 60 to 80 years old). In patients with asthma, the value for FEV₁/FVC may be in the normal range or it may be reduced by 5% or more, depending on asthma severity.

Peak expiratory flow (PEF) is defined as the maximal rate of airflow during expiration. To determine PEF, the patient exhales as forcefully as possible into a *peak flowmeter*, a relatively inexpensive, hand-held device. Patients should measure their peak flow every morning. If the value is less than 80% of their personal best, more frequent monitoring should be done.

Classification of Asthma Severity

As described in the EPR-3, chronic asthma has four classes of increasing severity: (1) intermittent, (2) mild persistent, (3) moderate persistent, and (4) severe persistent. Diagnostic criteria for these classes are summarized in Table 76-4. Note that severity classification is based on two separate “domains”: *impairment* and *risk*. Impairment refers to the impact of asthma on quality of life and functional capacity *in the present*. Risk refers to possible adverse events *in the future*, such as exacerbations and progressive loss of lung function. As shown in Table 76-4, as we progress from intermittent asthma to severe persistent asthma, both impairment and risk increase: asthma symptoms occur more often and last longer, use of SABAs for symptomatic control increases, limitations on physical activity become more substantial, FEV₁ decreases to less than 60% of predicted, FEV₁/FVC drops to 5% or more below normal, and the number of exacerbations that require oral glucocorticoids gets larger. It is important to note that the two domains of asthma—impairment and risk—may respond differently to drugs. Furthermore, patients can be at high risk of future events, even if their current level of impairment is low.

TABLE 76-4 ■ Classification of Asthma Severity and Recommended Step for Initial Treatment

	Intermittent Asthma	Persistent Asthma		
		Mild	Moderate	Severe
Current Impairment				
Symptoms	≤2 days/week	>2 days/week, but not daily	Daily	Throughout the day
Nighttime awakenings	≤2 times/month	3–4 times/month	>Once a week, but not nightly	Often 7 times/week
SABA used to control symptoms (but not to prevent EIB)	≤2 days/week	>2 days/week, but not daily, and not more than once on any day	Daily	Several times a day
Impact on normal activity	None	Minor limitation	Some limitation	Severe limitation
Lung function tests	<ul style="list-style-type: none"> • Normal FEV₁ between exacerbations • FEV₁ >80% of predicted • FEV₁/FVC normal* 	<ul style="list-style-type: none"> • FEV₁ >80% of predicted • FEV₁/FVC normal* 	<ul style="list-style-type: none"> • FEV₁ >60% but <80% of predicted • FEV₁/FVC reduced 5%* 	<ul style="list-style-type: none"> • FEV₁ <60% of predicted • FEV₁/FVC reduced >5%*
Future Risk				
Exacerbations requiring oral glucocorticoids	0–1/year	≥2/year	≥2/year	≥2/year
Recommended Step for Initial Treatment[†]	Step 1	Step 2	Step 3	Step 4 or 5

EIB = exercise-induced bronchospasm, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, SABA = short-acting beta₂ agonist.

*Normal values for FEV₁/FVC by age group: 8 to 19 years = 85%; 20 to 39 years = 80%, 40 to 59 years = 75%, 60 to 80 years = 70%.

[†]See Table 76-6 and text for drugs used at each step.

Adapted from National Asthma Education and Prevention Program: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007.

Treatment Goals

Treatment of chronic asthma is directed at two basic goals: reducing impairment and reducing risk. Components of each goal are listed below.

Reducing Impairment

- Preventing chronic and troublesome symptoms (eg, coughing or breathlessness after exertion and at all other times)
- Reducing use of SABAs for symptom relief to 2 days a week or less
- Maintaining normal (or near-normal) pulmonary function
- Maintaining normal activity levels, including exercise and attendance at school or work
- Meeting patient and family expectations regarding asthma care

Reducing Risk

- Preventing recurrent exacerbations
- Minimizing the need for emergency department visits or hospitalizations
- Preventing progressive loss of lung function (for children, preventing reduced lung growth)
- Providing maximum benefits with minimum adverse effects

Chronic Drug Therapy

In patients with chronic asthma, drugs are employed in two ways: some agents are taken to establish *long-term control* and some are taken for *quick relief* of an ongoing attack (Table 76-5). The long-term control drugs are taken every day, whereas the quick-relief drugs are taken PRN. Of the long-term control agents in current use, inhaled glucocorticoids are by far the most important. With regular dosing, these drugs reduce the frequency and severity of attacks, as well as the need for quick-relief medications. Of the quick-relief drugs in current use, inhaled SABAs are the most important. These drugs act promptly to reverse bronchoconstriction, and thereby provide rapid relief from cough, chest tightness, and wheezing.

For chronic drug therapy, EPR-3 recommends a *stepwise* approach, in which drug dosages and drug classes are stepped up as needed, and stepped down when possible. Six steps are described (Table 76-6). The basic concept is simple. First, all patients, starting with step 1, should use an inhaled SABA as needed for quick relief. Second, all patients—except those on step 1—should use a long-term control medication (preferably an inhaled glucocorticoid) to provide baseline control. Third, when patients move up a step, owing to increased impairment and risk, dosage of the control medication is increased and/or another control medication is added (typically a LABA). And fourth, after a period of sustained control, moving down a step should be tried.

For patients just beginning drug therapy, the step they start on is determined by the pretreatment classification of asthma severity. For example, a patient diagnosed with intermittent asthma would begin at step 1 (PRN use of an inhaled SABA), whereas a patient diagnosed with moderate persistent asthma would begin at step 3 (daily inhalation of a low-dose glucocorticoid plus daily inhalation of a LABA, supplemented with an inhaled SABA as needed).

TABLE 76-5 ■ Drugs for Asthma: Agents for Long-Term Control Versus Quick Relief

Long-Term Control Medications

Anti-inflammatory Drugs

Glucocorticoids (inhaled or oral)
Leukotriene modifiers
Cromolyn
Omalizumab

Bronchodilators

Long-acting inhaled beta₂ agonists*
Long-acting oral beta₂ agonists
Theophylline

Quick-Relief Medications

Bronchodilators

Short-acting inhaled beta₂ agonists
Anticholinergics

Anti-inflammatory Drugs

Glucocorticoids, systemic[†]

*For treatment of asthma, should always be combined with an inhaled glucocorticoid

†Considered quick-relief drugs when used in a short burst (3 to 10 days) at the start of therapy or during a period of gradual deterioration. Glucocorticoids are not used for immediate relief of an ongoing attack.

After treatment has been ongoing, stepping up or down is based on *assessment of asthma control*. Like the diagnosis of pretreatment severity, assessment of control is based on two domains: current impairment and future risk. In EPR-3, three classes of control are defined: well controlled, not well controlled, and very poorly controlled. Diagnostic criteria for each class are summarized in Table 76-7. Recommended actions for treatment are presented as well.

Drugs for Acute Severe Exacerbations

Acute severe exacerbations of asthma require immediate attention. The goal is to relieve airway obstruction and hypoxemia, and normalize lung function as quickly as possible. Initial therapy consists of

- Giving oxygen to relieve hypoxemia
- Giving a systemic glucocorticoid to reduce airway inflammation
- Giving a nebulized high-dose SABA to relieve airflow obstruction
- Giving nebulized ipratropium to further reduce airflow obstruction.

Severe cases may benefit from IV magnesium sulfate or inhalation of heliox (79% helium/21% oxygen). Following resolution of the crisis and hospital discharge, an oral glucocorticoid is taken for 5 to 10 days. All patients should also take a medium-dose inhaled glucocorticoid. Full recovery of lung function may take weeks.

Drugs for Exercise-Induced Bronchospasm

Exercise increases airway obstruction in practically all people with chronic asthma. The cause is bronchospasm secondary to loss of heat and/or water from the lung. Exercise-induced bronchospasm usually starts either during or immediately

TABLE 76-6 ■ Stepwise Approach to Managing Asthma in Patients Age 12 Years and Older

	Long-Term Control Drugs (Taken Daily)		Quick-Relief Drugs (Taken PRN)
	Preferred	Alternative	
Step 1	No daily medication needed		SABA
Step 2	Low-dose IGC	Cromolyn, LTRA, or theophylline	SABA
Step 3	Low-dose IGC + LABA <i>or</i> Medium-dose IGC	Low-dose IGC + either LTRA, theophylline, or zileuton	SABA
Step 4	Medium dose IGC + LABA	Medium-dose IGC + either LTRA, theophylline, or zileuton	SABA
Step 5	High-dose IGC + LABA		SABA
Step 6	High-dose IGC + LABA + oral glucocorticoid		SABA

IGC = inhaled glucocorticoid, LABA = long-acting beta₂ agonist, LTRA = leukotriene receptor antagonist, SABA = short-acting beta₂ agonist.

Adapted from National Asthma Education and Prevention Program: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007.

TABLE 76-7 • Assessment of Asthma Control in Patients Age 12 and Older and Recommended Action for Treatment

Components of Control	Classification of Control*		
	Well Controlled	Not Well Controlled	Very Poorly Controlled
Current Impairment			
Symptoms	≤2 days/week	>2 days/week	Throughout the day
Nighttime awakenings	≤2 times/month	1–3 times/week	≥4 times/week
SABA used to control symptoms (not to prevent EIB)	≤2 days/week	>2 days/week	Several times a day
Impact on normal activity	None	Some limitation	Severe limitation
Lung function tests:			
FEV ₁ (% of predicted)	FEV ₁ >80% <i>or</i>	FEV ₁ 60–80% <i>or</i>	FEV ₁ <60% <i>or</i>
PEF (% of personal best)	PEF >80%	PEF 60–80%	PEF <60%
Questionnaire Scores			
ATAQ	0	1–2	3–4
ACQ	≤0.75	≥1.5	N/A
ACT	≥20	16–19	≤15
Future Risk			
Exacerbations requiring oral glucocorticoids	0–1/year	≥2/year [†]	≥2/year [†]
Progressive loss of lung function	Evaluation requires long-term follow-up care.		
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment[‡]	Maintain current treatment step Follow up every 1–6 months to maintain control Consider step down if well controlled for 3 months or longer	Move up 1 step and reassess in 2–6 weeks To reduce side effects, consider changing drugs	Consider short course of oral glucocorticoids Move up 1 or 2 steps and reassess in 2 weeks To reduce side effects, consider changing drugs

ACQ = Asthma Control Questionnaire, ACT = Asthma Control Test, ATAQ = Asthma Therapy Assessment Questionnaire, EIB = exercise-induced bronchospasm, FEV₁ = forced expiratory volume in 1 second, N/A = not applicable, PEF = peak expiratory flow rate, SABA = short-acting beta₂ agonist.

*The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2 to 4 weeks and by FEV₁ or PEF. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.

[†]At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had two or more exacerbations requiring oral glucocorticoids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

[‡]Treatment steps are summarized in Table 76-6.

Adapted from National Asthma Education and Prevention Program: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007.

after exercise, peaks in 5 to 10 minutes, and resolves 20 to 30 minutes later.

With proper medication, most people with asthma can be as active as they wish. Indeed, many world-class athletes have had asthma, including Jackie Joyner-Kersey, Greg Louganis, and other Olympic gold medalists. To prevent EIB, patients can inhale a SABA or cromolyn prophylactically. Inhaled SABAs, which prevent EIB in more than 80% of patients, are more effective than cromolyn, and hence are preferred. Beta₂ agonists should be inhaled immediately before exercise; cromolyn should be inhaled 15 minutes before exercise.

Reducing Exposure to Allergens and Triggers

For patients with chronic asthma, the treatment plan should include measures to control allergens and other factors that can cause airway inflammation and exacerbate symptoms. Important sources of asthma-associated allergens include the house dust mite, warm-blooded pets, cockroaches, and molds. Factors that can exacerbate asthma include tobacco smoke, wood smoke, and household sprays. To the extent possible, exposure to these factors should be reduced or eliminated. For patients who are reluctant to part with Fluffy (the family cat) or Ralph (the family dog), weekly washing of the critter may

help. More importantly, the pet should be banned from the patient's bedroom.

The house dust mite is the most notorious cause of asthma. Allergy develops not to the microscopic mite itself, but rather to its even more microscopic feces. Measures to control or avoid dust mites and their feces include

- Encasing the patient's pillow, mattress, and box spring with covers that are impermeable to allergens

- Washing all bedding and stuffed animals weekly in a hot-water wash cycle (130°F)
- Removing carpeting or rugs from the bedroom
- Avoiding sleeping or lying on upholstered furniture
- Keeping indoor humidity below 50%

Unfortunately, even when these measures are implemented, their impact on asthma symptoms is generally small.

KEY POINTS

- Asthma is a chronic inflammatory disease characterized by inflammation of the airways, bronchial hyperreactivity, and bronchospasm. Allergy is often the underlying cause.
- Asthma is treated with anti-inflammatory drugs and bronchodilators.
- Most drugs for asthma are administered by inhalation, a route that increases therapeutic effects (by delivering drugs directly to their site of action), reduces systemic effects (by minimizing drug levels in blood), and facilitates rapid relief of acute attacks.
- Three devices are used for inhalation: metered-dose inhalers (MDIs), dry-powder inhalers (DPIs), and nebulizers. Patients will need instruction on their use.
- Glucocorticoids are the most effective antiasthma drugs available.
- Glucocorticoids reduce symptoms of asthma by suppressing inflammation. As an added bonus, glucocorticoids promote synthesis of bronchial β_2 receptors, and increase their responsiveness to β_2 agonists.
- Inhaled and systemic glucocorticoids are used for long-term prophylaxis of asthma—not for aborting an ongoing attack. Accordingly, they are administered on a fixed schedule—not PRN.
- Unless asthma is severe, glucocorticoids should be administered by inhalation.
- Inhaled glucocorticoids are generally very safe. Their principal side effects are oropharyngeal candidiasis and dysphonia, which can be minimized by employing a spacer device during administration and by gargling after.
- Inhaled glucocorticoids can slow the growth rate of children, but they do not reduce adult height.
- Inhaled glucocorticoids may pose a small risk of bone loss. To minimize loss, dosage should be as low as possible, and patients should perform regular weight-bearing exercise and should ensure adequate intake of calcium and vitamin D.
- Prolonged therapy with oral glucocorticoids can cause serious adverse effects, including adrenal suppression, osteoporosis, hyperglycemia, peptic ulcer disease, and growth suppression.
- Because of adrenal suppression, patients taking oral glucocorticoids (and patients who have switched from oral glucocorticoids to inhaled glucocorticoids) must be given supplemental doses of oral or IV glucocorticoids at times of stress.
- Cromolyn is an inhaled anti-inflammatory drug used for prophylaxis of asthma.
- Cromolyn reduces inflammation primarily by preventing release of mediators from mast cells.
- For long-term prophylaxis, cromolyn is taken daily on a fixed schedule. For prophylaxis of exercise-induced bronchospasm, cromolyn is taken 15 minutes before anticipated exertion.
- Cromolyn is the safest drug for asthma. Serious adverse effects are extremely rare.
- β_2 agonists promote bronchodilation by activating β_2 receptors in bronchial smooth muscle.
- Inhaled short-acting β_2 agonists (SABAs) are the most effective drugs for relieving acute bronchospasm and preventing exercise-induced bronchospasm.
- Three inhaled β_2 agonists—arformoterol, formoterol, and salmeterol—have a long duration of action, and hence are indicated for long-term control.
- Inhaled SABAs rarely cause systemic side effects.
- Excessive dosing with oral β_2 agonists can cause tachycardia and angina by activating β_1 receptors on the heart. (Selectivity is lost at high doses.)
- Inhaled long-acting β_2 agonists (LABAs) can increase the risk of asthma-related death, primarily when used alone. To reduce risk, LABAs should be used only by patients taking an inhaled glucocorticoid for long-term control, and only if the glucocorticoid has been inadequate by itself. For combined glucocorticoid/LABA therapy, the FDA recommends using a product that contains both drugs in the same inhaler.
- Theophylline, a member of the methylxanthine family, relieves asthma by causing bronchodilation.
- Although theophylline was used widely in the past, it has been largely replaced by safer and more effective medications.
- There are four classes of chronic asthma: intermittent, mild persistent, moderate persistent, and severe persistent. Diagnosis is based on current impairment and future risk.
- For therapeutic purposes, asthma drugs can be classified as long-term control medications (eg, inhaled glucocorticoids) and quick-relief medications (eg, inhaled SABAs).
- In the stepwise approach to asthma therapy, treatment becomes more aggressive as impairment and/or risk become more severe.
- The goals of stepwise therapy are to prevent symptoms, maintain near-normal pulmonary function, maintain normal activity, prevent recurrent exacerbations, minimize the need for SABAs, minimize drug side effects, minimize emergency department visits, prevent progressive

loss of lung function, and meet patient and family expectations about treatment.

- The step chosen for initial therapy is based on the pre-treatment classification of asthma severity, whereas moving up or down a step is based on ongoing assessment of asthma control.
- Intermittent asthma is treated PRN, using an inhaled SABA to abort the few acute episodes that occur.
- For persistent asthma (mild, moderate, or severe), the foundation of therapy is daily inhalation of a glucocorticoid. An inhaled LABA is added to the regimen when asthma is more severe. A SABA is inhaled PRN to suppress breakthrough attacks.
- For acute severe exacerbations of asthma, patients should receive oxygen (to reduce hypoxemia), a systemic glucocorticoid (to reduce airway inflammation), and a nebulized SABA plus nebulized ipratropium (to relieve airflow obstruction).

- To prevent exercise-induced bronchospasm, patients can inhale a SABA just prior to strenuous activity.
- Patients should avoid allergens that can cause airway inflammation and triggers that can provoke exacerbations. Important sources of allergens are the house dust mite, warm-blooded pets, cockroaches, and molds. Important triggers are tobacco smoke, wood smoke, and household sprays.

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Summary of Major Nursing Implications*

GLUCOCORTICOIDS

Inhaled

Beclomethasone
Budesonide
Ciclesonide
Flunisolide
Fluticasone
Mometasone

Oral

Prednisolone
Prednisone

The nursing implications summarized below refer specifically to the use of glucocorticoids in asthma. A full summary of nursing implications for glucocorticoids is presented in Chapter 72.

Preadministration Assessment

Therapeutic Goal

Glucocorticoids are used on a fixed schedule to suppress inflammation. They are not used to abort an ongoing attack.

Baseline Data

Determine FEV₁ and the frequency and severity of attacks, and attempt to identify trigger factors.

Identifying High-Risk Patients

Inhaled Glucocorticoids. These preparations are *contraindicated* for patients with persistently positive sputum cultures for *Candida albicans*.

Oral Glucocorticoids. These preparations are *contraindicated* for patients with systemic fungal infections and for individuals receiving live virus vaccines.

Use with *caution* in pediatric patients and in women who are pregnant or breast-feeding. Also, exercise *caution* in patients with hypertension, heart failure, renal impairment, esophagitis, gastritis, peptic ulcer disease, myasthenia gravis, diabetes mellitus, osteoporosis, or infections that are

resistant to treatment and in patients receiving potassium-depleting diuretics, digitalis glycosides, insulin, oral hypoglycemics, or nonsteroidal anti-inflammatory drugs.

Implementation: Administration

Routes

Inhalation, oral.

Administration

Inform patients that glucocorticoids are intended for preventive therapy—not for aborting an ongoing attack. Instruct patients to administer glucocorticoids on a regular schedule—not PRN.

Inhalation. Inhaled glucocorticoids are administered with an MDI, DPI, or nebulizer. Teach patients how to use these devices. Inform patients that delivery of glucocorticoids to the bronchial tree can be enhanced by inhaling a SABA 5 minutes prior to inhaling the glucocorticoid.

Oral. Alternate-day therapy is recommended to minimize adrenal suppression; instruct patients to take one dose every other day in the morning. During long-term treatment, supplemental doses must be given at times of severe stress.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Teach patients with chronic asthma to monitor and record PEF, symptom frequency and symptom intensity, nighttime awakenings, impact on normal activity, and SABA use.

Minimizing Adverse Effects

Inhaled Glucocorticoids. Advise patients to gargle after dosing to minimize dysphonia and oropharyngeal candidiasis. If candidiasis develops, it can be treated with anti-fungal medication.

Warn patients who have switched from long-term oral glucocorticoids to inhaled glucocorticoids that, because of adrenal suppression, they must take supplemental systemic glucocorticoids at times of severe stress (eg, trauma, surgery, infection); failure to do so can be fatal.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

To minimize possible *bone loss*, patients should use the lowest dose possible. Also, **advise patients to ensure adequate intake of calcium and vitamin D, and to perform weight-bearing exercise.**

Oral Glucocorticoids. Prolonged therapy can cause *adrenal suppression* and other serious adverse effects, including *osteoporosis, hyperglycemia, peptic ulcer disease, and growth suppression.* These effects can be reduced with alternate-day dosing. To compensate for adrenal suppression, patients taking glucocorticoids long term must be given supplemental oral or IV glucocorticoids at times of stress (eg, trauma, surgery, infection); failure to do so can be fatal. Additional nursing implications that apply to adverse effects of long-term glucocorticoid therapy are summarized in Chapter 72.

BETA₂-ADRENERGIC AGONISTS

Inhaled, Short Acting

Albuterol
Levalbuterol
Pirbuterol

Inhaled, Long Acting

Arformoterol
Formoterol
Indacaterol
Salmeterol

Oral

Albuterol
Terbutaline

Preadministration Assessment

Therapeutic Goal

Short-acting inhaled beta₂ agonists are used PRN for prophylaxis of EIB and to relieve ongoing asthma attacks. Oral and inhaled long-acting beta₂ agonists are used for maintenance therapy.

Baseline Data

Determine FEV₁ and the frequency and severity of attacks, and attempt to identify trigger factors.

Identifying High-Risk Patients

Systemic (oral, parenteral) beta₂ agonists are *contraindicated* for patients with tachydysrhythmias or tachycardia associated with digitalis toxicity.

Use systemic beta₂ agonists with *caution* in patients with diabetes, hyperthyroidism, organic heart disease, hypertension, or angina pectoris.

Implementation: Administration

Routes

Usual. Inhalation.

Occasional. Oral, subcutaneous.

Administration

Inhalation. Inhaled beta₂ agonists are administered with an MDI, DPI, or nebulizer. Teach patients how to use these devices. For patients who have difficulty with hand-lung coordination, using a spacer with a one-way valve may improve results.

Inform patients who are using MDIs or DPIs that, when 2 puffs are needed, an interval of at least 1 minute should elapse between puffs.

Warn patients against exceeding recommended dosages.

Inform patients that inhaled formoterol, arformoterol, and salmeterol (long-acting beta₂ agonists) should be taken on a fixed schedule—not PRN—and always in combination with an inhaled glucocorticoid, preferably in the same inhalation device.

Oral. Instruct patients to take oral beta₂ agonists on a fixed schedule—not PRN.

Instruct patients to swallow sustained-release preparations intact, without crushing or chewing.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Teach patients with chronic asthma to monitor and record PEF, symptom frequency and symptom intensity, nighttime awakenings, impact on normal activity, and SABA use.

Minimizing Adverse Effects

Inhaled Short-Acting Beta₂ Agonists. When used at recommended doses, SABAs are generally devoid of adverse effects. Cardiac stimulation and tremors are most likely with systemic therapy.

Inhaled Long-Acting Beta₂ Agonists. When used correctly, LABAs are very safe. When used *alone* for prophylaxis, they may *increase* the risk of severe asthma attacks and asthma-related death. To minimize risk, these drugs should always be combined with an inhaled glucocorticoid, preferably in the same inhalation device.

Oral Beta₂ Agonists. Excessive dosing can activate beta₁ receptors on the heart, resulting in anginal pain and tachydysrhythmias. **Instruct patients to report chest pain and changes in heart rate or rhythm.**

Tremor is common with systemic beta₂ agonists, and usually subsides with continued drug use. If necessary, tremor can be reduced by lowering the dosage.

CROMOLYN

Preadministration Assessment

Therapeutic Goal

Cromolyn is used for acute and long-term prophylaxis of asthma. The drug will not abort an ongoing asthma attack.

Baseline Data

Determine FEV₁ and the frequency and severity of attacks, and attempt to identify trigger factors.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Identifying High-Risk Patients

Cromolyn is *contraindicated* for the rare patient who has experienced an allergic response to cromolyn in the past.

Implementation: Administration

Route

Inhalation.

Administration

Administration Devices. Cromolyn is administered with either an MDI or a nebulizer. Instruct patients on the proper use of these devices.

Acute Prophylaxis. Instruct patients to administer cromolyn 15 minutes prior to exercise and exposure to other precipitating factors (eg, cold, environmental agents).

Long-Term Prophylaxis. Instruct patients to administer cromolyn on a regular schedule, and inform them that full therapeutic effects may take several weeks to develop.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Teach patients with chronic asthma to monitor and record PEF, symptom frequency and symptom intensity, nighttime awakenings, impact on normal activity, and SABA use.

Minimizing Adverse Effects and Interactions

Cromolyn is devoid of significant adverse effects and drug interactions.

THEOPHYLLINE

Preadministration Assessment

Therapeutic Goal

Theophylline is a bronchodilator taken on a regular schedule to decrease the intensity and frequency of moderate to severe asthma attacks.

Baseline Data

Determine FEV₁ and the frequency and severity of attacks.

Identifying High-Risk Patients

Theophylline is *contraindicated* for patients with untreated seizure disorders or peptic ulcer disease.

Use with *caution* in patients with heart disease, liver or kidney dysfunction, or severe hypertension.

Implementation: Administration

Routes

Oral, intravenous.

Administration

Oral. Dosage must be individualized. Doses are low initially and then increased gradually. The dosing objective is to produce plasma theophylline levels in the therapeutic

range, which for most patients is 5 to 15 mcg/mL. Warn patients that, if a dose is missed, the following dose should not be doubled.

Instruct patients to swallow enteric-coated and sustained-release formulations intact, without crushing or chewing.

Warn patients not to switch from one sustained-release formulation to another without consulting the prescriber.

Consult product information regarding compatibility with food, and advise the patient accordingly.

Intravenous. Administer slowly. Verify compatibility with other IV drugs prior to mixing.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor theophylline levels to ensure that they are in the therapeutic range (5 to 15 mcg/mL for most patients).

Teach patients with chronic asthma to monitor and record PEF, symptom frequency and symptom intensity, nighttime awakenings, impact on normal activity, and SABA use.

Minimizing Adverse Effects

Mild adverse effects (eg, nausea, vomiting, diarrhea, insomnia, restlessness) develop as plasma drug levels rise above 20 mcg/mL. Severe effects (convulsions, ventricular fibrillation) can occur at drug levels above 30 mcg/mL. Dosage should be adjusted to keep theophylline levels below 20 mcg/mL.

Minimizing Adverse Interactions

Caffeine. Caffeine can intensify the adverse effects of theophylline on the heart and CNS and can decrease theophylline metabolism. **Caution patients against consuming caffeine-containing beverages (eg, coffee, many soft drinks) and other sources of caffeine.**

Drugs That Reduce Theophylline Levels. *Phenobarbital, phenytoin, rifampin,* and other drugs can lower theophylline levels. In the presence of these drugs, the dosage of theophylline may need to be increased.

Drugs That Increase Theophylline Levels. *Cimetidine, fluoroquinolone antibiotics,* and other drugs can elevate theophylline levels. When combined with these drugs, theophylline should be used in reduced dosage.

Managing Toxicity. Theophylline overdose can cause severe dysrhythmias and convulsions. Death from cardiorespiratory collapse may occur. Manage toxicity by (1) discontinuing theophylline, and (2) administering activated charcoal (to decrease theophylline absorption) plus a cathartic (to accelerate fecal excretion). Give lidocaine to control ventricular dysrhythmias and IV diazepam to control seizures.

*Patient education information is highlighted as blue text.

Drugs for Allergic Rhinitis, Cough, and Colds

Drugs for Allergic Rhinitis

Intranasal Glucocorticoids

Antihistamines

Intranasal Cromolyn Sodium

Sympathomimetics (Decongestants)

Antihistamine/Sympathomimetic Combinations

Ipratropium, an Anticholinergic Agent

Montelukast, a Leukotriene Antagonist

Omalizumab

Drugs for Cough

Antitussives

Expectorants and Mucolytics

Cold Remedies: Combination Preparations

Box 77-1. Zinc for Kids with Colds?

The drugs addressed in this chapter are given to alleviate symptoms of common respiratory disorders. Our principal focus is allergic rhinitis.

DRUGS FOR ALLERGIC RHINITIS

Allergic rhinitis is an inflammatory disorder that affects the upper airway, lower airway, and eyes. Major symptoms are sneezing, rhinorrhea (runny nose), pruritus (itching), and nasal congestion (caused by dilation and increased permeability of nasal blood vessels). In addition, some patients experience conjunctivitis, sinusitis, and even asthma. Symptoms are triggered by airborne allergens, which bind to immunoglobulin E (IgE) antibodies on mast cells, and thereby cause release of inflammatory mediators, including histamine, leukotrienes, and prostaglandins. Allergic rhinitis is the most common allergic disorder, affecting 20 to 40 million Americans (10% to 30% of adults and up to 40% of children).

Allergic rhinitis has two major forms: seasonal and perennial. Seasonal rhinitis, also known as *hay fever* or *rose fever*, occurs in the spring and fall in reaction to outdoor allergens, including fungi and pollens from weeds, grasses, and trees. Perennial (nonseasonal) rhinitis is triggered by indoor allergens, especially the house dust mite and pet dander.

Several classes of drugs are used for allergic rhinitis (Table 77-1). Principal among these are (1) glucocorticoids (intranasal), (2) antihistamines (oral and intranasal), and (3) sympathomimetics (oral and intranasal). Glucocorticoids and anti-

histamines are considered first-line therapies. Of the two, glucocorticoids are much more effective. Sympathomimetics are used in conjunction with other agents to help relieve nasal congestion.

Approaches to rhinitis management discussed below are based in large part on an evidence-based guideline—*The Diagnosis and Management of Rhinitis: An Updated Practice Parameter*—released in 2008 by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

Intranasal Glucocorticoids

The basic pharmacology of the glucocorticoids is discussed in Chapter 72. Consideration here is limited to their use in allergic rhinitis.

Actions and Uses. Intranasal glucocorticoids are the most effective drugs for prevention and treatment of seasonal and perennial rhinitis. For patients with mild to moderate rhinitis, glucocorticoids are the initial treatment of choice. With proper use, over 90% of patients respond. Because of their anti-inflammatory actions, these drugs can prevent or suppress all of the major symptoms of allergic rhinitis: congestion, rhinorrhea, sneezing, nasal itching, and erythema. In the past, intranasal steroids were reserved for patients whose symptoms could not be controlled with more traditional drugs (antihistamines, sympathomimetics, intranasal cromolyn). However, because of their proven safety and superior efficacy, glucocorticoids have now replaced the histamine₁ (H₁) antagonists as the treatment of first choice. Seven glucocorticoids are available (Table 77-2). All appear equally effective.

Adverse Effects. Adverse effects are generally mild. The most common are *drying of the nasal mucosa* and a *burning or itching sensation*. *Sore throat*, *epistaxis* (nosebleed), and *headache* may also occur.

Systemic effects are possible, but are rare at recommended doses. Of greatest concern are adrenal suppression and slowing of linear growth in children (whether final adult height is reduced is unknown). Systemic effects are least likely with fluticasone and mometasone, which have very low bioavailability (see Table 77-2).

Preparations, Dosage, and Administration. Intranasal glucocorticoids are administered using a metered-dose spray device. Benefits are greatest when dosing is done daily, rather than PRN. Full doses are given initially (see Table 77-2). After symptoms are under control, the dosage should be reduced to the lowest effective amount. For patients with sea-

TABLE 77-1 ■ Overview of Drugs for Allergic Rhinitis

Drug or Class	Route	Actions	Adverse Effects
Glucocorticoids	Nasal	Prevent inflammatory response to allergens and thereby reduce all symptoms.	Nasal irritation; possible slowing of linear growth in children
Antihistamines	Oral/nasal	Block H ₁ receptors and thereby decrease itching, sneezing, and rhinorrhea; do <i>not</i> reduce congestion.	<i>Oral</i> : Sedation and anticholinergic effects (mostly with first-generation agents) <i>Nasal</i> : Bitter taste
Cromolyn	Nasal	Prevents release of inflammatory mediators from mast cells, and thereby can decrease all symptoms. However, benefits are modest.	None
Sympathomimetics	Oral/nasal	Activate vascular alpha ₁ receptors and thereby cause vasoconstriction, which reduces nasal congestion; do <i>not</i> decrease sneezing, itching, or rhinorrhea.	<i>Oral</i> : Restlessness, insomnia, increased blood pressure <i>Nasal</i> : Rebound nasal congestion
Anticholinergics	Nasal	Block nasal cholinergic receptors and thereby reduce secretions; do <i>not</i> decrease sneezing, nasal congestion, or postnasal drip.	Nasal drying and irritation
Antileukotrienes	Oral	Block leukotriene receptors and thereby reduce nasal congestion.	Rare neuropsychiatric effects

TABLE 77-2 ■ Some Glucocorticoid Nasal Sprays for Allergic Rhinitis

Drug	Trade Name	Intranasal Bioavailability (%)	Dose/Spray (mcg)	Patient Age (yr)	Initial Dosage (Sprays/Nostril)
Beclomethasone	Beconase AQ	44	42	6–11 12 and older	1 twice daily 1 or 2 twice daily
Budesonide	Rhinocort Aqua	34	32	6–11 12 and older	1 or 2 once daily 1–4 once daily
Ciclesonide	Omnaris	—	50	6 and older	2 once daily
Flunisolide	generic only	49	25	6–13 14 and older	2 twice daily or 1 thrice daily 2 twice or thrice daily
Fluticasone propionate	Flonase	0.5–2	50	4–11 12 and older	1 once daily 2 once daily
Fluticasone furoate	Veramyst	—	27.5	2–11 12 and older	1 once daily 2 once daily
Mometasone	Nasonex	0.1	50	2–11 12 and older	1 once daily 2 once daily
Triamcinolone	Nasacort AQ	46	55	6 and older	1 or 2 once daily

sonal allergic rhinitis, maximal effects may require a week or more to develop. However, an initial response can be seen within hours. For patients with perennial rhinitis, maximal responses may take 2 to 3 weeks to develop. If nasal passages are blocked, they should be cleared with a topical decongestant prior to glucocorticoid administration.

Antihistamines

The antihistamines are discussed at length in Chapter 70. Consideration here is limited to their use in allergic rhinitis.

Oral Antihistamines

Oral antihistamines (H₁ receptor antagonists) are first-line drugs for mild to moderate allergic rhinitis. These drugs can relieve sneezing, rhinorrhea, and nasal itching. However, they do not reduce nasal congestion. Because histamine is only one

of several mediators of allergic rhinitis, antihistamines are less effective than glucocorticoids. Because histamine does not contribute to symptoms of infectious rhinitis, antihistamines are of no value against the common cold.

For therapy of allergic rhinitis, antihistamines are most effective when taken *prophylactically*, and less helpful when taken after symptoms appear. Accordingly, antihistamines should be administered on a regular basis throughout the allergy season, even when symptoms are absent.

Adverse effects are usually mild. The most frequent complaint is *sedation*, which occurs often with the first-generation antihistamines (eg, diphenhydramine), and much less with the second-generation agents (eg, fexofenadine). Accordingly, second-generation agents are clearly preferred. *Anticholinergic effects* (eg, dry mouth, constipation, urinary hesitancy) are common with first-generation agents, and relatively rare with the second-generation agents.

TABLE 77-3 ■ Some Antihistamines for Allergic Rhinitis

Generic Name	Trade Name	Dosage
Oral Antihistamines		
First-Generation (Sedating)		
Chlorpheniramine	Chlor-Trimeton Allergy, Chlor-Tripolon [★] , others	Adults and children 12 yr and older: 4 mg q 4–6 h Children 6–11 yr: 2 mg q 4–6 h
Diphenhydramine	Benadryl, others	Adults: 25–50 mg q 4–6 h Children under 10 kg: 12.5–25 mg 3 or 4 times/day
Second-Generation (Nonsedating)		
Cetirizine*	Zyrtec, Reactine [★]	Adults and children 6 yr and older: 5 or 10 mg once daily
Levocetirizine	Xyzal	Adults and children 12 yr and older: 5 mg once daily Children 6–11 yr: 2.5 mg once daily
Fexofenadine	Allegra	Adults and children 12 yr and older: 60 mg twice daily or 180 mg once daily
Loratadine	Claritin, Alavert	Adults and children 6 yr and older: 10 mg once daily
Desloratadine	Clarinex, Aeries [★]	Adults and children 12 yr and older: 5 mg once daily
Intranasal Antihistamines		
Second-Generation (Nonsedating)		
Azelastine*	Astelin, Astepro	Adults and children 12 yr and older: 2 sprays/ nostril twice daily Children 5–11 yr: 1 spray/nostril twice daily [†]
Olopatadine	Patanase	Adults and children 12 yr and older: 2 sprays/ nostril twice daily (665 mcg/spray)

*May cause some sedation at recommended doses.

[†]Astelin only. Astepro is not approved for children under 12 years.

Dosages for some popular H₁ antagonists are presented in Table 77-3. A more complete list appears in Table 70-2 (Chapter 70).

Intranasal Antihistamines

Two antihistamines—*azelastine* [Astelin, Astepro] and *olopatadine* [Patanase]—are available for intranasal administration. Both drugs are indicated for allergic rhinitis in adults and children over 12 years old. Benefits equal those of oral antihistamines. Both drugs are supplied in metered-spray devices. The usual dosage is two sprays in each nostril twice daily. With both drugs, systemic absorption can be sufficient to cause somnolence. With olopatadine, some patients experience nosebleeds (3.2%) and headache (4.4%). With both formulations of azelastine (Astelin and Astepro), patients often complain of an unpleasant taste.

Intranasal Cromolyn Sodium

The basic pharmacology of cromolyn sodium is discussed in Chapter 76 (Drugs for Asthma). Consideration here is limited to its use in allergic rhinitis.

Actions and Uses. For treatment of allergic rhinitis, intranasal cromolyn [NasalCrom] is extremely safe, but only moderately effective. Benefits are much less than those of intranasal glucocorticoids. Cromolyn reduces symptoms by suppressing release of histamine and other inflammatory mediators from mast cells. Accordingly, the drug is best suited for prophylaxis—not treatment—and hence should be given before symptoms start. Responses may take a week or two to develop; patients should be informed of this delay. Adverse

reactions are minimal—less than with any other drug for allergic rhinitis.

Preparations, Dosage, and Administration. For treatment of allergic rhinitis, cromolyn sodium is available in a metered-dose spray device that delivers 5.2 mg/actuation. The usual dosage for adults and children over 2 years is 1 spray (5.2 mg) per nostril 4 to 6 times a day. If nasal congestion is present, a topical decongestant should be used before cromolyn. Like the antihistamines and glucocorticoids, cromolyn should be dosed on a regular schedule throughout the allergy season.

Sympathomimetics (Decongestants)

Actions and Uses

Sympathomimetics (eg, phenylephrine, pseudoephedrine) reduce nasal congestion. How? These drugs activate alpha₁-adrenergic receptors on nasal blood vessels, which causes vasoconstriction, which in turn causes shrinkage of swollen membranes followed by nasal drainage. With *topical* administration, vasoconstriction is both rapid and intense. With *oral* administration, responses are delayed, moderate, and prolonged.

In patients with allergic rhinitis, sympathomimetics only relieve stuffiness. They do not reduce rhinorrhea, sneezing, or itching. In addition to their use in allergic rhinitis, sympathomimetics can reduce congestion associated with sinusitis and colds. Routes and dosages are summarized in Table 77-4.

Adverse Effects

Rebound Congestion. Rebound congestion develops when *topical* agents are used more than a few days. With prolonged use, as the effects of each application wear off, congestion becomes progressively worse. To overcome this rebound conges-

TABLE 77-4 ■ Sympathomimetics Used for Nasal Decongestion

Decongestant	Mode of Use	Dosing Interval	Dosage Size*
Phenylephrine [Neo-Synephrine, others]	Drops	q 4 or more h	6 yr and older: 2–3 drops (0.25–1%) 2–6 yr: 2–3 drops (0.125%)
	Spray	q 4 or more h	12 yr and older: 2–3 sprays (0.25–1%) 6–12 yr: 2–3 sprays (0.25%) 2–6 yr: Not recommended
	Oral	q 4 h	12 yr and older: 10 mg 6–12 yr: 10 mg 2–6 yr: 1 mL (0.25% drops)
Pseudoephedrine [Sudafed, others]	Oral	q 4–6 h	12 yr and older: 60 mg 6–12 yr: 30 mg Less than 6 yr: 15 mg
	Oral SR	q 12 h	12 yr and older: 120 mg Less than 12 yr: Not recommended
	Oral CR	q 24 h	12 yr and older: 240 mg Less than 12 yr: Not recommended
Naphazoline [Privine]	Drops	q 6 or more h	12 yr and older: 1 or 2 drops (0.05%) Less than 12 yr: Not recommended
	Spray	q 6 or more h	12 yr and older: 1 or 2 sprays (0.05%) Less than 12 yr: Not recommended
Oxymetazoline [Afrin 12-Hour, Neo-Synephrine 12-Hour, Dristan 12-Hour, others]	Spray	q 10–12 h	6 yr and older: 2–3 sprays (0.05%) Less than 6 yr: Not recommended
Tetrahydrozoline [Tyzine]	Drops	q 3 or more h	6 yr and older: 2–4 drops (0.1%) 2–6 yr: 2–3 drops (0.05%)
	Spray	q 3 or more h	6 yr and older: 3–4 sprays (0.1%) Less than 6 yr: Not recommended
Xylometazoline [Otrivin]	Drops	q 8–10 h	12 yr and older: 2–3 drops (0.1%) 2–12 yr: 2–3 drops (0.05%)
	Spray	q 8–10 h	12 yr and older: 1–3 sprays (0.1%) 2–12 yr: 1 spray (0.05%)

CR = controlled release, SR = sustained release.

*For drops and sprays, dosage listed is applied to *each* nostril; numbers in parentheses indicate concentration of solution employed.

tion, the patient must use progressively larger and more frequent doses. Hence, once established, rebound congestion can lead to a cycle of escalating congestion and increased drug use. The cycle can be broken by abrupt decongestant withdrawal. However, this tactic can be extremely uncomfortable. A less drastic option is to discontinue the drug in one nostril at a time. An even better option is to use an intranasal glucocorticoid (in both nostrils) for 2 to 6 weeks, starting 1 week before discontinuing the decongestant. Development of rebound congestion can be minimized by limiting topical application to 3 to 5 days. Accordingly, topical sympathomimetics are not appropriate for individuals with chronic rhinitis.

Central Nervous System Stimulation. Central nervous system (CNS) excitation is the most common adverse effect of the *oral* sympathomimetics. Symptoms include restlessness, irritability, anxiety, and insomnia. These responses are unlikely with topical agents.

Cardiovascular Effects. By activating α_1 -adrenergic receptors on systemic blood vessels, sympathomimetics can cause widespread vasoconstriction. Generalized vasoconstriction is most likely with *oral* agents. However, if taken in ex-

cess, even the topical agents can cause significant systemic vasoconstriction. For most patients, effects on systemic vessels are inconsequential. However, for individuals with cardiovascular disorders—hypertension, coronary artery disease, cardiac dysrhythmias, cerebrovascular disease—widespread vasoconstriction can be hazardous.

Abuse. Two sympathomimetics—*pseudoephedrine* and *ephedrine*—are associated with abuse. Why? First, by causing CNS stimulation, these sympathomimetics can produce subjective effects similar to those of amphetamine. Second, both drugs can be readily converted to methamphetamine, a widely used drug of abuse. To reduce the availability of these drugs for methamphetamine production, Congress passed the *Combat Methamphetamine Epidemic Act of 2005*, which requires that all products containing ephedrine and pseudoephedrine be placed behind the counter (even though they can still be purchased without a prescription). Furthermore, purchasers must present identification and sign a log. Also, individuals can purchase no more than 9 gm per month or 3.6 gm on any day. Because of these constraints, many products are being reformulated to contain phenylephrine rather than ephedrine

and pseudoephedrine. Unfortunately, when taken orally, phenylephrine is not very effective.

Hemorrhagic Stroke. On November 6, 2000, the Food and Drug Administration (FDA) ordered that *phenylpropanolamine*, an alpha-adrenergic agonist, be removed from the market because it was shown to cause subarachnoid and intracerebral hemorrhage in women (but not in men). Although the risk of stroke is small, the FDA ruled that the risk was not justified by the relatively benign disorders for which phenylpropanolamine was used. (In addition to its use as a nasal decongestant, phenylpropanolamine had been used widely as an over-the-counter weight loss aid.) We do not know if other alpha agonists (eg, phenylephrine, ephedrine, pseudoephedrine) also pose a risk of hemorrhagic stroke.

Factors in Topical Administration

General Considerations. Because of the risk of rebound congestion, topical sympathomimetics should be used for no more than 5 consecutive days. To avoid systemic effects, doses should not exceed those recommended by the manufacturer. The applicator should be cleansed after each use to prevent contamination.

Drops. Drops should be administered with the patient in a lateral, head-low position. This causes the drops to spread slowly over the nasal mucosa, thereby promoting beneficial effects while reducing the amount that is swallowed. Because the number of drops can be precisely controlled, drops allow better control of dosage than do sprays. Accordingly, since young children are particularly susceptible to toxicity, drops are preferred for these patients.

Sprays. Sprays deliver the decongestant in a fine mist. Although convenient, sprays are less effective than an equal volume of properly instilled drops.

Summary of Contrasts Between Oral and Topical Agents

Oral and topical sympathomimetics differ in several important respects: (1) Topical agents act faster than the oral agents and are usually more effective. (2) Oral agents act longer than topical preparations. (3) Systemic effects (vasoconstriction, CNS stimulation) occur primarily with oral agents; topical agents elicit these responses only when dosage is too high. (4) Rebound congestion is common with prolonged use of topical agents, but is rare with oral agents.

Comparison of Phenylephrine, Ephedrine, and Pseudoephedrine

Phenylephrine is one of the most widely used nasal decongestants. The drug is administered topically (by itself) and orally (as a component of combination preparations). When administered topically, phenylephrine is both fast and effective.

When taken orally, the drug is much less effective, in large part because of extensive first-pass metabolism. However, even though absorption is poor, phenylephrine can still cause adverse cardiovascular effects.

Ephedrine and *pseudoephedrine* are only used orally. They are not available for intranasal administration. Ephedrine causes a high incidence of CNS stimulation. With pseudoephedrine, a stereoisomer of ephedrine, CNS stimulation is much lower. Compared with oral phenylephrine, pseudoephedrine is better absorbed and has a longer half-life, and hence is more effective. As noted, although ephedrine and pseudoephedrine are available without a prescription, both drugs are kept behind the counter to reduce diversion to labs that make methamphetamine.

Antihistamine/Sympathomimetic Combinations

Some patients require combined therapy with a sympathomimetic and an antihistamine. Although antihistamines alone are a first-line treatment, they do not relieve nasal congestion, and hence may be inadequate for some patients. For these patients, addition of a sympathomimetic may be indicated. This can be accomplished in two ways: by giving the antihistamine and sympathomimetic separately, or by using a combination product. Some popular antihistamine/sympathomimetic combinations are listed in Table 77-5.

Ipratropium, an Anticholinergic Agent

Ipratropium bromide [Atrovent] is an anticholinergic agent similar to atropine. The drug is indicated for allergic rhinitis, asthma, and the common cold. To treat allergic rhinitis, ipratropium is administered as a nasal spray (0.03% and 0.06%). Blockade of cholinergic receptors inhibits glandular secretions, and thereby decreases rhinorrhea. The drug does not decrease sneezing, nasal congestion, or postnasal drip. At the doses used for allergic rhinitis, side effects are minimal. The most common are nasal drying and irritation. Ipratropium does not readily cross membranes (it's a quaternary ammonium compound), and hence systemic effects are absent. Dosages for allergic rhinitis in patients 12 years and older range from 2 sprays of 0.03% ipratropium (42 mcg total) per nostril 2 to 3 times a day to 2 sprays of 0.06% ipratropium (84 mcg total) per nostril 4 times a day. Use of ipratropium for asthma is discussed in Chapter 76.

Montelukast, a Leukotriene Antagonist

Montelukast [Singulair], originally approved for asthma, is now approved for seasonal and perennial allergic rhinitis as well. Benefits derive from blocking binding of leukotrienes to their receptors. In people with allergic rhinitis, leukotrienes act primarily to cause nasal congestion (by promoting vasodilation and by increasing vascular permeability). Hence, by blocking leukotriene receptors, montelukast relieves nasal congestion, having little impact on sneezing or itching. When used alone or in combination with an antihistamine, montelukast is less effective than intranasal glucocorticoids. Although montelukast is generally well tolerated, it can cause rare but serious neuropsychiatric effects, including agitation, aggression, hallucinations, depression, insomnia, restlessness, and suicidal thinking and behavior. Because of these adverse effects, and because beneficial effects are limited, it's probably best to reserve montelukast for patients who don't respond to or can't tolerate intranasal glucocorticoids, antihistamines, or both. Administration is oral. Dosage, which varies with age, is the same as that used for asthma (see Chapter 76).

TABLE 77-5 ■ Some Antihistamine/Sympathomimetic Combinations

Antihistamine/Sympathomimetic	Trade Name	Dosage
Acrivastine/pseudoephedrine	Semprex-D Capsules	8 mg/60 mg 4 times daily
Chlorpheniramine/pseudoephedrine	Allerest Maximum Strength Tablets	4 mg/60 mg q 4-6 h
Fexofenadine/pseudoephedrine	Allegra-D 12-Hour Tablets	60 mg/120 mg twice daily
Loratadine/pseudoephedrine	Claritin-D 12-Hour Tablets	5 mg/120 mg q 12 h
Desloratadine/pseudoephedrine	Clarinet-D 12-Hour Tablets	2.5 mg/120 mg q 12 h
Triprolidine/pseudoephedrine	Actifed Cold & Allergy Tablets	2.5 mg/60 mg q 4-6 h

Omalizumab

Omalizumab [Xolair] is a monoclonal antibody directed against IgE, an immunoglobulin that plays a central role in the allergic release of inflammatory mediators from mast cells and basophils. In patients with ragweed-induced seasonal allergic rhinitis, omalizumab can greatly decrease nasal symptoms. In one study, patients received a 300-mg subQ dose just prior to ragweed season, followed by additional 300-mg subQ doses every 3 to 4 weeks during the season. The result? Omalizumab decreased serum levels of IgE by 95%, and prevented practically all symptoms of rhinitis. At this time, omalizumab is approved only for asthma (see Chapter 76).

DRUGS FOR COUGH

Cough is a complex reflex involving the CNS, the peripheral nervous system, and the muscles of respiration. The cough reflex can be initiated by irritation of the bronchial mucosa as well as by stimuli arising at sites distant from the respiratory tract. Cough is often beneficial, serving to remove foreign matter and excess secretions from the bronchial tree. Productive cough is characteristic of chronic lung disease (eg, emphysema, asthma, bronchitis) and should not be suppressed. Not all cough, however, is useful; cough frequently serves only to deprive us of comfort or sleep. Under these conditions, antitussive medication is appropriate. The most common use of cough medicines is suppression of nonproductive cough associated with the common cold and other upper respiratory infections.

Antitussives

Antitussives are drugs that suppress cough. Some agents act within the CNS; others act peripherally. The antitussives fall into two major groups: (1) opioid antitussives and (2) nonopioid antitussives. Interestingly, although the major antitussives—codeine, dextromethorphan, and diphenhydramine—are clearly effective against chronic nonproductive cough and experimentally induced cough, there is no good evidence that these drugs can suppress cough associated with the common cold.

Opioid Antitussives

All of the opioid analgesics have the ability to suppress cough. The two opioids used most often for cough suppression are *codeine* and *hydrocodone*. Both drugs act in the CNS to elevate cough threshold. Hydrocodone is somewhat more potent than codeine and carries a greater liability for abuse. The basic pharmacology of the opioids is discussed in Chapter 28.

Codeine. Codeine is the most effective cough suppressant available. The drug is active orally and can decrease both the frequency and intensity of cough. Doses are low, about one-tenth those needed to relieve pain. At these doses, the risk of physical dependence is small.

Like all other opioids, codeine can suppress respiration. Accordingly, the drug should be employed with caution in patients with reduced respiratory reserve. In the event of overdose, respiratory depression may prove fatal. An opioid antagonist (eg, naloxone) should be used to reverse toxicity.

When dispensed by itself, codeine has a significant potential for abuse, and therefore is classified under Schedule II of the Controlled Substances Act. However, the abuse potential of the antitussive mixtures that contain codeine is low. Accordingly, these mixtures are classified under Schedule V.

For treatment of cough, the adult dosage is 10 to 20 mg orally, 4 to 6 times a day. Codeine is rarely recommended for children.

Nonopioid Antitussives

Dextromethorphan. Dextromethorphan is the most effective nonopioid cough medicine, and the most widely used of all cough medicines. Benefits equal those of codeine, except against acute severe cough. Like the opioids, dextromethorphan acts in the CNS. Although dextromethorphan is a derivative of the opioids, it does not produce typical opioid-like euphoria or physical dependence. Nonetheless, when taken in high doses, dextromethorphan can cause euphoria, and is abused for this effect (see Chapter 40). Depending on the dose, subjective effects can range from mild inebriation to a state of mind-body dissociation, much like that caused by phencyclidine (PCP). At therapeutic doses, dextromethorphan does not depress respiration. Adverse effects are mild and rare. Dextromethorphan is the active ingredient in over 140 nonprescription cough medicines. The usual adult dosage is 10 to 30 mg every 4 to 8 hours.

In the past, dextromethorphan was considered devoid of analgesic actions; however, it now appears the drug can reduce pain. The mechanism is blockade of receptors for *N*-methyl-D-aspartate (NMDA) in the brain and spinal cord. In contrast, opioids relieve pain primarily through activation of mu receptors. Although dextromethorphan has minimal analgesic effects when used alone, it can enhance analgesic effects of the opioids. For example, we can double the analgesic response to 30 mg of morphine by combining morphine with 30 mg of dextromethorphan.

Other Nonopioid Antitussives. *Diphenhydramine* is an antihistamine with the ability to suppress cough. The mechanism is unclear. Like other antihistamines, diphenhydramine has sedative and anticholinergic properties. Cough suppression is achieved only at doses that produce prominent sedation. The usual adult dosage is 25 mg every 4 hours.

Benzonatate [Tessalon, Zonatuss] is a structural analog of two local anesthetics: tetracaine and procaine. The drug suppresses cough by decreasing the sensitivity of respiratory tract stretch receptors (components of the cough-reflex pathway). Adverse effects are usually mild (eg, sedation, dizziness, constipation). Nonetheless, severe effects can occur in children and adults. In children under 2 years old, accidental ingestion of just one or two capsules has been fatal. In older children and adults, overdose can cause seizures, dysrhythmia, and death. Smaller doses can cause confusion, chest numbness, visual hallucinations, and a burning sensation in the eyes. If the capsules are sucked or chewed, rather than swallowed, the drug can cause laryngospasm, bronchospasm, and circulatory collapse. Accordingly, benzonatate capsules should be swallowed intact. The usual adult dosage is 100 mg 3 times a day. Safety and efficacy have not been established in children under 10 years old.

Expectorants and Mucolytics

Expectorants. An expectorant is a drug that renders cough more productive by stimulating the flow of respiratory tract secretions. A variety of compounds (eg, terpin hydrate, ammonium chloride, iodide products) have been promoted for their supposed expectorant actions. However, in almost all cases, efficacy is doubtful. One agent—*guaifenesin* [Mucinex, Humbid, others]—may be an exception. However, for this drug to be effective, doses higher than those normally employed may be needed.

Mucolytics. A mucolytic is a drug that reacts directly with mucus to make it more watery. This action should help make cough more productive. Two preparations—*hypertonic saline* and *acetylcysteine* (formerly available as *Mucomyst*)—are employed for their mucolytic actions. Both are administered by inhalation. Unfortunately, both can trigger bronchospasm. Because of its sulfur content, acetylcysteine has the additional drawback of smelling like rotten eggs.

COLD REMEDIES: COMBINATION PREPARATIONS

Basic Considerations

The common cold is an acute *upper* respiratory infection of viral origin. Between 50% and 80% of colds are caused by the human rhinovirus, which can also cause serious infection of the *lower* respiratory tract. Characteristic symptoms of the common cold are rhinorrhea, nasal congestion, cough, sneezing, sore throat, hoarseness, headache, malaise, and myalgia; fever is common in children but rare in adults. Colds are self-limited and usually benign. Persistence or worsening of symp-

toms suggests development of a secondary bacterial infection. In the United States, the economic burden of the cold is estimated at over \$60 billion a year.

There is no cure for the cold, and hence treatment is purely symptomatic. Because colds are caused by viruses, there is no justification for the routine use of antibiotics. These agents are appropriate only if a bacterial co-infection arises. There is no evidence that vitamin C can prevent or cure colds. Benefits of zinc lozenges are unclear (Box 77-1).

Because no single drug can relieve all symptoms of a cold, the pharmaceutical industry has formulated a vast number of cold remedies that contain a mixture of ingredients. These

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BOX 77-1 ■ SPECIAL INTEREST TOPIC

ZINC FOR KIDS WITH COLDS?

In an effort to develop a cure for the common cold, researchers have looked at zinc. Results of 10 studies in adults have been mixed; in 5 studies, zinc reduced symptoms; in 5 others, zinc didn't help. Only one study has been done in children. The result? Zinc had no beneficial effect. However, until more research is done, a final conclusion cannot be drawn.

A theoretical basis for how zinc might work has not been firmly established. The predominant theory suggests that zinc blocks viral binding to cells of the nasal epithelium, and thereby suppresses infection. This theory is based on the observation that zinc can prevent rhinovirus (the most common cause of colds) from binding to epithelial cells grown in culture. However, there is no clear proof that zinc can block the adhesion of other cold viruses (eg, adenoviruses, respiratory syncytial virus, parainfluenza virus). Hence, experimental support for the reduced-adhesion theory is limited. Alternative theories posit that zinc may inhibit viral replication, boost immune function, enhance cytoprotection, or suppress cold-related inflammatory responses.

Having shown that zinc can benefit adults with colds, Dr. Michael Macknin of the Cleveland Clinic wanted to see if zinc would also benefit children. Accordingly, he and his team studied responses in 249 students in grades 1 through 12 from two school districts in the eastern suburbs of Cleveland, Ohio. The objective was to determine if zinc could shorten the duration of cold symptoms (cough, headache, hoarseness, muscle ache, nasal congestion, nasal drainage, scratchy throat, sore throat, sneezing). Treatment was begun within 24 hours of symptom onset and consisted of either placebo (cherry-flavored lozenges) or 10-mg zinc gluconate glycine lozenges (also cherry flavored) administered 5 or 6 times a day. The outcome? The time to resolution of symptoms was unaffected by zinc. Not only did zinc fail to accelerate recovery, it produced annoying side effects: bad taste in the mouth (60% vs. 38% for placebo); nausea (29% vs. 16%); diarrhea (11% vs. 4%), and mouth, tongue, or throat discomfort (37% vs. 24%).

Should we conclude from these results that zinc is unable to benefit children with colds? Not yet. Other interpretations are possible:

- Benefits may be related to zinc in the diet. Zinc is a normal micronutrient. If the children in this study had adequate zinc in their diets, it may be that little or no benefit would be seen

by giving additional zinc. Conversely, if the study had been done in a region where children are zinc deficient, beneficial effects might have been observed.

- The dosage may have been inadequate. In one successful study in adults, the dosage was 23.7 mg given 8 times a day—for a total of 190 mg each day. In the children's study, the daily dosage was only 50 to 60 mg—less than one-third the dosage used in adults. Since the mechanism by which zinc acts is unknown, it is impossible to predict how much is actually needed. Hence, perhaps a higher dosage would have worked.
- The causative viruses may have been insensitive. We know that zinc can block adhesion of *rhinoviruses* to nasal epithelial cells (at least in culture), but may not block adhesion of other cold viruses. If blockade of viral binding really is the mechanism by which zinc acts, treatment would fail if the causative viruses were not sensitive. Since causative agents may be different in different locales or at different times of the year, perhaps the outcome would have been successful if the study had been done in a different place or at a different time.
- The zinc may have been inactivated. In the successful studies done with adults, zinc was formulated in lemon-lime lozenges—not the cherry-flavored lozenges employed in the children's study. It may be that, somehow, the cherry flavoring inactivated the zinc.

At this time, it would be premature to dismiss zinc as a useful medication. More research is needed. Unanswered questions include

- How does zinc work?
- Which cold viruses are sensitive?
- What dosage is most effective?
- What formulation is most effective?
- Are benefits limited to children who are zinc deficient?

When these questions have been answered, we will be able to draw a more firm conclusion about the utility of zinc as a cold remedy for kids.

combination cold remedies should be reserved for patients with multiple symptoms. In addition, the combination chosen should contain only those agents that are appropriate for the symptoms at hand. Patients who require relief from just a single symptom (eg, rhinitis, cough, or headache) are best treated with a single-entity preparation.

Combination cold remedies frequently contain two or more of the following: (1) a nasal decongestant, (2) an antitussive, (3) an analgesic, (4) an antihistamine, and (5) caffeine. The purpose of the first three agents is self-evident. In contrast, the roles of antihistamines and caffeine require explanation. Since histamine has nothing to do with the symptoms of a cold, antihistamines are not present to block histamine receptors. Rather, because of their anticholinergic actions, antihistamines are included to suppress secretion of mucus. Caffeine is added to offset the sedative effects of the antihistamine.

Although they can be convenient, combination cold remedies do have disadvantages. As with all fixed-dose combinations, there is the chance that a dosage (eg, 1 capsule or 1 tablet) that produces therapeutic levels of one ingredient may produce levels of other ingredients that are either excessive or subtherapeutic. In addition, the combination may contain ingredients for which the patient has no need. Furthermore, under FDA regulations, a brand-name product can be reformulated and then sold under the same name. Hence, without carefully reading the label, the consumer has no assurance that the brand-name product purchased this year contains the same amounts of the same drugs that were present in last year's version of that combination product.

Use in Young Children

Many experts believe that over-the-counter (OTC) cold remedies should not be used by young children. Why? Because there is no proof of efficacy or safety in pediatric patients—while there *is* proof of the potential for serious harm. According to the Centers for Disease Control and Prevention, in 2004 and 2005 more than 1500 children under the age of 2 years were taken to emergency departments after receiving cough or cold products. Presenting symptoms included convulsions, tachycardia, hallucinations, and impaired consciousness. Some children died. Accordingly, in early 2008, the FDA recommended that OTC cold remedies no longer be given to children under 2 years of age, owing to the risk of potentially life-threatening events. The FDA is still reviewing the safety of these drugs in children 2 to 11 years old. Nonetheless, in August 2008, manufacturers voluntarily revised the labels of children's cold and cough preparations to indicate they should not be used in children younger than 4 years. In addition, for products that contain an antihistamine, they added a warning against use to sedate children. To minimize harm to pediatric patients, parents should

- Avoid OTC cold remedies in children under 4 years of age.
- Only use products labeled for pediatric use.
- Consult a healthcare professional before giving these drugs to a child.
- Read all product safety information before dosing.
- Use the measuring device provided with the product.
- Discontinue the medicine and seek professional care if the child's condition worsens (or fails to improve).
- Not use antihistamine-containing products to sedate children.

KEY POINTS

- Allergic rhinitis is the most common allergic disorder.
- Allergic rhinitis is treated primarily with intranasal glucocorticoids, oral and intranasal antihistamines, and oral and intranasal sympathomimetic decongestants.
- Intranasal glucocorticoids are the most effective drugs for allergic rhinitis. These first-line agents relieve rhinorrhea, congestion, itching, and sneezing.
- Antihistamines (H_1 receptor antagonists) are first-line drugs for allergic rhinitis. They relieve rhinorrhea, sneezing, and itching, but not congestion.
- Sedation and anticholinergic effects are common side effects of the first-generation antihistamines but not the second-generation antihistamines.
- Sympathomimetic drugs decrease nasal congestion by activating α_1 -adrenergic receptors on blood vessels, which causes vasoconstriction and thereby shrinks swollen nasal membranes.
- *Topical* sympathomimetics decrease nasal congestion rapidly and produce minimal systemic effects, but cause rebound congestion when used for more than a few days.
- *Oral* sympathomimetics decrease nasal congestion slowly and produce CNS and cardiovascular stimulation, but do *not* cause rebound congestion, and hence are suited for long-term use.
- Codeine, a member of the opioid family, is the most effective cough suppressant available. Doses are only one-tenth those used for analgesia.
- Dextromethorphan is the most effective nonopioid cough suppressant.
- There is not good evidence that codeine, dextromethorphan, or any other cough medicine can suppress cough associated with the common cold.
- OTC cough and cold remedies should not be given to children under the age of 4 years.

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Drugs for Peptic Ulcer Disease

Pathogenesis of Peptic Ulcers

- Defensive Factors
- Aggressive Factors
- Summary
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 - Cimetidine
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- Other Antiulcer Drugs
 - Sucralfate
 - Misoprostol
 - Antacids
 - Anticholinergics
 - Combination Packs

Box 78-1. Gastroesophageal Reflux Disease

The term *peptic ulcer disease* (PUD) refers to a group of upper GI disorders characterized by varying degrees of erosion of the gut wall. Severe ulcers can be complicated by hemorrhage and perforation. Although peptic ulcers can develop in any region exposed to acid and pepsin, ulceration is most common in the lesser curvature of the stomach and the duodenum. PUD is a common disorder that affects about 10% of Americans at some time in their lives. About 500,000 Americans get ulcers each year. Prior to the mid-1990s, PUD was considered a chronic, relapsing disorder of unknown cause and with no known cure; therapy promoted healing but did not prevent ulcer recurrence. Today, thanks to the pioneering work of two Australians—Barry J. Marshall and J. Robin Warren—we know that most cases of PUD are caused by in-

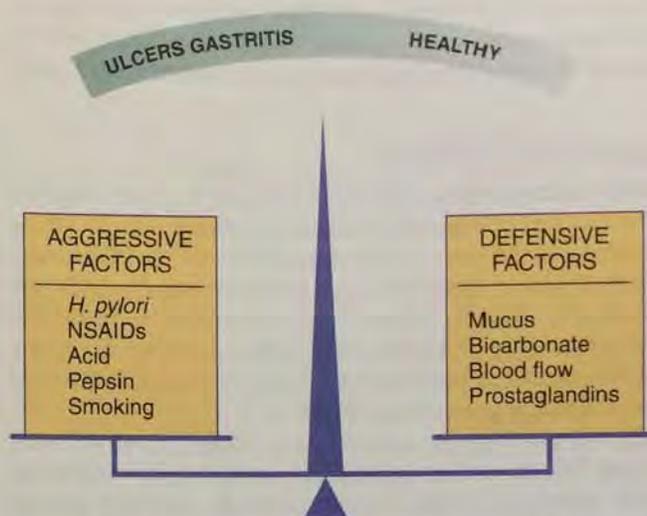


Figure 78-1 ■ The relationship of mucosal defenses and aggressive factors to health and peptic ulcer disease.

When aggressive factors outweigh mucosal defenses, gastritis and peptic ulcers result. (NSAIDs = nonsteroidal anti-inflammatory drugs.)

fection with *Helicobacter pylori*, and that eradication of this bacterium not only promotes healing, but greatly reduces the chance of recurrence.

PATHOGENESIS OF PEPTIC ULCERS

Peptic ulcers develop when there is an imbalance between mucosal defensive factors and aggressive factors (Fig. 78-1). The major defensive factors are mucus and bicarbonate. The major aggressive factors are *H. pylori*, nonsteroidal anti-inflammatory drugs (NSAIDs), gastric acid, and pepsin.

Defensive Factors

Defensive factors serve the physiologic role of protecting the stomach and duodenum from self-digestion. When defenses are intact, ulcers are unlikely. Conversely, when defenses are compromised, aggressive factors are able to cause injury. Two important agents that can weaken defenses are *H. pylori* and NSAIDs.

Mucus. Mucus is secreted continuously by cells of the GI mucosa, forming a barrier that protects underlying cells from attack by acid and pepsin.

Bicarbonate. Bicarbonate is secreted by epithelial cells of the stomach and duodenum. Most bicarbonate remains trapped in the mucus layer, where it serves to neutralize any hydrogen ions that penetrate the mucus. Bicarbonate pro-

duced by the pancreas is secreted into the lumen of the duodenum, where it neutralizes acid delivered from the stomach.

Blood Flow. Sufficient blood flow to cells of the GI mucosa is essential for maintaining mucosal integrity. If submucosal blood flow is reduced, the resultant local ischemia can lead to cell injury, thereby increasing vulnerability to attack by acid and pepsin.

Prostaglandins. Prostaglandins play an important role in maintaining defenses. These compounds stimulate secretion of mucus and bicarbonate, and they promote vasodilation, which helps maintain submucosal blood flow. They provide additional protection by suppressing secretion of gastric acid.

Aggressive Factors

Helicobacter pylori. *Helicobacter pylori* is a gram-negative bacillus that can colonize the stomach and duodenum. By taking up residence in the space between epithelial cells and the mucus barrier that protects these cells, the bacterium manages to escape destruction by acid and pepsin. Once established, *H. pylori* can remain in the GI tract for decades. Although about half of the world's population is infected with *H. pylori*, most infected people never develop symptomatic PUD.

Why do we think *H. pylori* causes PUD? First, between 60% and 75% of patients with PUD have *H. pylori* infection. Second, duodenal ulcers are much more common among people with *H. pylori* infection than among people who are not infected. Third, eradication of the bacterium promotes ulcer healing. And fourth, eradication of the bacterium minimizes ulcer recurrence. (One-year recurrence rates approach 80% when *H. pylori* remains present, compared with only 10% when the organism is gone.)

Although the mechanism by which *H. pylori* promotes ulcers has not been firmly established, likely possibilities are enzymatic degradation of the protective mucus layer, elaboration of a cytotoxin that injures mucosal cells, and infiltration of neutrophils and other inflammatory cells in response to the bacterium's presence. Also, *H. pylori* produces *urease*, an enzyme that forms carbon dioxide and ammonia (from urea in gastric juice); both compounds are potentially toxic to the gastric mucosa.

In addition to its role in PUD, *H. pylori* appears to promote gastric cancer. In fact, the bacterium has been declared a type I carcinogen (a definite cause of human cancer) by the International Agency for Research on Cancer. There is a strong association between *H. pylori* infection and the presence of gastric mucosa-associated lymphoid tissue (MALT) lymphomas. Furthermore, among patients with localized MALT lymphoma, eradicating *H. pylori* produces tumor regression in 60% to 90% of cases. Whether treatment for *H. pylori* reduces the risk of gastric adenocarcinoma is unclear.

Nonsteroidal Anti-inflammatory Drugs. NSAIDs are the underlying cause of many gastric ulcers and some duodenal ulcers. As discussed in Chapter 71, aspirin and other NSAIDs inhibit the biosynthesis of prostaglandins. By doing so, they can decrease submucosal blood flow, suppress secretion of mucus and bicarbonate, and promote secretion of gastric acid. Furthermore, NSAIDs can irritate the mucosa directly. NSAID-induced ulcers are most likely with long-term, high-dose therapy.

Gastric Acid. Gastric acid is an absolute requirement for peptic ulcer generation: In the absence of acid, no ulcer will

form. Acid causes ulcers directly by injuring cells of the GI mucosa and indirectly by activating pepsin, a proteolytic enzyme. In most cases, acid hypersecretion, by itself, is insufficient to cause ulcers. In fact, in most patients with gastric ulcers, acid secretion is normal or reduced, and among patients with duodenal ulcers, only one-third produce excessive amounts of acid. From these observations, we can conclude that, in the majority of patients with peptic ulcers, factors in addition to acid must be involved.

Zollinger-Ellison syndrome is the primary disorder in which hypersecretion of acid alone causes ulcers. The syndrome is caused by a tumor that secretes gastrin, a hormone that stimulates gastric acid production. The amount of acid produced is so large that it overwhelms mucosal defenses. Zollinger-Ellison syndrome is a rare disorder that accounts for only 0.1% of duodenal ulcers.

Pepsin. Pepsin is a proteolytic enzyme present in gastric juice. Like gastric acid, pepsin can injure unprotected cells of the gastric and duodenal mucosa.

Smoking. Smoking delays ulcer healing and increases the risk of recurrence. Possible mechanisms include reduction of the beneficial effects of antiulcer medications, reduced secretion of bicarbonate, and accelerated gastric emptying, which would deliver more acid to the duodenum.

Summary

Infection with *H. pylori* is the most common cause of gastric and duodenal ulcers. However, among people whose PUD can be ascribed to *H. pylori*, additional factors must be involved. Why? Because more than 50% of the population harbors *H. pylori*, but only 10% develop ulcers. Factors that may increase the risk of PUD in people infected with *H. pylori* include smoking, increased acid secretion, and reduced bicarbonate production. The second most common cause of gastric ulcers is NSAIDs. Hypersecretion of acid underlies a few cases of PUD that are not caused by *H. pylori* or NSAIDs.

OVERVIEW OF TREATMENT

Drug Therapy

The goal of drug therapy is to (1) alleviate symptoms, (2) promote healing, (3) prevent complications (hemorrhage, perforation, obstruction), and (4) prevent recurrence. With the exception of antibiotics, the drugs employed do not alter the disease process. Rather, they simply create conditions conducive to healing. Since nonantibiotic therapies do not cure ulcers, the relapse rate following their discontinuation is high. In contrast, the relapse rate following antibiotic therapy is low.

Classes of Antiulcer Drugs

As shown in Table 78-1, the antiulcer drugs fall into five major groups:

- Antibiotics
- Antisecretory agents (proton pump inhibitors, histamine₂ receptor antagonists)
- Mucosal protectants
- Antisecretory agents that enhance mucosal defenses
- Antacids

TABLE 78-1 ■ Classification of Antiulcer Drugs

Class	Drugs	Mechanism of Action
Antibiotics	Amoxicillin [Amoxil] Bismuth [Pepto-Bismol] Clarithromycin [Biaxin] Metronidazole [Flagyl] Tetracycline [Achromycin V] Tinidazole [Tindamax]	Eradicate <i>H. pylori</i>
Antisecretory Agents		
H ₂ receptor antagonists	Cimetidine [Tagamet] Famotidine [Pepcid] Nizatidine [Axid] Ranitidine [Zantac]	Suppress acid secretion by blocking H ₂ receptors on parietal cells
Proton pump inhibitors	Dexlansoprazole [Dexilant] Esomeprazole [Nexium] Lansoprazole [Prevacid] Omeprazole [Prilosec, Zegerid, Losec ♦] Pantoprazole [Protonix, Pantoloc ♦] Rabeprazole [Aciphex, Pariet ♦]	Suppress acid secretion by inhibiting H ⁺ , K ⁺ -ATPase, the enzyme that makes gastric acid
Mucosal Protectant	Sucralfate [Carafate, Sulcrate ♦]	Forms a barrier over the ulcer crater that protects against acid and pepsin
Antisecretory Agent That Enhances Mucosal Defenses	Misoprostol [Cytotec]	Protects against NSAID-induced ulcers by stimulating secretion of mucus and bicarbonate, maintaining submucosal blood flow, and suppressing secretion of gastric acid
Antacids	Aluminum hydroxide Calcium carbonate Magnesium hydroxide	React with gastric acid to form neutral salts

From this classification, we can see that drugs act in three basic ways to promote ulcer healing. Specifically, they can (1) eradicate *H. pylori* (antibiotics do this), (2) reduce gastric acidity (antisecretory agents, misoprostol, and antacids do this), and (3) enhance mucosal defenses (sucralfate and misoprostol do this).

Drug Selection

Helicobacter pylori–Associated Ulcers. In 1997, a National Institutes of Health Consensus Development Conference recommended that all patients with gastric or duodenal ulcers and documented *H. pylori* infection be treated with antibiotics. This recommendation applies to patients with newly diagnosed PUD, recurrent PUD, and PUD in which use of NSAIDs is a contributing factor. To hasten healing and relieve symptoms, an antisecretory agent should be given along with the antibiotics. By eliminating *H. pylori*, antibiotics can cure PUD, and can thereby prevent recurrence. Diagnosis of *H. pylori* infection and specific antibiotic regimens are discussed below under *Antibacterial Drugs*.

NSAID-Induced Ulcers. Prophylaxis. For patients with risk factors for ulcer development (eg, age over 60, history of ulcers, high-dose NSAID therapy), prophylactic therapy is indicated. Proton pump inhibitors (eg, omeprazole) are preferred. Misoprostol is also effective, but can cause diarrhea. Antacids, sucralfate, and histamine₂ receptor blockers are not recommended.

Treatment. NSAID-induced ulcers can be treated with any ulcer medication. However, histamine₂ receptor blockers and proton pump inhibitors are preferred. If possible, the offending NSAID should be discontinued, so as to accelerate healing. If the NSAID cannot be discontinued, a proton pump inhibitor is the best choice to promote healing.

Evaluation

We can evaluate ulcer healing by monitoring for relief of pain and by radiologic or endoscopic examination of the ulcer site. Unfortunately, evaluation is seldom straightforward. Why? Because cessation of pain and disappearance of the ulcer rarely coincide: In most cases, pain subsides prior to complete healing. However, the converse may also be true: Pain may persist even though endoscopic or radiologic examination reveals healing is complete.

Eradication of *H. pylori* can be determined with several methods, including breath tests, serologic tests, stool tests, and microscopic observation of a stained biopsy sample. These methods are discussed below under *Tests for Helicobacter pylori*.

A Note About the Effects of Drugs on Pepsin

Pepsin is a proteolytic enzyme that can contribute to ulcer formation. The enzyme promotes ulcers by breaking down protein in the gut wall.

Like most enzymes, pepsin is sensitive to pH. As pH rises from 1.3 (the usual pH of the stomach) to 2, peptic activity increases by a factor of 4. As pH goes even higher, peptic activity begins to decline. At a pH of 5, peptic

activity drops below baseline rates. When pH exceeds 6 to 7, pepsin undergoes irreversible inactivation.

Because the activity of pepsin is pH dependent, drugs that elevate gastric pH (eg, antacids, histamine₂ antagonists, proton pump inhibitors) can cause peptic activity to increase, thereby enhancing pepsin's destructive effects. For example, treatment that produces a 99% reduction in gastric acidity will cause pH to rise from a base level of 1.3 up to 3.3. At pH 3.3, peptic activity will be significantly increased. To avoid activation of pepsin, drugs that reduce acidity should be administered in doses sufficient to raise gastric pH above 5.

Nondrug Therapy

Optimal antiulcer therapy requires implementation of nondrug measures in addition to drug therapy.

Diet. Despite commonly held beliefs, diet plays a minor role in ulcer management. The traditional "ulcer diet," consisting of bland foods together with milk or cream, does not accelerate healing. Furthermore, there is no convincing evidence that caffeine-containing beverages (coffee, tea, colas) promote ulcer formation or interfere with recovery. A change in *eating pattern* may be beneficial: Consumption of five or six small meals a day, rather than three larger ones, can reduce fluctuations in intragastric pH, and may thereby facilitate recovery.

Other Nondrug Measures. *Smoking* is associated with an increased incidence of ulcers and also retards recovery. Accordingly, cigarettes should be avoided. Because of their ulcerogenic actions, *aspirin and other NSAIDs* should be avoided by patients with PUD. The exception to this rule is use of aspirin to prevent cardiovascular disease; in the low doses employed, aspirin is only a small factor in PUD. There are no hard data indicating that *alcohol* contributes to PUD. However, if the patient notes a temporal relationship between alcohol consumption and exacerbation of symptoms, then alcohol use should stop. Many people feel that reduction of *stress and anxiety* may encourage ulcer healing; however, there is no good evidence that this is true.

ANTIBACTERIAL DRUGS

Antibacterial drugs should be given to all patients with gastric or duodenal ulcers and confirmed infection with *H. pylori*. Antibiotics are not recommended for asymptomatic individuals who test positive for *H. pylori*.

Tests for *Helicobacter pylori*

Several tests for *H. pylori* are available. Some are invasive; some are not. The invasive tests require an endoscopically obtained biopsy sample, which can be evaluated in three ways: (1) staining and viewing under a microscope to see if *H. pylori* is present; (2) assaying for the presence of urease (a marker enzyme for *H. pylori*); and (3) culturing and then assaying for the presence of *H. pylori*.

In the United States, three types of noninvasive tests are available: breath, serologic, and stool tests. In the breath test, patients are given radiolabeled urea. If *H. pylori* is present, the urea is converted to carbon dioxide and ammonia; radiolabeled carbon dioxide can then be detected in the breath. In the serologic test, blood samples are evaluated for antibodies to *H. pylori*. In the stool test, fecal samples are evaluated for the presence of *H. pylori* antigens.

Antibiotics Employed

The antibiotics employed most often are clarithromycin, amoxicillin, bismuth, metronidazole, and tetracycline. None is effective alone. Furthermore, if these drugs are used alone, the risk of developing resistance is increased.

Clarithromycin. Clarithromycin [Biaxin] suppresses growth of *H. pylori* by inhibiting protein synthesis. In the absence of resistance, treatment is highly effective. Unfortunately, the rate of resistance is rising, exceeding 20% in some areas. The most common side effects are nausea, diarrhea, and distortion of taste. The basic pharmacology of clarithromycin is presented in Chapter 86.

Amoxicillin. *Helicobacter pylori* is highly sensitive to amoxicillin. The rate of resistance is low, only about 3%. Amoxicillin kills bacteria by disrupting the cell wall. Antibacterial activity is highest at neutral pH, and hence can be enhanced by reducing gastric acidity with an antisecretory agent (eg, omeprazole). The most common side effect is diarrhea. The basic pharmacology of amoxicillin is discussed in Chapter 84.

Bismuth. Bismuth compounds—bismuth subsalicylate and bismuth subcitrate—act topically to disrupt the cell wall of *H. pylori*, thereby causing lysis and death. Bismuth may also inhibit urease activity and may prevent *H. pylori* from adhering to the gastric surface.

Bismuth can impart a harmless black coloration to the tongue and stool. Patients should be forewarned. Stool discoloration may confound interpretation of gastric bleeding. Long-term therapy may carry a risk of neurologic injury.

Tetracycline. Tetracycline, an inhibitor of bacterial protein synthesis, is highly active against *H. pylori*. Resistance is rare (less than 1%). Because tetracycline can stain developing teeth, it should not be used by pregnant women or young children. The pharmacology of tetracycline is discussed in Chapter 86.

Metronidazole. Metronidazole [Flagyl] is very effective against sensitive strains of *H. pylori*. Unfortunately, over 40% of strains are now resistant. The most common side effects are nausea and headache. A disulfiram-like reaction can occur if metronidazole is used with alcohol, and hence alcohol must be avoided. Metronidazole should not be taken during pregnancy. The basic pharmacology of metronidazole is discussed in Chapter 99.

Tinidazole. Tinidazole [Tindamax] is very similar to metronidazole, and shares that drug's adverse effects and interactions. Like metronidazole, tinidazole can cause a disulfiram-like reaction, and hence must not be combined with alcohol. The basic pharmacology of tinidazole is discussed in Chapter 99.

Antibiotic Regimens

In 2007, the American College of Gastroenterology (ACG) issued updated guidelines for managing *H. pylori* infection. To minimize emergence of resistance, the guidelines recommend using at least two antibiotics, and preferably three. An antisecretory agent—proton pump inhibitor (PPI) or histamine₂ receptor antagonist (H₂RA)—should be included as well. Eradication rates are good with a 10-day course, and slightly better with a 14-day course.

Table 78-2 presents four ACG-recommended regimens. In regions where resistance to clarithromycin is low (below

TABLE 78-2 ■ First-Line Regimens for Eradicating *H. pylori*

Drugs	Duration (days)	Eradication Rate (%)	Comments
Clarithromycin-Based Triple Therapy 1			
Standard-dose PPI*	10–14	70–85	Consider in non-penicillin-allergic patients who have not previously received clarithromycin or another macrolide
Clarithromycin (500 mg twice daily)			
Amoxicillin (1 gm twice daily)			
Clarithromycin-Based Triple Therapy 2			
Standard-dose PPI*	10–14	70–85	Consider in penicillin-allergic patients who have not previously received a macrolide or are unable to tolerate bismuth quadruple therapy
Clarithromycin (500 mg twice daily)			
Metronidazole (500 mg twice daily)			
Bismuth-Based Quadruple Therapy			
Bismuth subsalicylate (525 mg 4 times daily)	10–14	75–90	Consider in penicillin-allergic patients, and in patients with clarithromycin-resistant <i>H. pylori</i>
Metronidazole (250 mg 4 times daily)			
Tetracycline (500 mg 4 times daily)			
Standard-dose PPI* or ranitidine (150 mg twice daily)			
Sequential Therapy			
Standard-dose PPI* + amoxicillin (1 gm twice daily) for 5 days, followed by:	10	Over 90	Efficacy in North America requires validation
Standard-dose PPI* + clarithromycin (500 mg once daily) + tinidazole (500 mg twice daily) for 5 days			

*Standard doses for PPIs are as follows: dexlansoprazole, 30 to 60 mg once daily; esomeprazole, 40 mg once daily; lansoprazole, 30 mg twice daily; omeprazole, 40 mg twice daily; pantoprazole, 40 mg twice daily; and rabeprazole 20 mg twice daily. Adapted from Chey WD, Wong BCY, and Practice Parameters Committee of the American College of Gastroenterology: American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 102:1808–1825, 2007.

20%), the preferred treatment is *clarithromycin-based triple therapy*, consisting of clarithromycin plus amoxicillin plus a PPI. For patients with penicillin allergy, metronidazole can be substituted for amoxicillin. In regions where resistance to clarithromycin is high (above 20%), the preferred regimen is *bismuth-based quadruple therapy*, consisting of bismuth subsalicylate plus metronidazole plus tetracycline, all three combined with a PPI or an H₂RA. For patients who can't use triple therapy or quadruple therapy, *sequential therapy* is an option. This regimen consists of taking a PPI plus amoxicillin for 5 days, followed by a PPI plus clarithromycin plus tinidazole for 5 days. At this time, the efficacy of sequential therapy in North America has not been established.

For several reasons, compliance with antibiotic therapy can be difficult. First, antibiotic regimens are complex, requiring the patient to ingest as many as 12 pills a day. Second, side effects—especially nausea and diarrhea—are common. Third, a course of treatment is somewhat expensive (about \$200). However, it costs much less to eradicate *H. pylori* with antibiotics than it does to treat ulcers over and over again with traditional antiulcer drugs, which merely promote healing without eliminating the cause.

HISTAMINE₂ RECEPTOR ANTAGONISTS

The histamine₂ receptor antagonists (H₂RAs) are effective drugs for treating gastric and duodenal ulcers. These agents promote ulcer healing by suppressing secretion of gastric acid. Four H₂RAs are available: cimetidine, ranitidine, famotidine, and nizatidine. All four are equally effective. Serious side effects are uncommon.

Cimetidine

Cimetidine [Tagamet], introduced in 1977, was the first H₂RA available and will serve as our prototype for the group. At one time, cimetidine was the most frequently prescribed drug in the United States. Cimetidine was the first drug with sales over \$1 billion, making it our first “blockbuster” drug.

Mechanism of Action

As discussed in Chapter 70, histamine acts through two types of receptors, named H₁ and H₂. Activation of H₁ receptors produces symptoms of allergy. Activation of H₂ receptors, which are located on parietal cells of the stomach (Fig. 78–2), promotes secretion of gastric acid. By blocking H₂ receptors, cimetidine reduces both the volume of gastric juice and its hydrogen ion concentration. Cimetidine suppresses basal acid secretion and secretion stimulated by gastrin and acetylcholine. Because cimetidine produces selective blockade of H₂ receptors, the drug cannot suppress symptoms of allergy.

Pharmacokinetics

Cimetidine may be used orally, IM, or IV. Comparable blood levels are achieved with all three routes. When the drug is taken orally, food decreases the rate of absorption but not the extent. Hence, if cimetidine is taken with meals, absorption will be slowed and beneficial effects prolonged. Cimetidine crosses the blood-brain barrier—albeit with difficulty—and central nervous system (CNS) side effects can occur. Although some hepatic metabolism takes place, most of each dose is eliminated intact in the urine. The half-life is relatively short (about 2 hours), but increases in patients with renal impairment. Accordingly, dosage should be reduced in these patients.

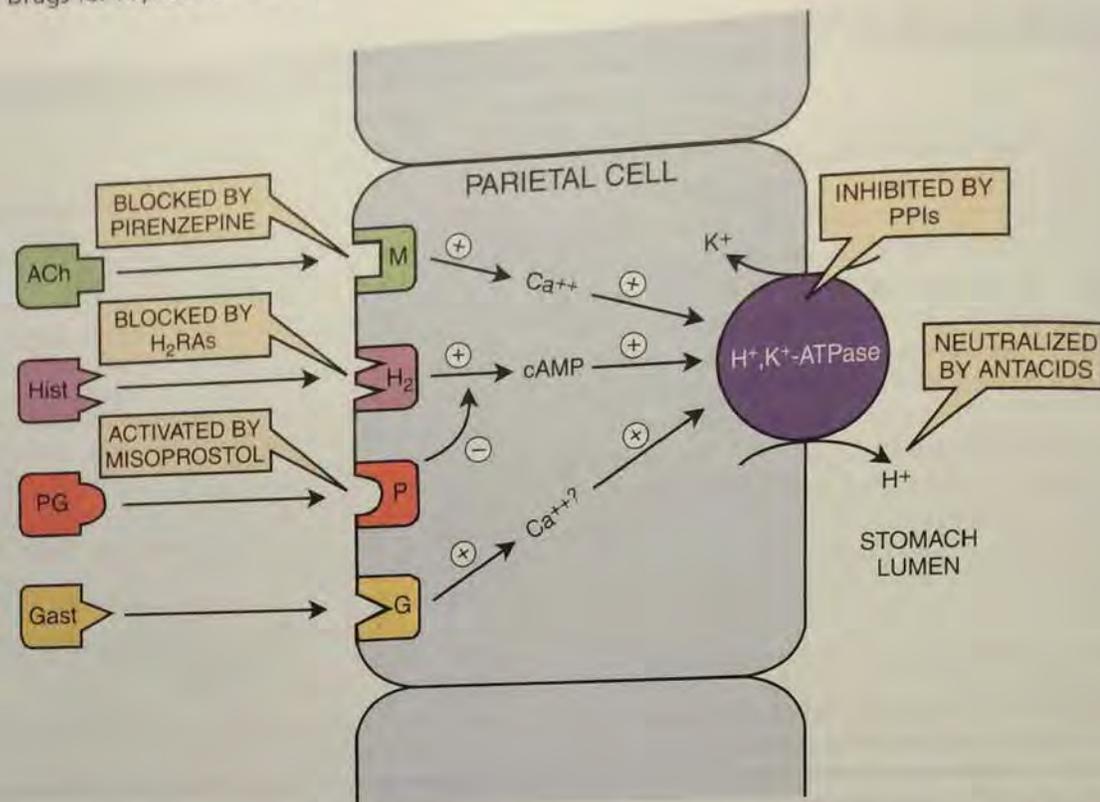


Figure 78-2 ■ A model of the regulation of gastric acid secretion showing the actions of antisecretory drugs and antacids.

Production of gastric acid is stimulated by three endogenous compounds: (1) acetylcholine (ACh) acting at muscarinic (M) receptors; (2) histamine (Hist) acting at histamine₂ (H₂) receptors; and (3) gastrin (Gast) acting at gastrin (G) receptors. As indicated, all three compounds act through intracellular messengers—either calcium (Ca⁺⁺) or cyclic AMP (cAMP)—to increase the activity of H⁺,K⁺-ATPase, the enzyme that actually produces gastric acid. Prostaglandins (PG) decrease acid production, perhaps by suppressing production of intracellular cAMP. The actions of histamine₂ receptor antagonists (H₂RAs), proton pump inhibitors (PPIs), and other drugs are indicated. (P = prostaglandin receptor.)

Therapeutic Uses

Gastric and Duodenal Ulcers. Cimetidine promotes healing of gastric and duodenal ulcers. To heal duodenal ulcers, 4 to 6 weeks of therapy are generally required. To heal gastric ulcers, 8 to 12 weeks may be needed. Long-term therapy with low doses may be given as prophylaxis against recurrence of gastric and duodenal ulcers.

Gastroesophageal Reflux Disease (GERD). Reflux esophagitis is an inflammatory condition caused by reflux of gastric contents back into the esophagus. Cimetidine is a drug of choice for relieving symptoms. However, cimetidine does little to hasten healing.

Zollinger-Ellison Syndrome. This syndrome is characterized by hypersecretion of gastric acid and development of peptic ulcers. The underlying cause is secretion of gastrin from a gastrin-producing tumor. Cimetidine can promote healing of ulcers in patients with Zollinger-Ellison syndrome, but only if high doses are employed. At these doses, significant adverse effects can occur.

Aspiration Pneumonitis. Anesthesia suppresses the glottal reflex, permitting aspiration of gastric acid. When acid is aspirated, pulmonary injury develops within seconds and can be fatal. Surgical patients at high risk for this disorder include obese patients and women undergoing obstetric procedures. Cimetidine is a drug of choice for preventing aspiration pneumonitis. Gastric acidity can be reduced sub-

stantially by administering cimetidine 60 to 90 minutes prior to anesthesia.

Heartburn, Acid Indigestion, and Sour Stomach. Cimetidine is available over the counter to treat these common acid-related symptoms.

Adverse Effects

The incidence of side effects is low, and those that do occur are usually benign.

Antiandrogenic Effects. Cimetidine binds to androgen receptors, producing receptor blockade. As a result, the drug can cause gynecomastia, reduced libido, and impotence—all of which reverse when dosing stops.

CNS Effects. Effects on the CNS are most likely in elderly patients who have renal or hepatic impairment. Possible reactions include confusion, hallucinations, CNS depression (lethargy, somnolence), and CNS excitation (restlessness, seizures).

Pneumonia. Elevation of gastric pH with an antisecretory agent increases the risk of pneumonia. Why? Because, when gastric acidity is reduced, bacterial colonization of the stomach increases, resulting in a secondary increase in colonization of the respiratory tract. Among people using an H₂RA, the relative risk of acquiring pneumonia is doubled. However, the absolute risk is still low (about 1 extra case for every 500 people using the drug).

Other Adverse Effects. When administered by IV bolus, cimetidine can cause hypotension and dysrhythmias. These reactions are rare and do not occur with oral therapy. By reducing gastric acidity, cimetidine may permit growth of *Candida* in the stomach. Hematologic effects (neutropenia, leukopenia, thrombocytopenia) occur rarely. Minor side effects include headache, dizziness, myalgia, nausea, diarrhea, constipation, rash, and pruritus.

Drug Interactions

Interactions Related to Inhibition of Drug Metabolism. Cimetidine inhibits hepatic drug-metabolizing enzymes, and hence can cause levels of many other drugs to rise. Drugs of particular concern are *warfarin*, *phenytoin*, *theophylline*, and *lidocaine*, all of which have a narrow margin of safety. If these drugs are used with cimetidine, their dosages should be reduced.

Antacids. Antacids can decrease absorption of cimetidine. Accordingly, cimetidine and antacids should be administered at least 1 hour apart.

Preparations, Dosage, and Administration

Oral. Cimetidine [Tagamet, Tagamet HB 200] is available in tablets (200, 300, 400, and 800 mg) and an oral solution (300 mg/5 mL). For treatment of duodenal and gastric ulcers, dosing may be done once daily (800 mg at bedtime), twice daily (400 mg each dose), or 4 times a day (300 mg with meals and at bedtime). In patients with renal impairment, dosage should be lowered to 300 mg every 12 hours. For prophylaxis against ulcer recurrence, a single 400-mg dose at bedtime may be employed. Patients with Zollinger-Ellison syndrome require high doses, but not more than 2.4 gm/day.

Parenteral. Parenteral cimetidine is reserved for patients with hypersecretory conditions (eg, Zollinger-Ellison syndrome) and ulcers that have failed to respond to oral therapy. The usual dosage (IM or IV) is 300 mg every 6 to 8 hours. Intramuscular injections are made with a concentrated solution (300 mg/2 mL). For IV administration, two concentrations may be employed: (1) 300 mg may be diluted in 20 mL of 0.9% sodium chloride and injected slowly (over 2 minutes), or (2) 300 mg may be diluted in 100 mL of 0.9% sodium chloride and infused over 15 minutes.

Ranitidine

Ranitidine [Zantac, Zantac EFFERdose] shares many of the properties of cimetidine. However, although similar to cimetidine, the drug differs in three important respects: ranitidine is more potent, produces fewer adverse effects, and causes fewer drug interactions.

Actions. Like cimetidine, ranitidine suppresses secretion of gastric acid by blocking H_2 receptors on gastric parietal cells. It does not block H_1 receptors, and hence does not reduce symptoms of allergy.

Pharmacokinetics. Ranitidine can be administered PO, IM, or IV. Oral bioavailability is about 50%. In contrast to cimetidine, ranitidine is absorbed at the same rate in the presence or absence of food. Ranitidine's ability to enter the CNS is even less than that of cimetidine. Elimination is by hepatic metabolism and renal excretion. Accumulation will occur in patients with renal impairment unless the dosage is reduced. The half-life is 2 to 3 hours.

Adverse Effects. Significant side effects are uncommon. Because ranitidine penetrates the blood-brain barrier poorly, CNS effects are rare. In contrast to cimetidine, ranitidine does not bind to androgen receptors, and hence does not cause antiandrogenic effects (eg, gynecomastia, impotence). Elevation of gastric pH may increase the risk of pneumonia.

Drug Interactions. Ranitidine has few drug interactions. In contrast to cimetidine, ranitidine is a weak inhibitor of hepatic drug-metabolizing enzymes, and therefore does not greatly depress metabolism of other drugs. Antacids have a small effect on ranitidine absorption.

Therapeutic Uses. Ranitidine has the same indications as cimetidine: (1) short-term treatment of gastric and duodenal ulcers, (2) prophylaxis of recurrent duodenal ulcers, (3) treatment of Zollinger-Ellison syndrome and other hypersecretory states, and (4) treatment of GERD. Because it produces fewer side effects than cimetidine, and because of its greater potency, ranitidine is preferred to cimetidine for treating hypersecretory states (eg, Zollinger-Ellison syndrome).

Preparations, Dosage, and Administration. **Preparations.** Ranitidine [Zantac, Zantac EFFERdose] is available in standard tablets (75, 150, and 300 mg), effervescent tablets (25 and 150 mg), capsules (150 and 300 mg), and a syrup (15 mg/mL) for oral use, and in solution (1 and 25 mg/mL) for parenteral use.

Oral Dosage. The usual adult dosage for gastric or duodenal ulcers is 150 mg twice a day. (Note that this dosage is considerably lower than that for cimetidine.) Alternatively, a 300-mg dose can be given once daily at bedtime. For patients with Zollinger-Ellison syndrome, higher doses may be required. The dosage for preventing recurrence of duodenal ulcers is 150 mg once daily at bedtime. Ranitidine can be administered without regard to meals.

Parenteral Dosage. The usual parenteral dosage (IM or IV) is 50 mg every 6 to 8 hours. Intramuscular doses can be injected without dilution. For IV injection, the preparation should be diluted to a volume of 20 mL in 0.9% sodium chloride injection and administered slowly (over 5 or more minutes). For IV infusion, the drug should be diluted in 100 mL of 0.9% sodium chloride injection and administered over 15 to 20 minutes.

Famotidine

Basic and Clinical Pharmacology. Famotidine [Pepcid, Pepcid AC, Pepcid RPD] is much like ranitidine. The drug is approved for treatment and prevention of duodenal ulcers, and treatment of gastric ulcers, GERD, and hypersecretory states (eg, Zollinger-Ellison syndrome). An over-the-counter formulation is approved for heartburn, acid indigestion, and sour stomach. Like ranitidine, famotidine does not bind to androgen receptors, and hence does not have antiandrogenic effects. Elevation of gastric pH may increase the risk of pneumonia. Famotidine does not inhibit hepatic drug-metabolizing enzymes, and hence does not suppress the metabolism of other drugs.

Preparations, Dosage, and Administration. Prescription-strength famotidine [Pepcid, Pepcid RPD] is available in standard tablets (20 and 40 mg), orally disintegrating tablets (20 and 40 mg), powder for oral suspension (40 mg/5 mL when reconstituted), and solution (0.4 and 10 mg/mL) for IV use. For treatment of duodenal and gastric ulcers, the dosage is 20 mg twice daily or 40 mg once daily at bedtime. To prevent recurrence of duodenal ulcers, the dosage is 20 mg once daily at bedtime. For treatment of GERD, the dosage is 20 to 40 mg twice daily. For treatment of hypersecretory states, the initial dosage is 20 mg every 6 hours; severe cases may require up to 160 mg every 6 hours. All doses should be reduced in patients with moderate to severe renal impairment.

Over-the-counter famotidine is available in 20-mg standard tablets marked as *Pepcid AC Maximum Strength*, and in three 10-mg formulations—standard tablets, chewable tablets, and gelscaps—marketed as *Pepcid AC*. Indications are prevention and relief of heartburn, acid indigestion, and sour stomach. To prevent symptoms, the drug is taken 1 hour before eating. The dosage for prevention or relief is 10 mg, taken with a glass of water. As with prescription-strength famotidine, dosages should be reduced in patients with moderate to severe renal impairment.

Nizatidine

Basic and Clinical Pharmacology. Nizatidine [Axid, Axid AR] is much like ranitidine and famotidine. The drug is used to treat and prevent duodenal ulcers and to treat gastric ulcers, GERD, heartburn, acid indigestion, and sour stomach. Like ranitidine and famotidine, nizatidine does not have antiandrogenic effects and does not inhibit the metabolism of other drugs. Elevation of gastric pH may increase the risk of pneumonia.

Preparations, Dosage, and Administration. Prescription-strength nizatidine is available in capsules (150 and 300 mg) and in an oral solution (15 mg/mL). The dosage for treatment of active gastric and duodenal ulcers is 150 mg twice daily or 300 mg once daily at bedtime. To prevent recurrence of duodenal ulcers, the dosage is 150 mg once daily at bedtime. For treatment of GERD, the dosage is 150 mg twice daily.

Over-the-counter nizatidine [Axid AR] is available in 75-mg capsules. The dosage for preventing heartburn is 75 mg, taken any time in the 30-minute interval preceding a meal.

PROTON PUMP INHIBITORS

The PPIs are the most effective drugs we have for suppressing gastric acid secretion. Indications include gastric and duodenal ulcers and GERD. Similarities among the PPIs are more profound than the differences. Hence, selecting among them is based largely on cost and prescriber preference. In 2009, the PPIs were the third most widely prescribed class of drugs in the United States. Over 110 million prescriptions were written, leading to \$13.6 billion in sales.

Although PPIs are generally well tolerated, they *can* increase the risk of serious adverse events, including fractures, pneumonia, acid rebound, and, possibly, intestinal infection with *Clostridium difficile*. To ensure that the benefits of treatment outweigh the risks, treatment should be limited to appropriate candidates, who should take the lowest dose needed for the shortest time possible.

Omeprazole

Omeprazole [Prilosec, Prilosec OTC, Zegerid, Zegerid OTC, Losec[®]] was the first PPI available and will serve as our prototype for the group. Acid suppression is greater than with the H₂RAs. Side effects from short-term therapy are minimal.

Mechanism of Action. Omeprazole is a prodrug that undergoes conversion to its active form within parietal cells of the stomach. The active form then causes irreversible inhibition of H⁺.K⁺-ATPase (proton pump), the enzyme that generates gastric acid (see Fig. 78-2). Because it blocks the final common pathway of gastric acid production, omeprazole can inhibit basal and stimulated acid release. A single 30-mg oral dose reduces acid production by 97% within 2 hours. Because inhibition of the ATPase is not reversible, effects persist until new enzyme is synthesized. Partial recovery occurs 3 to 5 days after stopping treatment. Full recovery may take weeks.

Pharmacokinetics. After oral dosing, about 50% of the drug reaches the systemic circulation. Omeprazole undergoes hepatic metabolism followed by renal excretion. The plasma half-life is short—about 1 hour. However, because omeprazole acts by irreversible enzyme inhibition, effects persist long after the drug has left the body.

Omeprazole is acid labile, and hence must be protected from stomach acid. To accomplish this, the drug is formulated in a capsule that contains protective enteric-coated granules. The capsule dissolves in the stomach, but the granules remain intact until they reach the relatively alkaline environment of the duodenum.

Therapeutic Use. Omeprazole is approved for short-term therapy of duodenal ulcers, gastric ulcers, erosive esophagitis, and GERD, and for long-term therapy of hypersecretory conditions (eg, Zollinger-Ellison syndrome). Except for therapy of hypersecretory states, treatment should be limited to 4 to 8 weeks.

In hospitals, omeprazole and other PPIs are widely used to prevent stress ulcers. However, about two-thirds of patients who receive PPIs don't really need them. Ulcer prophylaxis is indicated only for patients in intensive care units, and then only if they have an additional risk factor, such as multiple trauma, spinal cord injury, or prolonged mechanical ventilation (more than 48 hours). General medical and surgical patients are at low risk for stress ulcers, and should not receive PPIs for prophylaxis.

How does omeprazole compare with H₂RAs? Omeprazole and other PPIs reduce 24-hour acid secretion by 90%, compared with 65% for H₂RAs. Also, PPIs act faster than H₂RAs to reduce gastric acidity and relieve ulcer symptoms. Patients who fail to respond to H₂RAs can often benefit from a PPI.

Use of omeprazole and other PPIs for GERD is discussed in Box 78-1.

Adverse Effects. Minor Effects. Effects seen with short-term therapy are generally inconsequential. Like the H₂RAs, omeprazole can cause headache, diarrhea, nausea, and vomiting. The incidence of these effects is less than 1%.

Pneumonia. Omeprazole and other PPIs increase the risk of community-acquired and hospital-acquired pneumonia. Possible causes include alteration of upper GI flora (owing to reduced gastric acidity) and impairment of white blood cell function. Of note, the time frame for increased risk is limited to the first few days of PPI use. After that, risk is no higher than in nonusers.

Fractures. Long-term therapy, especially in high doses, increases the risk of osteoporosis and fractures. How? By reducing acid secretion, omeprazole may decrease absorption of calcium, and may thereby promote osteoporosis. However, the risk appears to be low. For example, only 1 extra hip fracture would be expected for each 1200 patients. To minimize fracture risk, treatment should use the lowest dose needed for the shortest duration possible. Also, patients should be encouraged to maintain adequate intake of calcium and vitamin D.

Rebound Acid Hypersecretion. When patients stop taking PPIs, they often experience dyspepsia brought on by rebound hypersecretion of gastric acid. Acid rebound can be minimized by using PPIs in the lowest effective dose for the shortest time needed, and by tapering the dose when stopping treatment. Dyspepsia can be managed with an antacid, and perhaps with an H₂RA. Acid rebound can persist for several months after the PPI is discontinued.

Hypomagnesemia. With long-term use, PPIs can lower magnesium levels, perhaps by reducing intestinal magnesium absorption. In severe cases, serum magnesium may drop below 1 mg/dL. (The normal range is 1.8 to 2.3 mg/dL.) Symptoms include tremors, muscle cramps, seizures, and dysrhythmias. The risk of hypomagnesemia is increased by other drugs that lower magnesium, especially thiazide and loop diuretics. Low magnesium can be treated with oral magnesium (eg, SloMag, MagOx). Severe cases may require IV magnesium. If magnesium levels remain low, the patient can be switched to an H₂ blocker. Following PPI withdrawal, magnesium levels usually normalize within 2 weeks. For long-term PPI therapy, consider measuring magnesium at baseline and periodically thereafter.

Clostridium difficile Infection. In retrospective, observational studies, omeprazole and other PPIs have been associated with a dose-related increase in the risk of infection with *C. difficile*, a bacterium that can cause severe diarrhea. However, a causal relationship has not been established. Furthermore, since the spores of *C. difficile* are naturally resistant to acid, it is not clear why decreasing GI acidity would facilitate their growth.

Gastric Cancer. In theory, long-term PPI use may pose a risk of cancer. Gastric carcinoid tumors have developed in rats given omeprazole daily for 2 years. Tumor generation is related to hypersecretion of gastrin, which occurs in response to omeprazole-induced suppression of gastric acidity. Gastrin stimulates hyperplasia of gastric epithelial cells, whose growth may ultimately result in a gastric carcinoid tumor. However, despite this theoretical mechanism for cancer promotion, the FDA has concluded that PPIs do not pose a cancer risk.

BOX 78-1 ■ SPECIAL INTEREST TOPIC

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is a common disorder characterized by heartburn and acid regurgitation. The disease is formally defined by the presence of troublesome symptoms or complications caused by passage of gastric contents into the esophagus. How common is GERD? Among American adults, heartburn develops in 44% at least once a month, in 14% at least once a week, and in up to 7% every day. GERD is also common among children.

GERD is associated with a wide range of symptoms and complications. On the basis of endoscopic examination, patients fall into two major groups; those with *erosive esophagitis* and those with *nonerosive reflux disease* (NERD). Erosive esophagitis is characterized by breaks in the esophageal mucosa. In contrast, mucosal breaks are absent in people with NERD. Less than 50% of patients with GERD have the erosive form. Complications of erosive GERD include difficulty swallowing, painful swallowing, esophageal stricture, ulcers, GI bleeding, anemia, and persistent vomiting. Erosive GERD can also lead to esophageal adenocarcinoma and Barrett's esophagus, a premalignant condition that can evolve into adenocarcinoma.

Why does GERD occur? The primary problem is inappropriate relaxation of the lower esophageal sphincter (LES), a ring of smooth muscle that normally prevents reflux of gastric acid. In people with GERD, the LES undergoes frequent, transient relaxation, thereby allowing pressure in the stomach to force gastric contents up into the esophagus. Other factors that can contribute to GERD include obesity, hiatal hernia, delayed

gastric emptying, and impaired clearance of acid from the esophagus. Of note, *Helicobacter pylori*, the bacterium that causes most gastric and duodenal ulcers, appears to play little or no role in GERD.

We can treat GERD with drugs or with surgery. For most patients, drugs are preferred. As a rule, surgery should be reserved for young, healthy patients who either cannot or will not take drugs chronically. With either drug therapy or surgery, treatment has three goals: relief of symptoms, promotion of healing, and prevention of complications.

For drug therapy, the principal options are proton pump inhibitors (PPIs) and histamine₂ receptor antagonists (H₂RAs). However, since PPIs are much better than H₂RAs at healing esophagitis and maintaining remission, PPIs are considered the clear drugs of choice. For patients with NERD, PPIs may be taken PRN. For patients with erosive GERD, PPIs should be taken continuously until symptoms resolve (typically 4 to 8 weeks). Unfortunately, when PPIs are discontinued, the relapse rate is high, occurring in 80% to 90% of patients within 6 to 12 months. Accordingly, for patients with severe GERD, long-term maintenance therapy is recommended.

Lifestyle changes can complement drug therapy—but should not be substituted for drugs. Measures that may help include smoking cessation, weight loss, avoidance of alcohol and late-night meals, and sleeping with the head elevated. Certain foods—citrus fruits, tomatoes, onions, spicy foods, and carbonated beverages—aggravate symptoms for some patients, and hence should be avoided if they do.

Drug Interactions. By elevating gastric pH, PPIs can significantly reduce absorption of *atazanavir* [Reyataz], *delavirdine* [Rescriptor], and *nelfinavir* [Viracept], all used to treat HIV/AIDS. These drugs should not be combined with a PPI. Reducing gastric pH can also decrease the absorption of two antifungal drugs: *ketoconazole* and *itraconazole*.

Clopidogrel. Omeprazole and other PPIs can reduce the adverse effects of clopidogrel [Plavix], but may also reduce its beneficial effects. Clopidogrel is an antiplatelet drug used to decrease thrombotic events. Unfortunately, by suppressing platelet aggregation, the drug can promote gastric bleeding. To reduce the risk of GI bleeding, clopidogrel is often combined with a PPI. Unfortunately, in addition to protecting against GI bleeding, the PPI may reduce the beneficial effects of clopidogrel. Why? Because PPIs inhibit CYP2C19, the isozyme of cytochrome P450 that converts clopidogrel to its active form. Hence the dilemma: If clopidogrel is used alone, there is a significant risk of GI bleeding; however, if clopidogrel is combined with a PPI, the risk of GI bleeding will be reduced, but antiplatelet effects may be reduced as well. After considering the available evidence, three organizations—the American College of Cardiology, the American Heart Association, and the American College of Gastroenterology—issued a consensus document on the problem. This document, published in November 2010, concludes that, although PPIs may reduce the antiplatelet effects of clopidogrel, there is no

evidence that the reduction is large enough to be clinically relevant. Accordingly, for patients with risk factors for GI bleeding (eg, advanced age, use of NSAIDs or anticoagulants), the benefits of combining a PPI with clopidogrel probably outweigh any risk from reduced antiplatelet effects, and hence combining a PPI with clopidogrel is probably OK. Conversely, for patients who lack risk factors for GI bleeding, combined use of clopidogrel with a PPI may reduce the antiplatelet effects of clopidogrel without offering any real benefit, and hence combining a PPI with clopidogrel in these patients should generally be avoided.

Preparations, Dosage, and Administration. Prescription-strength omeprazole is available in three formulations: (1) delayed-release capsules (10, 20, and 40 mg) marketed as *Prilosec*, (2) a delayed-release suspension (2.5 and 10 mg) marketed as *Prilosec*, and (3) a powder (20 and 40 mg), marketed as *Zegerid*, used to make an immediate-release oral suspension. (The powder contains *sodium bicarbonate*, which elevates gastric pH and thereby protects omeprazole from acid destruction. Each dose contains 460 mg of sodium, making the product unsuitable for people who must restrict sodium intake.) To treat active duodenal ulcer and GERD, the usual dosage is 20 mg once a day, taken before a meal, for 4 to 8 weeks. To treat Zollinger-Ellison syndrome and other hypersecretory states, doses up to 120 mg 3 times a day may be needed.

Like prescription-strength omeprazole, over-the-counter omeprazole is available in two formulations: (1) 20-mg delayed-release tablets, marketed as *Prilosec OTC*, and (2) a powder (20 mg omeprazole plus sodium bicarbonate), marketed as *Zegerid OTC*, used to make an immediate-release oral suspension. These products are indicated for adults with frequent heart-

burn (two or more episodes a week). The dosage is 20 mg once daily for 14 days, taken before the first meal of the day.

Esomeprazole

Esomeprazole [Nexium, Nexium I.V.] is nearly identical to omeprazole [Prilosec]. Structurally, esomeprazole is the *S*-isomer of omeprazole (which is a mixture of *S*- and *R*-isomers). The *S*-isomer (esomeprazole) is metabolized more slowly than the *R*-isomer, and hence esomeprazole achieves higher blood levels than omeprazole, and its effects last somewhat longer. Otherwise the two drugs are essentially the same. The most common adverse effects are headache and diarrhea. In addition, esomeprazole may cause nausea, flatulence, abdominal pain, and dry mouth. Elevation of gastric pH may increase the risk of pneumonia. As with omeprazole, long-term therapy may pose a risk of hypomagnesemia as well as osteoporosis and fractures. Approved indications are erosive esophagitis, GERD, and duodenal ulcers associated with *H. pylori* infection. In addition, the drug may be used for prophylaxis of NSAID-induced ulcers.

For oral therapy, esomeprazole is available in two formulations: (1) delayed-release capsules (20 and 40 mg) and (2) enteric-coated granules (10, 20, and 40 mg) that form a delayed-release suspension when mixed with water (1 tablespoon). To treat erosive gastritis, the usual dosage is 20 or 40 mg once daily, taken at least 1 hour before a meal, for 4 to 8 weeks. To treat GERD, the usual dosage is 20 mg once daily for 4 to 8 weeks. To treat duodenal ulcers associated with *H. pylori*, one ACG-recommended regimen consists of triple therapy—esomeprazole (20 mg twice daily), amoxicillin (1000 mg twice daily), and clarithromycin (500 mg twice daily)—administered for 14 days. The goal is to eradicate *H. pylori*.

For intravenous therapy, esomeprazole is supplied as a powder (20 and 40 mg) to be reconstituted with 0.9% sodium chloride for injection. Intravenous therapy is indicated only for GERD with a history of erosive gastritis. For adults, dosing is done by either injection (over 3 minutes or longer) or infusion (over 10 to 30 minutes). For children, dosing is done by infusion only. For all patients, dosing is done once a day for up to 10 days. For adults, the daily dose is 20 or 40 mg. For children age 1 month to less than 1 year, the daily dose is 0.5 mg/kg. For children age 1 year to 17 years, the daily dose is either 10 mg (for those who weigh less than 55 kg) or 20 mg (for those who weigh 55 kg or greater).

Lansoprazole

Lansoprazole [Prevacid, Prevacid IV, Prevacid 24 HR] is very similar to omeprazole. Both drugs cause prolonged inhibition of H^+K^+ -ATPase. Hence, suppression of acid secretion is sustained. Like omeprazole, lansoprazole is well tolerated. The most common adverse effects are diarrhea, abdominal pain, and nausea. Elevation of gastric pH may increase the risk of pneumonia. Prolonged, high-dose therapy may pose a risk of hypomagnesemia, as well as osteoporosis and fracture.

Lansoprazole may be administered PO or IV. Three oral formulations are available: (1) delayed-release capsules (15 and 30 mg); (2) orally disintegrating, delayed-release tablets (15 and 30 mg); and (3) enteric-coated granules (15 and 30 mg/packet) that form a suspension when mixed with water (2 tablespoons). All three formulations should be taken immediately before a meal. The dosage for duodenal ulcers (prevention and treatment) and GERD is 15 mg once daily. The dosage for erosive gastritis and active gastric ulcers is 30 mg once daily. For hypersecretory states, the initial dosage is 60 mg/day; for severe cases, up to 90 mg twice daily may be needed.

For IV therapy, lansoprazole is available as a powder (30 mg/vial) to be reconstituted with 5 mL of sterile water, and then diluted with 50 mL of either 0.9% sodium chloride injection, lactated Ringer's injection, or 5% dextrose in water. Infusions are done over 30 minutes. An in-line filter *must* be used to trap particulate matter. Dosages are the same as for oral therapy.

Dexlansoprazole

Dexlansoprazole—originally called *Kapidex* and now called *Dexilant*—is simply the *R*-enantiomer of lansoprazole. Although both enantiomers are active, the *R*-enantiomer has a longer duration. Like lansoprazole and all other PPIs, dexlansoprazole reduces gastric acidity by inhibiting gastric H^+K^+ -ATPase. To prolong effects, dexlansoprazole is formulated in dual delayed-release capsules that contain two types of pH-sensitive granules. Following ingestion, some of these granules release lansoprazole when they reach the proximal small intestine, and the remainder release lansoprazole when they reach the distal small intestine. As a result, drug levels first peak 1 to 2 hours after dosing, and then peak again 4 to 5 hours after dosing. In clinical trials, the most common adverse effects were diarrhea, abdominal pain, nausea, vomiting, flatulence, and upper respiratory infection. Long-term therapy may pose a risk of

hypomagnesemia, as well as osteoporosis and fractures. Dexlansoprazole is approved for treatment and maintenance of erosive esophagitis, and for treatment of symptomatic GERD (heartburn). Two strengths are available: 30 mg and 60 mg. The dosage for *treating* erosive esophagitis is 60 mg once daily for up to 8 weeks, and the dosage for *maintenance* is 30 mg once daily for up to 6 months. The usual dosage for treating symptomatic GERD is 30 mg once daily for 4 weeks. Dexlansoprazole capsules may be swallowed whole, or they may be opened and sprinkled onto 1 tablespoon of applesauce, and swallowed immediately. Dosing may be done with or without food.

Rabeprazole

Rabeprazole [Aciphex, Pariet⁺] is much like omeprazole and lansoprazole in actions, uses, and adverse effects. The drug is approved for *H. pylori* eradication, duodenal ulcers, GERD, and hypersecretory states, such as Zollinger-Ellison syndrome. Like other PPIs, rabeprazole suppresses acid secretion by inhibiting H^+K^+ -ATPase in parietal cells. However, in contrast to omeprazole, the drug causes *reversible* inhibition of H^+K^+ -ATPase, and hence its effects are less durable. In addition to suppressing acid secretion, rabeprazole has antibacterial activity. As a result, it may help other antibacterial drugs eradicate *H. pylori*. The most common adverse effects are diarrhea, headache, dizziness, malaise, nausea, and rash. Elevation of gastric pH may increase the risk of pneumonia. Long-term therapy may pose a risk of hypomagnesemia, as well as osteoporosis and fractures. Although rabeprazole is metabolized by cytochrome P450 enzymes, it does not appear to influence the metabolism of other drugs. However, it *can* increase digoxin levels by 20%. Accordingly, levels of digoxin should be monitored. Rabeprazole is available in 20-mg delayed-release, enteric-coated tablets. The dosage for GERD and duodenal ulcers is 20 mg once daily, taken with or without food. The initial dosage for hypersecretory states is 60 mg once daily; for severe cases, 60 mg twice daily may be needed. Although rabeprazole is not approved for treating gastric ulcers, 20 to 40 mg once daily has been effective.

Pantoprazole

Pantoprazole [Protonix, Protonix I.V., Pantoloc⁺] is similar to omeprazole and the other PPIs. The drug is approved for treating GERD and hypersecretory states. Like other PPIs, pantoprazole is well tolerated. Like lansoprazole, pantoprazole may be administered PO or IV. With oral therapy, the most common adverse effects are diarrhea (1.5%), headache (1.3%), and dizziness (0.7%). With IV therapy, the most common adverse effects are diarrhea, headache, nausea, dyspepsia, and injection-site reactions, including thrombophlebitis and abscess. With both routes, elevation of gastric pH may increase the risk of pneumonia. Long-term therapy may pose a risk of hypomagnesemia, as well as osteoporosis and fractures. Pantoprazole does not affect cytochrome P450 enzymes, and hence does not affect the metabolism of other drugs. Pantoprazole is available in three formulations:

- Delayed-release tablets (20 and 40 mg)
- Enteric-coated granules (40 mg) that can be sprinkled on applesauce or mixed with 5 mL of apple juice for oral administration, or mixed with 10 mL of apple juice for administration by nasogastric tube
- Powder (40 mg/vial) to be reconstituted for IV use

Oral doses may be taken with or without food. Infusions are done over 15 minutes, and an in-line filter *must* be used to remove precipitates. The usual dosage, either PO or IV, is 40 mg/day.

OTHER ANTIULCER DRUGS

Sucralfate

Sucralfate [Carafate, Sulcrate⁺] is an effective antiulcer medication notable for minimal side effects and lack of significant drug interactions. The drug promotes ulcer healing by creating a protective barrier against acid and pepsin. Sucralfate has no acid-neutralizing capacity and does not decrease acid secretion.

Mechanism of Antiulcer Action. Sucralfate is a complex substance composed of sulfated sucrose and aluminum hydroxide. Under mildly acidic conditions (pH below 4), sucralfate undergoes polymerization and cross-linking reactions. The resultant product is a viscid and very sticky gel that adheres to the ulcer crater, creating a barrier to back-diffusion

of hydrogen ions, pepsin, and bile salts. Attachment to the ulcer appears to last up to 6 hours.

Pharmacokinetics. Sucralfate is administered orally, and systemic absorption is minimal (3% to 5%). About 90% of each dose is eliminated in the feces.

Therapeutic Uses. Sucralfate is approved for acute therapy and maintenance therapy of duodenal ulcers. Rates of healing are comparable to those achieved with cimetidine. Controlled trials indicate that sucralfate can also promote healing of gastric ulcers.

Adverse Effects. Sucralfate has no known serious adverse effects. The most significant side effect is constipation, which occurs in 2% of patients. Because sucralfate is not absorbed, systemic effects are absent.

Drug Interactions. Interactions with other drugs are minimal. By raising gastric pH above 4, antacids may interfere with sucralfate's effects. This interaction can be minimized by administering these drugs at least 30 minutes apart.

Sucralfate may impede the absorption of some drugs, including phenytoin, theophylline, digoxin, warfarin, and fluoroquinolone antibiotics (eg, ciprofloxacin, norfloxacin). These interactions can be minimized by administering sucralfate at least 2 hours apart from these other drugs.

Preparations, Dosage, and Administration. Sucralfate [Carafate] is available in 1-gm tablets and a suspension (1 gm/10 mL) for oral dosing. Administer on an empty stomach. The recommended adult dosage is 1 gm 4 times a day, taken 1 hour before meals and at bedtime. However, a dosing schedule of 2 gm twice a day appears equally effective. Treatment should continue for 4 to 8 weeks. Sucralfate tablets are large and difficult to swallow, especially by the elderly. The oral suspension is much easier to ingest.

Misoprostol

Therapeutic Use. Misoprostol [Cytotec] is an analog of prostaglandin E₁. In the United States, the drug's only approved GI indication is prevention of gastric ulcers caused by long-term therapy with NSAIDs. In other countries, misoprostol is also used to treat peptic ulcers unrelated to NSAIDs. In addition to its use in PUD, misoprostol is used to promote cervical ripening (see Chapter 64), and, in combination with mifepristone (RU 486), to induce abortion (see Chapter 62).

Mechanism of Action. In normal individuals, prostaglandins help protect the stomach by suppressing secretion of gastric acid, promoting secretion of bicarbonate and cytoprotective mucus, and maintaining submucosal blood flow (by promoting vasodilation). As discussed in Chapter 71, aspirin and other NSAIDs cause gastric ulcers in part by inhibiting prostaglandin biosynthesis. Misoprostol prevents NSAID-induced ulcers by serving as a replacement for endogenous prostaglandins.

Adverse Effects. The most common reactions are dose-related diarrhea (13% to 40%) and abdominal pain (7% to 20%). Some women experience spotting and dysmenorrhea.

Misoprostol is contraindicated during pregnancy. The drug is classified in Food and Drug Administration Pregnancy Risk Category X: the risk of use by pregnant women clearly outweighs any possible benefits. Prostaglandins stimulate uterine contractions. Use during pregnancy has caused partial or complete expulsion of the developing fetus. If women of child-bearing age are to use misoprostol, they must (1) be able to comply with birth control measures, (2) be given oral and written warnings about the dangers of misoprostol, (3) have a

negative serum pregnancy test result within 2 weeks prior to beginning therapy, and (4) begin therapy only on the second or third day of the next normal menstrual cycle.

Preparations, Dosage, and Administration. Misoprostol [Cytotec] is supplied in 100- and 200-mcg tablets for oral administration. The usual dosage is 200 mcg 4 times a day administered with meals and at bedtime. Patients who cannot tolerate this dosage may try 100 mcg 4 times a day.

Antacids

Antacids are alkaline compounds that neutralize stomach acid. Their principal indications are PUD and GERD.

Beneficial Actions

Antacids react with gastric acid to produce neutral salts or salts of low acidity. By neutralizing acid, these drugs decrease destruction of the gut wall. In addition, if treatment raises gastric pH above 5, these drugs will reduce pepsin activity as well. Antacids may also enhance mucosal protection by stimulating production of prostaglandins. These drugs do not coat the ulcer crater to protect it from acid and pepsin. With the exception of sodium bicarbonate, antacids are poorly absorbed, and therefore do not alter systemic pH.

Therapeutic Uses

Peptic Ulcer Disease. The primary indication for antacids is PUD. Rates of healing are equivalent to those achieved with H₂RAs. In the past, antacids were the mainstay of antiulcer therapy. However, these drugs have been largely replaced by newer options (H₂RAs, PPIs, sucralfate) that are equally effective and more convenient to administer, and cause fewer side effects.

Other Uses. Antacids are administered prior to anesthesia to prevent aspiration pneumonitis. In addition, they can provide prophylaxis against stress-induced ulcers. For patients with GERD, antacids can produce symptomatic relief, but they do not accelerate healing. Although antacids are used widely by the general public to relieve functional symptoms (dyspepsia, heartburn, acid indigestion), there are no controlled studies that demonstrate efficacy in these conditions.

Potency, Dosage, and Formulations

Potency. Antacid potency is expressed as acid-neutralizing capacity (ANC). ANC is defined as the number of milliequivalents of hydrochloric acid that can be neutralized by a given weight or volume of antacid. Individual antacids differ widely in ANC. The ANCs of commonly used proprietary preparations are listed in Table 78-3.

Dosage. The objective of peptic ulcer therapy is to promote healing, and not simply to relieve pain. Consequently, antacids should be taken on a regular schedule, not just in response to discomfort. In the usual dosing schedule, antacids are administered 7 times a day: 1 and 3 hours after each meal and at bedtime.

Dosage recommendations should be based on ANC and not on weight or volume of antacid. The ANC of a single dose usually ranges from 20 to 80 mEq. Single doses for gastric ulcers are relatively low (20 to 40 mEq), whereas single doses for duodenal ulcers are higher (40 to 80 mEq). Frequent dosing with even larger amounts (120 mEq) may be required if ulceration is especially severe.

To provide maximum benefits, treatment should elevate gastric pH above 5. At this pH there is inhibition of pepsin activity in addition to nearly complete (greater than 99.9%) neutralization of acid.

Antacids are inconvenient and unpleasant to ingest, making adherence difficult—especially in the absence of pain. Patients should be encouraged to take their medication as prescribed, even after symptoms are gone.

Formulations. Antacids are available in tablet and liquid formulations. Antacid tablets should be chewed thoroughly and followed with a glass of water or milk. Liquid preparations should be shaken before dispensing. As a rule, liquids (suspensions) are more effective than tablets.

Adverse Effects

Constipation and Diarrhea. Most antacids affect the bowel. Some (eg, aluminum hydroxide) promote constipation, whereas others (eg, magnesium hydroxide) promote diarrhea. Effects on the bowel can be minimized by

TABLE 78-3 ■ Composition and Acid-Neutralizing Capacity of Commonly Used Over-the-Counter Antacid Suspensions

Product	Acid Neutralizing Capacity (mEq/5 mL)	Active Ingredients (mg/5 mL)			Sodium (mg/5 mL)
		Al(OH) ₃	Mg(OH) ₂	Simethicone	
AlternaGEL	16	600			<2.5
Aludrox Suspension	12	307	103		2.3
Maalox Regular Strength	13	200	200		1.4
Milk of Magnesia	14		390		0.1
Mylagen II Liquid	24	400	400	40	1.3
Mylanta Maximum Liquid	25	400	400	40	1.1
Riopan	15				<0.1
Riopan Plus Suspension	15			40	<0.1
Riopan Plus DS Suspension	30			40	0.3

DS = double strength.

combining an antacid that promotes constipation with one that promotes diarrhea. Patients should be taught to adjust the dosage of one agent or the other to normalize bowel function.

Sodium Loading. Some antacid preparations contain substantial amounts of sodium (see Table 78-3). Because sodium excess can exacerbate hypertension and heart failure, patients with these disorders should avoid preparations that have a high sodium content.

Drug Interactions

By raising gastric pH, antacids can influence the dissolution and absorption of many other drugs, including *cimetidine* and *ranitidine*. These interactions can be minimized by allowing 1 hour between taking antacids and these other drugs.

Antacids can interfere with the actions of sucralfate. To minimize this interaction, administer these drugs at least 1 hour apart.

If absorbed in substantial amounts, antacids can alkalinize the urine. Elevation of urinary pH can accelerate excretion of acidic drugs and delay excretion of basic drugs.

Antacid Families

There are four major groups of antacids: (1) aluminum compounds, (2) magnesium compounds, (3) calcium compounds, and (4) sodium compounds. Individual agents that belong to each group are listed in Table 78-4. Representative members of these groups are discussed below.

Representative Antacids

Antacids differ from one another with respect to ANC, onset and duration of action, effects on the bowel, systemic effects, and special applications. In this section, we discuss the two most commonly used antacids—magnesium hydroxide and aluminum hydroxide—and two less commonly used drugs—calcium carbonate and sodium bicarbonate. The distinguishing properties of these agents are summarized in Table 78-5.

Magnesium Hydroxide. This antacid is rapid acting, has high ANC, and produces long-lasting effects. These properties make magnesium hydroxide an antacid of choice. The liquid formulation of magnesium hydroxide is often referred to as milk of magnesia.

The most prominent adverse effect is diarrhea, which results from retention of water in the intestinal lumen. To compensate for this effect, magnesium hydroxide is usually administered in combination with aluminum hydroxide, an antacid that promotes constipation. However, if the dose of magnesium hydroxide is sufficiently high, no amount of aluminum hydroxide will prevent diarrhea. Since stimulation of the bowel can be hazardous for patients with intestinal obstruction or appendicitis, magnesium hydroxide should be avoided in those with undiagnosed abdominal pain. Because of its effect on the bowel, magnesium hydroxide is frequently employed as a laxative (see Chapter 79). In patients with renal impairment, magnesium may accumulate to high levels, causing signs of toxicity (eg, CNS depression).

Aluminum Hydroxide. This drug has relatively low ANC and is slow acting, but produces effects of long duration. Although rarely used alone, this

TABLE 78-4 ■ Classification of Antacids

Aluminum Compounds

Aluminum hydroxide

Magnesium Compounds

Magnesium hydroxide (milk of magnesia)

Magnesium oxide

Calcium Compounds

Calcium carbonate

Sodium Compounds

Sodium bicarbonate

Other

Magaldrate (a complex of magnesium and aluminum compounds)

compound is widely used in combination with magnesium hydroxide (see Table 78-3). Aluminum hydroxide preparations contain significant amounts of sodium; appropriate caution should be exercised. The most common adverse effect is constipation.

Aluminum hydroxide adsorbs a variety of compounds. Binding of certain drugs (eg, tetracyclines, warfarin, digoxin) may reduce their effects. Aluminum hydroxide has a high affinity for phosphate. By binding with phosphate, the drug can reduce phosphate absorption, and can thereby cause hypophosphatemia. Aluminum hydroxide can also bind to pepsin, which may facilitate ulcer healing.

Calcium Carbonate. Calcium carbonate, like magnesium hydroxide, is rapid acting, has high ANC, and produces effects of long duration. Because of these properties, calcium carbonate was once considered the ideal antacid. However, because of concerns about acid rebound (stimulation of acid secretion), use of calcium carbonate has declined. The principal adverse effect is constipation, which can be overcome by combining calcium carbonate with a magnesium-containing antacid (eg, magnesium hydroxide). Calcium carbonate releases carbon dioxide in the stomach, and can thereby cause eructation (belching) and flatulence. Rarely, systemic absorption is sufficient to produce the milk-alkali syndrome, a condition characterized by hypercalcemia, metabolic alkalosis, soft tissue calcification, and impaired renal function. The palatability of calcium carbonate is low, and can detract from adherence.

Sodium Bicarbonate. Although capable of neutralizing gastric acid, sodium bicarbonate is unfit for treating ulcers. This agent has a rapid onset but effects are short lasting. Like calcium carbonate, sodium bicarbonate liberates carbon dioxide, thereby increasing intra-abdominal pressure and promoting eructation and flatulence. Absorption of sodium can exacerbate hypertension and heart failure. In patients with renal impairment, sodium bicarbonate can cause systemic alkalosis. (Other antacids rarely alter sys-

TABLE 78-5 ■ Representative Antacids: Summary of Distinguishing Properties

Antacid	Effect on the Bowel		Effect on Systemic pH	Comments
	Constipation	Diarrhea		
Aluminum hydroxide	Yes	No	None	Can cause hypophosphatemia; can treat hyperphosphatemia
Magnesium hydroxide	No	Yes	None	Can cause Mg toxicity (CNS depression) in patients with renal impairment
Calcium carbonate	Yes	No	None	May cause acid rebound or milk-alkali syndrome; releases CO ₂
Sodium bicarbonate	No	No	Increase	Not used routinely for ulcers; used to treat acidosis and to alkalinize urine; high risk of sodium loading; releases CO ₂

temic pH.) Because of its brief duration, high sodium content, and ability to cause alkalosis, sodium bicarbonate is inappropriate for treating PUD. The drug is useful, however, for treating acidosis and elevating urinary pH to promote excretion of acidic drugs following overdose.

Anticholinergics

Atropine and other classic muscarinic antagonists have a very limited role in treating PUD. Why? Because the doses required to inhibit acid secretion are so high that they produce muscarinic blockade throughout the body. Hence, when used to treat ulcers, these drugs cause a high incidence of anticholinergic side effects, such as dry mouth, constipation, urinary retention, and visual disturbances.

Pirenzepine. Pirenzepine is a unique muscarinic antagonist that produces "selective" blockade of the muscarinic receptors that regulate gastric acid secretion (see Fig. 78-2). As a result, the drug can inhibit acid secretion without causing pronounced anticholinergic side effects. For treatment of duodenal ulcers, pirenzepine (50 mg 2 to 3 times/day) is about equal to cimetidine (1 gm/day).

Following oral administration, about 20% to 30% of the drug is absorbed. Very little crosses the blood-brain barrier. About 80% is excreted unchanged in the urine. The half-life is approximately 10 hours.

The most common side effect is dry mouth. In addition, pirenzepine can cause constipation, visual disturbances, nausea, vomiting, and diarrhea.

Combination Packs

Three combination packs—Helidac, Pylera, and Prevpac—are available for treating *H. pylori*-associated ulcers. The purpose of these packs is to simplify the purchase and administration of drugs for triple and quadruple therapy of PUD.

Helidac. The Helidac pack contains bismuth subsalicylate tablets (262.4 mg), metronidazole tablets (250 mg), and tetracycline capsules (500 mg). One dose consists of 2 bismuth tablets, 1 metronidazole tablet, and 1 tetracycline capsule. Patients take four such doses a day, along with two daily doses of a PPI or H₂RA.

Pylera. The Pylera pack consists of capsules that contain three drugs each: bismuth subcitrate potassium (140 mg), metronidazole (125 mg), and tetracycline (125 mg). One dose consists of 3 capsules. Patients take four such doses a day, along with two daily doses of a PPI or H₂RA.

Prevpac. The Prevpac pack contains lansoprazole [Prevacid] capsules (30 mg), amoxicillin capsules (500 mg), and clarithromycin tablets (500 mg). One dose consists of 1 lansoprazole capsule, 2 amoxicillin capsules, and 1 clarithromycin tablet. Patients take two of these doses a day.

KEY POINTS

- The term *peptic ulcer disease* (PUD) refers to a group of upper GI disorders characterized by varying degrees of erosion of the gut wall.
- PUD develops when aggressive factors (*H. pylori*, NSAIDs, acid, pepsin) outweigh defensive factors (mucus, bicarbonate, submucosal blood flow, prostaglandins).
- Gastric acid is an absolute requirement for ulcer formation. In the absence of acid, no ulcer will form.
- The most common cause of PUD is infection with *H. pylori*.
- The next most common cause is use of NSAIDs.
- The goal of PUD therapy is to alleviate symptoms, promote healing, prevent complications (hemorrhage, perforation, obstruction), and prevent recurrence.
- The major drugs used to treat PUD are antibiotics and antisecretory agents (H₂RAs, PPIs).
- With the exception of antibiotics, antiulcer drugs do not alter the disease process; rather, they simply create conditions conducive to healing. Because nonantibiotic therapies do not cure ulcers, the relapse rate with them alone is high. In contrast, the relapse rate following successful antibiotic therapy is low.
- All patients with gastric or duodenal ulcers and confirmed infection with *H. pylori* should be treated with antibiotics in combination with an antisecretory agent.
- The antibiotics employed most often are clarithromycin, amoxicillin, bismuth, tetracycline, and metronidazole.
- To avoid resistance and increase efficacy, at least two antibiotics should be used.
- Cimetidine and other H₂RAs suppress secretion of gastric acid by blocking histamine₂ receptors on parietal cells of the stomach.

- Cimetidine inhibits hepatic drug-metabolizing enzymes, and can thereby cause levels of other drugs to rise.
 - In contrast to cimetidine, ranitidine has little effect on drug metabolism.
 - Proton pump inhibitors (eg, omeprazole, lansoprazole) suppress acid secretion by inhibiting gastric H^+,K^+ -ATPase, the enzyme that makes gastric acid.
 - PPIs are the most effective inhibitors of acid secretion.
 - Although generally safe, PPIs can increase the risk of fractures, pneumonia, and hypomagnesemia, and can cause acid rebound when treatment stops.
- Sucralfate promotes ulcer healing by creating a protective barrier against acid and pepsin.
 - Misoprostol, an analog of prostaglandin E_1 , is used to prevent gastric ulcers caused by NSAIDs.
 - Misoprostol stimulates uterine contraction and hence is contraindicated during pregnancy.

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Summary of Major Nursing Implications*

H₂ RECEPTOR ANTAGONISTS

Cimetidine
Famotidine
Nizatidine
Ranitidine

Preadministration Assessment

Therapeutic Goal

H₂RAs are used primarily to treat PUD. The objective is to relieve pain, promote healing, prevent ulcer recurrence, and prevent complications.

Baseline Data

Definitive diagnosis of PUD requires radiographic or endoscopic visualization of the ulcer and testing for *H. pylori* infection, either by a noninvasive method (urea breath test, stool antigen test, or serologic antibody test) or by an invasive method involving evaluation of a biopsy sample by either (1) staining and viewing under a microscope to see if *H. pylori* is present, (2) assaying for the presence of urease, or (3) culturing and then assaying for the presence of *H. pylori*.

Identifying High-Risk Patients

Use H₂RAs with *caution* in patients with renal or hepatic dysfunction.

Implementation: Administration

Routes

Cimetidine and Ranitidine. Oral, IM, and IV.
Famotidine. Oral and IV.
Nizatidine. Oral only.

Administration

Oral. Inform patients that H₂RAs may be taken without regard to meals.

With all H₂RAs, dosing may be done twice daily or once daily at bedtime. With ranitidine, dosing may also

be done 4 times a day (with meals and at bedtime). Make sure the patient knows which dosing schedule has been prescribed.

Intramuscular: Cimetidine and Ranitidine. Use concentrated solutions for IM injections.

Intravenous: Cimetidine, Famotidine, and Ranitidine. For IV injection, dilute in a small volume (eg, 20 mL) of 0.9% sodium chloride and inject slowly (over 5 or more minutes). For IV infusion, dilute in a large volume (100 mL) of 0.9% sodium chloride and infuse over 15 to 20 minutes.

Implementation: Measures to Enhance Therapeutic Effects

Advise patients to avoid cigarettes and ulcerogenic over-the-counter drugs (aspirin and other NSAIDs). Advise patients to stop drinking alcohol if drinking exacerbates their ulcer symptoms. Inform patients that five or six small meals per day may be preferable to three larger meals.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Ulcer Healing. Monitor for relief of pain. Radiologic or endoscopic examination of the ulcer site may also be employed. Monitor gastric pH; treatment should increase pH to 5 or above. Educate patients about signs of GI bleeding (eg, black, tarry stools; "coffee-grounds" vomitus), and instruct them to notify the prescriber if these occur.

Helicobacter pylori. If *H. pylori* was present at the onset of treatment, it may be useful to determine if the infection was eradicated.

Minimizing Adverse Effects

Antiandrogenic Effects. Inform patients that cimetidine can cause gynecomastia, reduced libido, and impotence, and that these effects reverse after drug withdrawal.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

CNS Effects. *Cimetidine* can cause confusion, hallucinations, lethargy, somnolence, restlessness, and seizures. These responses are most likely in elderly patients who have renal or hepatic impairment. **Inform patients about possible CNS effects and instruct them to notify the prescriber if they occur.** CNS effects are less likely with ranitidine, famotidine, and nizatidine.

Pneumonia. Elevation of gastric pH increases the risk of pneumonia. **Inform patients about signs of respiratory infection and instruct them to inform the prescriber if they occur.**

Minimizing Adverse Interactions

Interactions Secondary to Inhibition of Drug Metabolism. *Cimetidine* inhibits hepatic drug-metabolizing enzymes and can thereby increase levels of other drugs. Drugs of particular concern are *warfarin*, *phenytoin*, *theophylline*, and *lidocaine*. Dosages of these drugs may require reduction.

Ranitidine inhibits drug metabolism, but to a lesser degree than *cimetidine*. *Famotidine* and *nizatidine* do not inhibit drug metabolism.

Antacids. Antacids can decrease absorption of *cimetidine* and *ranitidine*. At least 1 hour should separate administration of antacids and these drugs.

PROTON PUMP INHIBITORS

Dexlansoprazole
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole

Preadministration Assessment

Therapeutic Goal

PPIs are used primarily to treat PUD. The objective is to relieve pain, promote healing, prevent ulcer recurrence, and prevent complications.

Baseline Data

Consider obtaining a baseline value for magnesium when long-term PPI therapy is planned. For other nursing implications, see *Baseline Data* for *H₂ Receptor Antagonists*.

Identifying High-Risk Patients

PPIs are very safe when used short-term. Their only *contraindication* is hypersensitivity to the drug itself or to a component of the formulation.

Implementation: Administration

Routes

Dexlansoprazole, Esomeprazole, Omeprazole, and Rabeprazole. Oral only.
Pantoprazole and Lansoprazole. Oral and IV.

Administration

Oral. Inform patients that capsules and tablets should be swallowed intact—not opened, split, crushed, or chewed.

Instruct patients to take esomeprazole at least 1 hour before a meal, and to take omeprazole or lansoprazole just before eating. Inform patients that dexlansoprazole, pantoprazole, and rabeprazole may be taken without regard to food.

Intravenous. For IV therapy with pantoprazole or lansoprazole, an in-line filter *must* be used to remove any precipitate.

Implementation: Measures to Enhance Therapeutic Effects

See Nursing Implications for *H₂ Receptor Antagonists*.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See Nursing Implications for *H₂ Receptor Antagonists*.

Minimizing Adverse Effects

In General. When PPIs are used short term for appropriate patients, the benefits of treatment generally outweigh the risks. Conversely, when PPIs are used long-term or for inappropriate patients, the risks clearly outweigh any benefits.

Pneumonia. During the first few days of treatment, PPIs may increase the risk of community-acquired and hospital-acquired pneumonia. **Inform patients about signs of respiratory infection and instruct them to inform the prescriber if they occur.**

Fractures. Long-term, high-dose therapy may increase the risk of osteoporosis and fractures. To minimize fracture risk, use the lowest dose needed for the shortest time possible. **Encourage patients to maintain adequate intake of calcium and vitamin D.**

Rebound Acid Hypersecretion. Discontinuing a PPI may trigger acid rebound and associated dyspepsia. **Advise patients that acid rebound can be minimized by using the lowest dose needed for the shortest time possible, and by tapering the PPI dose when stopping treatment. Inform patients about the risk of acid rebound and advise them to manage symptoms with an antacid, and perhaps an H₂RA.**

Hypomagnesemia. Long-term use can lower magnesium levels. Risk is increased by other drugs that lower magnesium, especially thiazide and loop diuretics. **Inform patients about symptoms of hypomagnesemia (eg, tremors, muscle cramps, seizures, dysrhythmias), and have them inform the prescriber if they develop.** Magnesium levels can be raised with oral or IV magnesium. If these measures fail, magnesium can be raised by switching to an H₂ blocker; magnesium typically normalizes within 2 weeks. For long-term PPI therapy, consider measuring magnesium at baseline and periodically thereafter.

*Patient education information is highlighted as **blue text**.

Summary of Major Nursing Implications*—cont'd

Minimizing Adverse Interactions

Atazanavir, Delavirdine, and Nelfinavir. By elevating gastric pH, PPIs significantly reduce the absorption of these drugs, which are used to treat HIV/AIDS. Therefore, concurrent use of PPIs and these drugs should be avoided.

Clopidogrel. PPIs can protect against clopidogrel-induced GI bleeding, but may also reduce the antiplatelet effects of clopidogrel. In patients with risk factors for GI

bleeding (eg, advanced age, use of NSAIDs or glucocorticoids) the benefits of combining a PPI with clopidogrel outweigh any risk from a possible reduction in antiplatelet effects, and hence use of the combination makes sense. Conversely, in patients who lack risk factors for GI bleeding, the combination of clopidogrel with a PPI should generally be avoided.

*Patient education information is highlighted as **blue text**.

General Considerations

Basic Pharmacology of Laxatives

Bulk-Forming Laxatives

Surfactant Laxatives

Stimulant Laxatives

Osmotic Laxatives

Other Laxatives

Bowel Cleansing Products for Colonoscopy

Laxative Abuse

Laxatives are used to ease or stimulate defecation. These agents can soften the stool, increase stool volume, hasten fecal passage through the intestine, and facilitate evacuation from the rectum. When properly employed, laxatives are valuable medications. However, these agents are also subject to abuse. Misuse of laxatives is largely the result of misconceptions about what constitutes normal bowel function.

Before we talk about laxatives, we need to distinguish between two terms: *laxative effect* and *catharsis*. The term *laxative effect* refers to production of a soft, formed stool over a period of 1 or more days. In contrast, the term *catharsis* refers to a prompt, fluid evacuation of the bowel. Hence, a laxative effect is leisurely and relatively mild, whereas catharsis is relatively fast and intense.

GENERAL CONSIDERATIONS

Function of the Colon

The principal function of the colon is to absorb water and electrolytes. Absorption of nutrients is minimal. Normally, about 1500 mL of fluid enters the colon each day, and approximately 90% gets absorbed. When the colon is working correctly, the extent of fluid absorption is such that the resulting stool is soft (but formed) and capable of elimination without strain. However, when fluid absorption is excessive, as can happen when transport through the intestine is delayed, the resultant stool is dehydrated and hard. Conversely, if insufficient fluid is absorbed, watery stools result.

Frequency of bowel evacuation varies widely among individuals. For some people, bowel movements occur 2 or 3 times a day. For others, elimination may occur only 2 times a week. Because of this wide individual variation, we can't define a normal frequency for bowel movements. Put another way, although a daily bowel movement may be normal for many people, it may be abnormal for many others.

TABLE 79-1 ■ Rome II Criteria for Constipation

Adults

Two or more of the following for at least 12 weeks (not necessarily consecutive) in the preceding 12 months:

- Straining during more than 25% of bowel movements
- Lumpy or hard stools for more than 25% of bowel movements
- Sensation of incomplete evacuation for more than 25% of bowel movements
- Sensation of anorectal blockage for more than 25% of bowel movements
- Manual maneuvers (eg, digital evacuation; support of the pelvic floor) to facilitate more than 25% of bowel movements
- Fewer than three bowel movements per week
- Loose stools not present, and insufficient criteria to permit diagnosis of irritable bowel syndrome

Infants and Children

- Pebble-like, hard stools for a majority of bowel movements for at least 2 weeks
- Firm stools twice a week or less for at least 2 weeks
- No evidence of structural, endocrine, or metabolic disease

Dietary Fiber

Proper function of the bowel is highly dependent on dietary fiber—the component of vegetable matter that escapes digestion in the stomach and small intestine. Fiber facilitates colonic function in two ways. First, fiber absorbs water, thereby softening the feces and increasing their mass. Second, fiber can be digested by colonic bacteria, whose subsequent growth increases fecal mass. The best source of fiber is bran. Fiber can also be obtained from fruits and vegetables. Ingestion of 20 to 60 gm of fiber a day should optimize intestinal function.

Constipation

Constipation is one of the most common GI disorders. In the United States, people seek medical help for constipation at least 2.5 million times a year, and spend hundreds of millions on laxatives.

Constipation is defined in terms of symptoms, which include hard stools, infrequent stools, excessive straining, prolonged effort, a sense of incomplete evacuation, and unsuccessful defecation. Scientists who do research on constipation usually define it using the Rome II criteria (Table 79-1). As Table 79-1 shows, constipation is determined more by stool *consistency* (degree of hardness) than by *how often* bowel movements occur. Hence, if the interval between bowel movements becomes prolonged, but the stool remains soft and hydrated, a diagnosis of constipation would be improper. Conversely, if bowel movements occur with regularity, but the

TABLE 79-2 ■ Classification of Laxatives by Pharmacologic Category

Class and Agent	Site of Action	Mechanism of Action
Bulk-Forming Laxatives Methylcellulose Psyllium Polycarbophil	Small intestine and colon	Absorb water, thereby softening and enlarging the fecal mass; fecal swelling promotes peristalsis
Surfactant Laxatives Docusate sodium Docusate calcium	Small intestine and colon	Surfactant action softens stool by facilitating penetration of water; also cause secretion of water and electrolytes into intestine
Stimulant Laxatives Bisacodyl Senna Castor oil	Colon Colon Small intestine	(1) Stimulate peristalsis and (2) soften feces by increasing secretion of water and electrolytes into the intestine and decreasing water and electrolyte absorption
Osmotic Laxatives Magnesium hydroxide Magnesium sulfate Magnesium citrate Sodium phosphate Polyethylene glycol Lactulose	Small intestine and colon	Osmotic action retains water and thereby softens the feces; fecal swelling promotes peristalsis
Miscellaneous Laxatives Lubiprostone	Small intestine and colon	Opens chloride channels in the intestinal epithelium and thereby increases intestinal motility and secretion of fluid into the lumen
Mineral oil	Colon	Lubricates and reduces water absorption
Glycerin suppository	Colon	Lubricates and causes reflex rectal contraction
Polyethylene glycol– electrolyte solution	Small intestine and colon	Similar to osmotic laxatives

feces are hard and dry, constipation can be diagnosed—despite the regular and frequent passage of stool.

A common cause of constipation is poor diet—specifically, a diet deficient in fiber and fluid. Other causes include dysfunction of the pelvic floor and anal sphincter, slow intestinal transit, and use of certain drugs (eg, opioids, anticholinergics, some antacids).

In most cases, constipation can be readily corrected. Stools will become softer and more easily passed within days of increasing fiber and fluid in the diet. Mild exercise, especially after meals, also helps improve bowel function. If necessary, a laxative may be employed—but only briefly and only as an adjunct to improved diet and exercise.

Indications for Laxative Use

Laxatives can be highly beneficial when employed for valid indications. By softening the stool, laxatives can reduce the painful elimination that can be associated with episiotomy and with hemorrhoids and other anorectal lesions. In patients with cardiovascular diseases (eg, aneurysm, myocardial infarction, disease of the cerebral or cardiac vasculature), softening the stool decreases the amount of strain needed to defecate, thereby avoiding dangerous elevation of blood pressure. In elderly patients, laxatives can help compensate for loss of tone in abdominal and perineal muscles. As an adjunct to anthelmintic

therapy, laxatives can be used for (1) obtaining a fresh stool sample for diagnosis; (2) emptying the bowel prior to treatment (so as to increase parasitic exposure to anthelmintic medication); and (3) facilitating export of dead parasites following anthelmintic use. Additional applications include (1) emptying of the bowel prior to surgery and diagnostic procedures (eg, radiologic examination, colonoscopy); (2) modifying the effluent from an ileostomy or colostomy; (3) preventing fecal impaction in bedridden patients; (4) removing ingested poisons; and (5) correcting constipation associated with pregnancy and certain drugs, especially opioid analgesics.

Precautions and Contraindications to Laxative Use

Laxatives are contraindicated for individuals with certain disorders of the bowel. Specifically, laxatives must be avoided by individuals experiencing abdominal pain, nausea, cramps, or other symptoms of appendicitis, regional enteritis, diverticulitis, and ulcerative colitis. Laxatives are also contraindicated for patients with acute surgical abdomen. In addition, laxatives should not be used in patients with fecal impaction or obstruction of the bowel, because increased peristalsis could cause bowel perforation. Lastly, laxatives should not be employed habitually to manage constipation. Reasons why are discussed below under *Laxative Abuse*.

TABLE 79-3 ■ Classification of Laxatives by Therapeutic Response

Group I: Produce Watery Stool in 2–6 Hr	Group II: Produce Semifluid Stool in 6–12 Hr	Group III: Produce Soft Stool in 1–3 Days
Osmotic Laxatives (in High Doses) Magnesium salts Sodium salts Polyethylene glycol	Osmotic Laxatives (in Low Doses) Magnesium salts Sodium salts Polyethylene glycol	Bulk-Forming Laxatives Methylcellulose Psyllium Polycarbophil
Others Castor oil Polyethylene glycol–electrolyte solution	Stimulant Laxatives (Except Castor Oil) Bisacodyl, oral* Senna	Surfactant Laxatives Docusate sodium Docusate calcium
		Others Lactulose Lubiprostone

*Bisacodyl suppositories act in 15 minutes.

Laxatives should be used with caution during pregnancy (because GI stimulation might induce labor) and during lactation (because the laxative may be excreted in breast milk).

Laxative Classification Schemes

Traditionally, laxatives have been classified according to general *mechanism of action*. This scheme has four major categories: (1) bulk-forming laxatives, (2) surfactant laxatives, (3) stimulant laxatives, and (4) osmotic laxatives. Representative drugs are listed in Table 79-2.

From a clinical perspective, it can be useful to classify laxatives according to *therapeutic effect* (time of onset and impact on stool consistency). When these properties are considered, most laxatives fall into one of three groups, labeled I, II, and III in this chapter. Group I agents act rapidly (within 2 to 6 hours) and give a watery consistency to the stool. Laxatives in group I are especially useful when preparing the bowel for diagnostic procedures or surgery. Group II agents have an intermediate latency (6 to 12 hours) and produce a stool that is semifluid. Group II agents are the ones most frequently abused by the general public. Group III laxatives act slowly (in 1 to 3 days) to produce a soft but formed stool. Uses for this group include treating chronic constipation and preventing straining at stool. Representative members of groups I, II, and III are listed in Table 79-3.

BASIC PHARMACOLOGY OF LAXATIVES

Bulk-Forming Laxatives

The bulk-forming laxatives (eg, methylcellulose, psyllium, polycarbophil) have actions and effects much like those of dietary fiber. These agents consist of natural or semisynthetic polysaccharides and celluloses derived from grains and other plant material. The bulk-forming agents belong to our therapeutic group III, producing a soft, formed stool after 1 to 3 days of use.

Mechanism of Action. Bulk-forming agents have the same impact on bowel function as dietary fiber. Following ingestion, these agents, which are nondigestible and nonab-

sorbable, swell in water to form a viscous solution or gel, thereby softening the fecal mass and increasing its bulk. Fecal volume may be further enlarged by growth of colonic bacteria, which can utilize these materials as nutrients. Transit through the intestine is hastened because swelling of the fecal mass stretches the intestinal wall, and thereby stimulates peristalsis.

Indications. Bulk-forming laxatives are preferred agents for temporary treatment of constipation. Also, they are widely used in patients with diverticulosis and irritable bowel syndrome. In addition, by altering fecal consistency, they can provide symptomatic relief of diarrhea and can reduce discomfort and inconvenience for patients with an ileostomy or colostomy.

Adverse Effects. Untoward effects are minimal. Because the bulk-forming agents are not absorbed, systemic reactions are rare. *Esophageal obstruction* can occur if they are swallowed in the absence of sufficient fluid. Accordingly, bulk-forming laxatives should be administered with a full glass of water or juice. If their passage through the intestine is arrested, they may produce *intestinal obstruction* or *impaction*. Accordingly, they should be avoided if there is narrowing of the intestinal lumen.

Preparations, Dosage, and Administration. *Psyllium* (prepared from *Plantago* seed), *methylcellulose*, and *polycarbophil* are the principal bulk-forming laxatives. All three preparations should be administered with a full glass of water or juice. Dosages and trade names are presented in Table 79-4.

Surfactant Laxatives

Actions. The surfactants (eg, docusate sodium) are group III laxatives: They produce a soft stool several days after the onset of treatment. Surfactants alter stool consistency by lowering surface tension, which facilitates penetration of water into the feces. The surfactants may also act on the intestinal wall to (1) inhibit fluid absorption and (2) stimulate secretion of water and electrolytes into the intestinal lumen. In this respect, surfactants resemble the stimulant laxatives (see below).

TABLE 79-4 ■ Representative Laxatives: Trade Names, Dosage Forms, and Dosages

Drug Class and Generic Name	Trade Names	Dosage Forms	Dosage and Administration
Bulk-Forming			
Methylcellulose	Citrucel	Powder	<i>Powder:</i> 1 heaping tbsp in 8 oz cold water 1–3 times a day
Psyllium	Metamucil, others	Powder, wafer	<i>Adults:</i> 1 rounded tsp (or 1 packet) mixed with water or other fluid, taken 1–3 times daily <i>Children over 6 yr:</i> 1/3 to 1/2 adult dose
Polycarbophil	FiberCon, others	Tablets	<i>Adults:</i> 1 gm 1–4 times a day <i>Children 6–12 yr:</i> 500 mg 1–4 times a day
Surfactant			
Docusate sodium	Colace, others	Capsules, tablets, syrup, liquid	<i>Adults and children over 12 yr:</i> 50–500 mg/day <i>Children 6–12 yr:</i> 40–120 mg/day (All doses taken with a full glass of water)
Stimulant			
Bisacodyl	Correctol, Dulcolax, Feen-a-mint, Fleet Laxative, others	Tablets, suppositories	<i>Adults:</i> 10–15 mg (tablets) or 10-mg suppository once daily <i>Children:</i> 5-mg tablet or 5-mg suppository once daily
Senna	Senokot, ex-lax, others	Tablets	<i>Adults:</i> 2 tablets once or twice a day <i>Children 6–12 yr:</i> 1 tablet once or twice a day
Osmotic			
Polyethylene glycol	GlycoLax, MiraLax, Peglax*, Realax*, Sealax*	Powder	<i>Adults:</i> 17 gm (dissolved in 8 oz of water) once a day
Lactulose	Constulose, Enulose, others	Liquid	<i>Adults:</i> 15–30 mL daily, increased to 60 mL if needed
Magnesium hydroxide (milk of magnesia)	Phillips' Milk of Magnesia, others	Liquid	<i>Low dose:</i> 15–30 mL <i>High dose:</i> 30–60 mL
Sodium phosphate	Fleet Phospho-Soda	Liquid	<i>Adults:</i> 20–45 mL/day <i>Children 10–11 yr:</i> 10–20 mL/day <i>Children 5–9 yr:</i> 5–10 mL/day
Other			
Lubiprostone	Amitiza	Capsule	<i>Adults:</i> 24 mcg twice a day with food
Mineral oil	generic only	Liquid	<i>Adults:</i> 45 mL PO twice a day <i>Children:</i> 5–20 mL PO at bedtime

Preparations, Dosage, and Administration. The surfactant family consists of two *docusate salts*: docusate sodium and docusate calcium. The dosage for docusate sodium [Colace, others], the prototype surfactant, is presented in Table 79-4. Administration should be accompanied by a full glass of water.

Stimulant Laxatives

The stimulant laxatives (eg, bisacodyl, castor oil) have two effects on the bowel. First, they stimulate intestinal motility—hence their name. Second, they increase the amount of water and electrolytes within the intestinal lumen. How? By increasing secretion of water and ions into the intestine, and by

reducing water and electrolyte absorption. Most stimulant laxatives are group II agents: They act on the colon to produce a semifluid stool within 6 to 12 hours.

Stimulant laxatives are widely used—and abused—by the general public, and are of concern for this reason. They have few legitimate applications. Two applications that are legitimate are (1) treatment of opioid-induced constipation and (2) treatment of constipation resulting from slow intestinal transit. Properties of individual agents are discussed below.

Bisacodyl. Bisacodyl [Correctol, Dulcolax, Feen-a-mint, others] is unique among the stimulant laxatives in that it can be administered by rectal suppository as well as by mouth. Oral bisacodyl acts within 6 to 12 hours. Hence, tablets may be given at bedtime to produce a response the following

morning. Bisacodyl *suppositories* act rapidly (in 15 to 60 minutes). Dosages for bisacodyl are presented in Table 79-4.

Bisacodyl tablets are enteric coated to prevent gastric irritation. Accordingly, patients should be advised to swallow them intact, without chewing or crushing. Because milk and antacids accelerate dissolution of the enteric coating, the tablets should be administered no sooner than 1 hour after ingesting these substances.

Bisacodyl suppositories may cause a burning sensation and, with continued use, proctitis may develop. Accordingly, long-term use should be discouraged.

Senna. Senna [Senokot, ex-lax, others] is a plant-derived laxative that contains *anthraquinones* as active ingredients. The actions and applications of senna are similar to those of bisacodyl. Anthraquinones act on the colon to produce a soft or semifluid stool in 6 to 12 hours. Systemic absorption followed by renal secretion may impart a harmless yellowish-brown or pink color to the urine. Dosages are presented in Table 79-4.

Castor Oil. Castor oil is the only stimulant laxative that acts on the *small intestine*. As a result, the drug acts quickly (in 2 to 6 hours) to produce a watery stool. Hence, unlike other stimulant laxatives, which are all group II agents, castor oil belongs to group I. Use of castor oil is limited to situations in which rapid and thorough evacuation of the bowel is desired (eg, preparation for radiologic procedures). The drug is far too powerful for routine treatment of constipation. Because of its relatively prompt action, castor oil should not be administered at bedtime. The drug has an unpleasant taste that can be improved by chilling and mixing with fruit juice.

Osmotic Laxatives

Laxative Salts

Actions and Uses. The laxative salts (eg, sodium phosphate, magnesium hydroxide) are poorly absorbed salts whose osmotic action draws water into the intestinal lumen. Accumulation of water causes the fecal mass to soften and swell, thereby stretching the intestinal wall, which stimulates peristalsis. When administered in low doses, the osmotic laxatives produce a soft or semifluid stool in 6 to 12 hours. In high doses, these agents act rapidly (in 2 to 6 hours) to cause a fluid evacuation of the bowel. High-dose therapy is employed to empty the bowel in preparation for diagnostic and surgical procedures. High doses are also employed to purge the bowel of ingested poisons, and to evacuate dead parasites following anthelmintic therapy.

Preparations. We have two groups of laxative salts: (1) *magnesium salts* (magnesium hydroxide, magnesium citrate, and magnesium sulfate), and (2) one *sodium salt* (sodium phosphate). Dosages for magnesium hydroxide solution (also known as milk of magnesia) and sodium phosphate are presented in Table 79-4.

Adverse Effects. Osmotic laxatives can cause substantial *loss of water*. To avoid dehydration, patients should increase fluid intake. Although the osmotic laxatives are poorly and slowly absorbed, some absorption does take place. In patients with renal impairment, *magnesium can accumulate to toxic levels*. Accordingly, magnesium salts are contraindicated in patients with kidney disease. Sodium absorption (from sodium phosphate) can cause *fluid retention*, which in turn can

exacerbate heart failure, hypertension, and edema. Accordingly, sodium phosphate is contraindicated for patients with these disorders. Sodium phosphate can also cause *acute renal failure* in vulnerable patients, especially those with kidney disease and those taking drugs that alter renal function (eg, diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]). The mechanism involves dehydration and precipitation of calcium and phosphate in renal tubules. Accordingly, sodium phosphate should be avoided in this vulnerable group.

Polyethylene Glycol

Polyethylene glycol (PEG) [MiraLax, GlycoLax, Peglax*, Realax*, Sealax*] is an osmotic laxative used widely for chronic constipation. Like the laxative salts, PEG is a nonabsorbable compound that retains water in the intestinal lumen, causing the fecal mass to soften and swell. The most common adverse effects are nausea, abdominal bloating, cramping, and flatulence. High doses may cause diarrhea. For management of chronic constipation, PEG is superior to lactulose with regard to relief of abdominal pain and improvements in stool consistency and frequency per week, although side effects are similar. The recommended dosage is 17 gm once a day, dissolved in 4 to 8 ounces of water, juice, soda, coffee, or tea. Bowel movement may not occur for another 2 to 4 days. As discussed below, products that contain PEG plus electrolytes can be used to cleanse the bowel prior to colonoscopy and other procedures.

Lactulose

Lactulose [Constulose, Enulose, others] is a semisynthetic disaccharide composed of galactose and fructose. Lactulose is poorly absorbed and cannot be digested by intestinal enzymes. In the colon, resident bacteria metabolize lactulose to lactic acid, formic acid, and acetic acid. These acids exert a mild osmotic action, producing a soft, formed stool in 1 to 3 days. Although lactulose can relieve constipation, this agent is more expensive than equivalent drugs (bulk-forming laxatives), and causes more unpleasant side effects (flatulence and cramping are common). Accordingly, lactulose should be reserved for patients who do not respond adequately to a bulk-forming agent.

In addition to its laxative action, lactulose can enhance intestinal excretion of ammonia. This property has been exploited to lower blood ammonia content in patients with portal hypertension and hepatic encephalopathy secondary to chronic liver disease.

Other Laxatives

Lubiprostone

Lubiprostone [Amitiza] is the first representative of a new class of drugs: the selective *chloride channel activators*. By activating (opening) chloride channels in epithelial cells lining the intestine, lubiprostone (1) promotes secretion of chloride-rich fluid into the intestine and (2) enhances motility in the small intestine and colon. The result is spontaneous evacuation of a semisoft stool, usually within 24 hours. Lubiprostone has two indications: (1) chronic idiopathic constipation in adults and (2) irritable bowel syndrome with constipation (IBS-C) in women at least 18 years old. In clinical trials, the drug reduced constipation severity, abdominal bloating, and discomfort. Lubiprostone is taken orally, and very little is absorbed. Nausea is the most common side effect (30%) and can be reduced by taking lubiprostone with food and water. Other GI effects include diarrhea (13.2%), abdominal distention (7.1%), abdominal pain

TABLE 79-5 ■ Oral Bowel Cleansing Products for Colonoscopy

Product Type and Brand Name	Adult Dosage	Total Volume to Swallow	
		Bowel Cleanser	Clear Liquid
Sodium Phosphate Tablets			
Visicol	20 tablets with clear liquid in the evening <i>plus</i> 20 tablets with clear liquid the next day		3.4 L
OsmoPrep	20 tablets with clear liquid in the evening <i>plus</i> 20 tablets with clear liquid the next day		1.9 L
Sodium Phosphate Solutions			
Fleet Phospho-Soda	45 mL with clear liquid in the evening <i>plus</i> 30–45 mL with clear liquid the next day	90 mL	2.2 L
Polyethylene Glycol plus Electrolytes			
GoLYTELY, NuLyte, CoLyte, TriLyte	240 mL every 10 min until 4 L is ingested or until rectal effluent is clear	4 L	
HalfLyte plus bisacodyl	240 mL every 10 min until 2 L is ingested*	2 L	
MoviPrep [†]	240 mL every 15 min until 1 L is ingested, then repeat 1.5 hr later, then drink 1 more L of clear liquid [‡]	2 L	1 L

*Before drinking the solution, patients should take 4 bisacodyl delayed-release tablets and wait for a bowel movement or for 6 hours, whichever comes first.

[†]Formulated with ascorbic acid, which allows use of a smaller volume than traditional PEG-electrolyte products.

[‡]Dosage can be split by ingesting 1 L of the prep plus 0.5 L clear liquid in the evening, followed by 1 L of the prep plus 0.5 L clear liquid the next day.

(6.7%), gas (6.1%), vomiting (4.6%), and loose stools (3.4%). Headache (13.2%) is the major non-GI effect. About 2.4% of patients experience difficulty breathing in association with a sense of tightness in the chest, starting 30 to 60 minutes after the first dose and resolving in a few hours. Lubiprostone is categorized in FDA Pregnancy Risk Category C, and hence should be used only if benefits are deemed to outweigh potential risks to the fetus. (In animal studies, lubiprostone was not teratogenic. However, when given to guinea pigs in doses more than 100 times the human dose, lubiprostone did cause fetal loss.) Interactions with other drugs have not been studied, but seem unlikely. Why? Because lubiprostone is poorly absorbed and does not alter the activity of cytochrome P450 drug-metabolizing enzymes. Lubiprostone is available in 8- and 24-mcg soft-gelatin capsules that should be taken with food and water. The recommended dosage is 24 mcg twice daily for constipation and 8 mcg twice daily for IBS-C. The role of lubiprostone in IBS-C is discussed further in Chapter 80.

Mineral Oil

Mineral oil is a mixture of indigestible and poorly absorbed hydrocarbons. Laxative action is produced by lubrication. Mineral oil is especially useful when administered by enema to treat fecal impaction.

Mineral oil can produce a variety of adverse effects. Aspiration of oil droplets can cause lipid pneumonia. Anal leakage can cause pruritus and soiling. Systemic absorption can produce deposition of mineral oil in the liver. Excessive dosing can decrease absorption of fat-soluble vitamins. Dosages for adults and children are presented in Table 79-4.

Glycerin Suppository

Glycerin is an osmotic agent that softens and lubricates inspissated (hardened, impacted) feces. The drug may also stimulate rectal contraction. Evacuation occurs about 30 minutes after suppository insertion. Glycerin suppositories have been useful for re-establishing normal bowel function following termination of chronic laxative use.

Bowel Cleansing Products for Colonoscopy

Colonoscopy is the most effective method for early detection of colorectal cancer, the second leading cause of cancer deaths in the United States. Prior to the procedure, the bowel must be cleansed to permit good visualization. Two kinds of bowel cleansers are used. One consists of sodium phosphate. The other consists of polyethylene glycol (PEG) plus electrolytes (ELS). Both kinds are equally effective. The PEG-ELS products are isotonic with body fluids, and hence do not alter water or electrolyte status. In contrast, the sodium phosphate products are hypertonic, and hence can cause dehydration and electrolyte disturbances. In addition, the sodium phosphate products can cause kidney damage. However, despite their greater potential for harm, the sodium phosphate products have better patient acceptance. Why? Because the PEG-ELS products require ingestion of a large volume of bad-tasting liquid, whereas the sodium phosphate products do not. Nonetheless, sodium phosphate products should be avoided by patients at risk, including those with electrolyte abnormalities, renal impairment, and hypovolemia. Representative bowel cleansers are shown in Table 79-5.

Polyethylene Glycol–Electrolyte Solutions

These bowel-cleansing solutions [CoLyte, GoLYTELY, others] contain PEG, a nonabsorbable osmotic agent, together with ELS (usually potassium chloride, sodium chloride, sodium sulfate, and sodium bicarbonate). The mixture is isotonic with body fluids, and hence water and electrolytes are neither absorbed from nor secreted into the intestinal lumen. As a result, dehydration does not occur and electrolyte balance is preserved. Because effects on water and electrolytes are minimal, PEG-ELS solutions can be used safely by pa-

nents who are dehydrated and by those who are especially sensitive to alteration of electrolyte levels (eg, patients with renal impairment or cardiovascular disease).

With traditional PEG-ELS products (eg, CoLyte, GoLYTELY, the volume administered is huge, typically 4 L. Patients must ingest 250 to 300 mL every 10 minutes for 2 to 3 hours. With two newer products—HalfLyte and MoviPrep—the volume is cut in half. How is this possible? Patients using HalfLyte take a stimulant laxative—bisacodyl—along with the PEG-ELS solution, and hence don't need the full 4-L dose. Volume reduction with MoviPrep is possible owing to addition of ascorbic acid and sodium ascorbate to the PEG-ELS solution. With all PEG products, bowel movements commence about 1 hour after the first dose.

PEG-ELS products are generally well tolerated. The most common adverse effects are nausea, bloating, and abdominal discomfort. These effects are less intense with the reduced-volume formulations. Because PEG-ELS products don't alter water and electrolyte status, they are safer than sodium phosphate products for patients with electrolyte imbalances, heart failure, kidney disease, or advanced liver disease.

Sodium Phosphate Products

As discussed above, sodium phosphate is an osmotic laxative that draws water into the intestinal lumen, which then softens and swells the fecal mass, which then stretches the intestinal wall to stimulate peristalsis. Dosing consists of swallowing a tablet or small volume of liquid (see Table 79-5) along with a large volume of water or some other clear liquid. Since the clear liquid is more palatable than the PEG-ELS solutions, patients find the sodium phosphate regimens more appealing.

Like the PEG-ELS products, the sodium phosphate products can cause nausea, bloating, and abdominal discomfort. In addition, the sodium phosphate products can cause adverse effects not seen with the PEG-ELS products, especially dehydration, electrolyte disturbances, and kidney damage. By drawing a large volume of fluid into the intestinal lumen, sodium phosphate can cause dehydration. To prevent dehydration, patients must drink a large volume of clear fluid before, during, and after dosing.

Rarely, phosphate is absorbed in amounts sufficient to cause hyperphosphatemia, which can cause *acute, reversible renal damage, and possibly chronic, irreversible renal damage*. Risk factors for hyperphosphatemia and kidney damage include hypovolemia, advanced age, delayed bowel transit,

active colitis, pre-existing kidney disease, and use of drugs that can alter kidney function, including diuretics, ACE inhibitors, ARBs, and nonsteroidal anti-inflammatory drugs. Patients who have these risk factors should probably use a PEG-ELS product rather than sodium phosphate.

LAXATIVE ABUSE

Causes. Many people believe that a daily and bountiful bowel movement is a requisite of good health, and that any deviation from this pattern merits correction. Such misconceptions are reinforced by aggressive marketing of OTC laxative preparations. Not infrequently, the combination of tradition supported by advertising has led to habitual self-prescribing of laxatives by people who don't need them.

Laxatives can help perpetuate their own use. Strong laxatives can purge the entire bowel. When this occurs, spontaneous evacuation is impossible until bowel content has been replenished, which can take 2 to 5 days. During this time, the laxative user, having experienced no movement of the bowel, often becomes convinced that constipation has returned. In response, he or she takes yet another dose, which purges the bowel once more, and thereby sets the stage for a repeating cycle of laxative use and purging.

Consequences. Chronic exposure to laxatives can diminish defecatory reflexes, leading to further reliance on laxatives. Laxative abuse may also cause more serious pathologic changes, including electrolyte imbalance, dehydration, and colitis.

Treatment. The first step in breaking the laxative habit is abrupt cessation of laxative use. Following drug withdrawal, bowel movements will be absent for several days; the patient should be informed of this fact. Any misconceptions that the patient has regarding bowel function should be corrected: The patient should be taught that a once-daily bowel movement may not be normal for him or her and that stool *quality* is more important than frequency or quantity. Instruction on bowel training (heeding the defecatory reflex, establishing a consistent time for bowel movements) should be provided. Increased consumption of fiber (bran, fruits, vegetables) and fluid should be stressed. The patient should be encouraged to exercise daily, especially after meals. Finally, the patient should be advised that, if a laxative must be used, it should be used briefly and in the smallest effective dose. Agents that produce catharsis must be avoided.

KEY POINTS

- Laxatives promote defecation.
- Constipation is defined primarily by stool consistency, not by frequency or volume of bowel movements.
- Legitimate indications for laxatives include cardiovascular disorders, episiotomy, hemorrhoids, emptying the bowel before surgery and diagnostic procedures, ileostomy or colostomy, prevention of fecal impaction in bedridden patients, and constipation associated with pregnancy and certain drugs, especially opioid analgesics.
- Like dietary fiber, bulk-forming laxatives swell in water to form a viscous solution or gel, thereby softening the feces and increasing fecal mass. Increased mass stretches the bowel wall, and thereby stimulates peristalsis.
- Administer bulk-forming laxatives with fluid to avoid esophageal obstruction.
- Patients receiving osmotic laxatives must increase fluid intake to avoid dehydration.

- Because of their relatively rapid onset, group I laxatives (castor oil, high-dose osmotic agents) should not be given at bedtime.
- Laxatives—especially the stimulant type—are commonly misused (abused) by the public. To reduce abuse, educate patients about normal bowel function and about alternatives to laxatives (diet high in fiber and fluids, exercise, establishing regular bowel habits).
- Bowel cleansing prior to colonoscopy can be accomplished with two types of equally effective products: sodium phosphate cleansers and PEG-ELS solutions.
- Sodium phosphate cleansers are easier to take than PEG-ELS cleansers, but pose a greater risk of adverse effects, namely dehydration, electrolyte disturbances, and kidney damage.

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Summary of Major Nursing Implications*

LAXATIVES

Implications That Apply to All Laxatives

Identifying High-Risk Patients

Laxatives are *contraindicated* for individuals with abdominal pain, nausea, cramps, and other symptoms of appendicitis, regional enteritis, diverticulitis, and ulcerative colitis. Laxatives are also *contraindicated* for patients with acute surgical abdomen, fecal impaction, and obstruction of the bowel.

Laxatives should be used with *caution* during pregnancy and lactation.

Reducing Laxative Abuse

Patient education is a key factor in reducing laxative abuse. Educate patients about normal bowel function to correct misconceptions. Provide instruction on establishing good bowel habits (heeding the defecatory reflex, establishing a consistent time for bowel movements). Advise patients to exercise—especially after meals—and to increase consumption of fluids and fiber (bran, fruits, vegetables). Inform patients that laxatives should be used only when clearly necessary and then only briefly in the lowest effective dosage. Warn patients against using cathartics.

Implications That Apply to Specific Laxatives

Bulk-Forming Laxatives: Psyllium, Methylcellulose, and Polycarbophil

Instruct patients to take bulk-forming agents with a full glass of water or juice to prevent esophageal obstruction.

Bulk-forming laxatives are *contraindicated* for individuals with narrowing of the intestinal lumen, a condition that increases the risk of intestinal obstruction and impaction.

Surfactants: Docusate Salts

Instruct patients to take surfactant agents with a full glass of water.

Stimulant Laxatives

Stimulant agents are the laxatives most commonly abused by the general public. **Discourage patients from inappropriate use of these drugs.** These drugs are commonly—and appropriately—used to manage opioid-induced constipation.

Bisacodyl. Administer PO and by rectal suppository. Instruct patients to take oral bisacodyl no sooner than 1 hour after ingesting milk or antacids. Instruct patients to swallow the tablets intact, without crushing or chewing.

Inform patients that bisacodyl suppositories may cause a burning sensation, and warn them that prolonged use can cause proctitis.

Senna. Inform patients that senna can impart a harmless yellowish-brown or pink color to urine.

Castor Oil. Castor oil acts rapidly (in 2 to 6 hours); do not administer at bedtime. Advise patients not to take castor oil late at night. Warn patients that castor oil is a powerful laxative and should not be used to treat routine constipation. Administer in chilled fruit juice to improve palatability.

Osmotic Laxatives: Magnesium Salts and Sodium Salts

Effects are dose dependent. Low doses produce a soft or semifluid stool in 6 to 12 hours. Higher doses cause watery evacuation of the bowel in 2 to 6 hours.

To prevent dehydration, increase fluid intake during treatment.

Magnesium salts are contraindicated for patients with renal dysfunction.

Sodium phosphate is contraindicated for patients with heart failure, hypertension, or edema, and should be used with caution, if at all, by patients with kidney disease and by those taking drugs that alter renal function (eg, diuretics, ACE inhibitors, ARBs).

*Patient education information is highlighted as blue text.

Other Gastrointestinal Drugs

Antiemetics

The Emetic Response

Antiemetic Drugs

Chemotherapy-Induced Nausea and Vomiting

Nausea and Vomiting of Pregnancy

Drugs for Motion Sickness

Antidiarrheal Agents

Nonspecific Antidiarrheal Agents

Management of Infectious Diarrhea

Drugs for Irritable Bowel Syndrome

Nonspecific Drugs

IBS-Specific Drugs

Drugs for Inflammatory Bowel Disease

Prokinetic Agents

Palifermin

Pancreatic Enzymes

Drugs Used to Dissolve Gallstones

Anorectal Preparations

In this chapter we discuss an assortment of GI drugs with indications ranging from emesis to colitis to hemorrhoids. Four groups are emphasized: (1) antiemetics, (2) antidiarrheals, (3) drugs for irritable bowel syndrome, and (4) drugs for inflammatory bowel disease.

ANTIEMETICS

Antiemetics are given to suppress nausea and vomiting. We begin our discussion by reviewing the emetic response. Next we discuss the major antiemetic classes. And then we finish by considering the most important application of these drugs: management of chemotherapy-induced nausea and vomiting (CINV).

The Emetic Response

Emesis is a complex reflex brought about by activating the vomiting center, a nucleus of neurons located in the medulla oblongata. Some stimuli activate the vomiting center directly; others act indirectly (Fig. 80-1). Direct-acting stimuli include signals from the cerebral cortex (anticipation or fear), signals from sensory organs (upsetting sights, noxious odors, or pain), and signals from the vestibular apparatus of the inner ear. Indirect-acting stimuli first activate the chemoreceptor trigger zone (CTZ), which in turn activates the vomiting center. Activation of the CTZ occurs in two ways: (1) by signals from the stomach and small intestine (traveling along vagal afferents); and (2) by the direct action of emetogenic com-

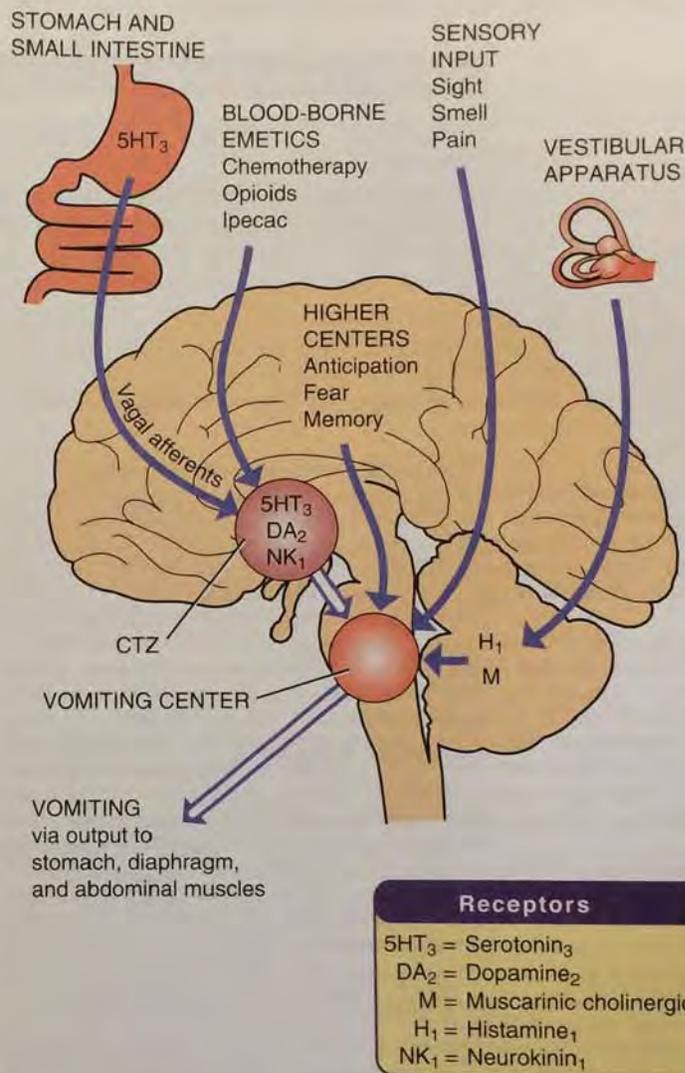


Figure 80-1 ■ The emetic response: stimuli, pathways, and receptors.

(CTZ = chemoreceptor trigger zone.)

pounds (eg, anticancer drugs, opioids, ipecac) that are carried to the CTZ in the blood. Once activated, the vomiting center signals the stomach, diaphragm, and abdominal muscles; the resulting coordinated response expels gastric contents.

Several types of receptors are involved in the emetic response. Important among these are receptors for serotonin, glucocorticoids, substance P, neurokinin₁, dopamine, acetylcholine, and histamine. Many antiemetics, including ondansetron [Zofran], dexamethasone, aprepitant [Emend], prochlorperazine, and dimenhydrinate, act by blocking (or activating) one or more of these receptors.

Antiemetic Drugs

Several types of antiemetics are available. Their classes, trade names, and dosages are summarized in Table 80-1. Uses and mechanisms are summarized in Table 80-2. Properties of the principal classes are discussed below.

Serotonin Receptor Antagonists

Serotonin receptor antagonists are the most effective drugs available for suppressing nausea and vomiting caused by cisplatin and other highly emetogenic anticancer drugs. These

drugs are also highly effective against nausea and vomiting associated with radiation therapy, anesthesia, viral gastritis, and pregnancy. Four serotonin antagonists are available for treating emesis: ondansetron, granisetron, dolasetron, and palonosetron.

Ondansetron. Ondansetron [Zofran, Zofran ODT, Zuplenz] was the first serotonin receptor antagonist approved for CINV. The drug is also used to prevent nausea and vomiting associated with radiotherapy and anesthesia. In addition, the drug is used off-label to treat nausea and vomiting from other

TABLE 80-1 ■ Antiemetic Drugs: Classes, Trade Names, and Dosages

Class and Generic Name	Trade Name	Adult Dosage
Serotonin Antagonists		
Ondansetron	Zofran, Zuplenz	See text
Granisetron	Granisol, Kytril, Sancuso	See text
Dolasetron	Anzemet	See text
Palonosetron	Aloxi	See text
Glucocorticoids		
Dexamethasone	generic only	10–20 mg IV before chemotherapy, then 4–8 mg
Methylprednisolone	Solu-Medrol	2 doses of 125–500 mg IV 6 hr apart before chemotherapy
Substance P/Neurokinin₁ Antagonists		
Aprepitant	Emend	125 mg PO on day 1, then 80 mg PO on days 2 and 3
Fosaprepitant	Emend	115 mg IV, used in place of the first (125-mg) dose of aprepitant in the regimen above
Benzodiazepines		
Lorazepam	Ativan	1–1.5 mg IV before chemotherapy
Diazepam	Valium	2–5 mg PO every 3 hr
Dopamine Antagonists		
Phenothiazines		
Chlorpromazine	generic only	10–25 mg (PO, IM, IV) every 4–6 hr PRN
Perphenazine	generic only	8–30 mg/day in divided doses (PO, IM, IV)
Prochlorperazine	generic only	5–10 mg (PO, IM, IV) 3–4 times a day PRN
Promethazine*	Phenergan	12.5–25 mg (PO, IM, IV) every 4–6 hr
Butyrophenones		
Haloperidol	Haldol	1–5 mg (PO, IM, IV) every 12 hr PRN
Droperidol	generic only	2.5–5 mg (IM, IV) every 4–6 hr PRN
Others		
Metoclopramide [†]	Reglan	See Table 80-3
Cannabinoids		
Dronabinol	Marinol	5 mg/m ² PO every 4–6 hr PRN
Nabilone	Cesamet	1–2 mg PO twice daily
Anticholinergics		
Antihistamines		
Cyclizine	Marezine	50 mg (PO, IM) every 4–6 hr PRN
Dimenhydrinate	generic only	50–100 mg (PO, IM, IV) every 4–6 hr PRN
Diphenhydramine	Benadryl	10–50 mg (PO, IM, IV) every 4–6 hr PRN
Hydroxyzine	Vistaril	25–100 mg (PO, IM) every 6 hr PRN
Meclizine	Bonine, Antivert	25–50 mg PO every 24 hr PRN
Others		
Scopolamine	Transderm Scōp Scopace	0.5 mg transdermal every 72 hr PRN 0.4–0.8 mg PO every 8 hr PRN

*Promethazine is contraindicated for children under 2 years of age owing to a risk of fatal respiratory depression.

[†]Also blocks serotonin receptors.

TABLE 80-2 ■ Antiemetic Drugs: Uses and Mechanism of Action

Class	Prototype	Antiemetic Use	Mechanism of Antiemetic Action
Serotonin antagonists	Ondansetron [Zofran, Zuplenz]	Chemotherapy, radiation, postoperative	Block serotonin receptors on vagal afferents and in the CTZ
Glucocorticoids	Dexamethasone (generic only)	Chemotherapy	Unknown
Substance P/neurokinin ₁ antagonists	Aprepitant [Emend]	Chemotherapy	Block receptors for substance P/ neurokinin ₁ in the brain
Dopamine antagonists	Prochlorperazine (generic only)	Chemotherapy, postoperative, general	Block dopamine receptors in the CTZ
Cannabinoids	Dronabinol [Marinol]	Chemotherapy	Unknown, but probably activate cannabinoid receptors associated with the vomiting center
Anticholinergics	Scopolamine [Transderm Scōp]	Motion sickness	Block muscarinic receptors in the pathway from the inner ear to the vomiting center
Antihistamines	Dimenhydrinate (generic only)	Motion sickness	Block H ₁ receptors and muscarinic receptors in the pathway from the inner ear to the vomiting center

causes, including childhood viral gastritis and morning sickness of pregnancy. In all cases, benefits derive from blocking type 3 serotonin receptors (5-HT₃ receptors*) located in the CTZ and on afferent vagal neurons in the upper GI tract. The drug is very effective by itself, and even more effective when combined with dexamethasone. Administration may be oral or parenteral. The most common side effects are headache, diarrhea, and dizziness. Of much greater concern, ondansetron prolongs the QT interval and hence poses a risk of Torsades de Pointes, a potentially life-threatening dysrhythmia. Accordingly, the drug should not be given to patients with long QT syndrome, and should be used with caution in patients with electrolyte abnormalities, heart failure, or bradydysrhythmias, and in those taking other QT drugs. Since ondansetron does not block dopamine receptors, it does not cause the extrapyramidal effects (eg, akathisia, acute dystonia) seen with antiemetic phenothiazines. As discussed in Chapter 38, ondansetron is under investigation for treating early-onset alcoholism.

Administration is PO, IM, or IV. For oral dosing, ondansetron is available in solution (sold as Zofran), standard tablets (sold as Zofran), orally disintegrating tablets (sold as Zofran ODT), and a soluble film (sold as Zuplenz). To prevent CINV, the recommended IV dose is 0.15 mg/kg infused slowly (over 15 minutes) beginning 30 minutes before chemotherapy; this dose is repeated 4 and 8 hours later. Alternatively, ondansetron can be given as a single 32-mg IV dose. The dosage for patients undergoing radiation therapy is 8 mg PO (tablets, solution, or soluble film) 3 times a day. The dosage for postoperative nausea and vomiting is 16 mg PO (tablets, solution, or soluble film) 1 hour before induction of anesthesia.

Granisetron. Like ondansetron, granisetron [Granisol, Kytril, Sancuso] suppresses emesis by blocking 5-HT₃ receptors on afferent vagal neurons and in the CTZ. The drug is approved for preventing nausea and vomiting associated with cancer chemotherapy, radiation therapy, and surgery. Principal adverse effects are headache (responsive to acetaminophen), weakness, tiredness, and either diarrhea or constipation. Administration is PO, IV, or transdermal. The recommended dosage for CINV is either (1) 10 mcg/kg IV infused over 5 minutes, starting 30 minutes before chemotherapy, or (2) a single transdermal patch [Sancuso] applied 24 to 48 hours before chemo-

therapy, and removed 24 hours after chemotherapy is completed (but no more than 7 days after application). The dosage for patients undergoing radiation therapy is 2 mg (tablets or oral solution) once daily given within 1 hour of radiation treatment. The dosage for preventing postoperative nausea and vomiting is 1 mg IV injected slowly (over 30 seconds) either prior to induction of anesthesia or just before reversing anesthesia.

Dolasetron. Dolasetron [Anzemet] is approved for CINV and postoperative nausea and vomiting. Administration is PO or IV. Side effects are like those of other serotonin antagonists, with one important exception: When given IV in high doses, dolasetron poses a significant risk of fatal dysrhythmias. Accordingly, high-dose IV therapy should not be used. Oral therapy and low-dose IV therapy are considered safe. The recommended dosage for CINV in adults is 100 mg PO 1 hour before chemotherapy. The dosage to prevent postoperative nausea and vomiting is 100 mg PO 2 hours before anesthesia or 12.5 mg IV 15 minutes before anesthesia is stopped.

Palonosetron. Palonosetron [Aloxi], indicated for CINV and postoperative nausea and vomiting, has the same mechanism, efficacy, and side effects as other serotonin antagonists, but differs from the others in two clinically significant ways. First, palonosetron has a much longer half-life (40 hours vs. about 8 hours). Second, because of its long half-life, palonosetron is effective against *delayed* emesis (as well as acute emesis), whereas the others are most effective against acute emesis. Palonosetron also has much greater affinity for 5-HT₃ receptors than the other serotonin antagonists, but this difference does not appear to have clinical significance. Palonosetron is available only in an IV formulation. Capsules for oral dosing have been withdrawn. The recommended dosage for CINV in adults is 250 mcg IV delivered over 30 seconds starting 30 minutes before chemotherapy. To prevent postoperative nausea and vomiting, the dosage is 75 mcg IV delivered over 10 seconds immediately before induction of anesthesia.

Glucocorticoids

Two glucocorticoids—*methylprednisolone* [Solu-Medrol] and *dexamethasone*—are commonly used to suppress CINV, even though they are not approved by the Food and Drug Administration (FDA) for this application. Glucocorticoids are effective alone and in combination with other antiemetics. The mechanism by which glucocorticoids suppress emesis is unknown. Both dexamethasone and methylprednisolone are administered IV. Because antiemetic use is intermittent and short term, serious side effects are absent. The pharmacology of the glucocorticoids is discussed in Chapter 72.

*Serotonin is also known as 5-hydroxytryptamine (5-HT). Hence the abbreviation 5-HT₃ for type 3 serotonin receptors.

Substance P/Neurokinin₁ Antagonists

Two substance P/neurokinin₁ antagonists are currently available: aprepitant and fosaprepitant, a prodrug that undergoes conversion to aprepitant in the body. Their principal application is prevention of CINV. A third drug—casopitant—is in development.

Aprepitant. *Actions and Use.* Aprepitant [Emend] is an important antiemetic. The drug is approved for preventing postoperative nausea and vomiting and CINV. Owing to its unique mechanism of action—blockade of neurokinin₁-type receptors (for substance P) in the CTZ—aprepitant can enhance responses when combined with other antiemetic drugs. Aprepitant has a prolonged duration of action, and hence can prevent *delayed* CINV as well as *acute* CINV. Aprepitant can be used *alone* for managing postoperative nausea and vomiting. However, since the drug is only moderately effective, it must be combined with other antiemetic drugs—specifically, a glucocorticoid (eg, dexamethasone) and a serotonin antagonist (eg, ondansetron)—for managing CINV.

Pharmacokinetics. Oral aprepitant is well absorbed, both in the presence and absence of food. Plasma levels peak 4 hours after dosing. The drug undergoes extensive hepatic metabolism—primarily by CYP3A4 (the 3A4 isozyme of cytochrome P450)—followed by excretion in the urine and feces. The plasma half-life is 9 to 13 hours.

Adverse Effects. Aprepitant is generally well tolerated. Compared with patients receiving ondansetron and dexamethasone, those receiving aprepitant plus ondansetron and dexamethasone experience more fatigue and asthenia (17.8% vs. 11.8%), hiccups (10.8% vs. 5.6%), dizziness (6.6% vs. 4.4%), and diarrhea (10.3% vs. 7.5%). Aprepitant may also cause a mild, transient elevation of circulating aminotransferases, indicating possible liver injury.

Drug Interactions. The potential for drug interactions is complex. Why? Because aprepitant is a substrate for, inhibitor of, and inducer of CYP3A4, a major drug-metabolizing enzyme. Inhibitors of CYP3A4 (eg, itraconazole, ritonavir) can raise levels of aprepitant. Conversely, inducers of CYP3A4 (eg, rifampin, phenytoin) can decrease levels of aprepitant. By inhibiting CYP3A4, aprepitant can raise levels of CYP3A4 substrates, including many drugs used for cancer chemotherapy. Among these are docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. Also, aprepitant can raise levels of glucocorticoids used to prevent CINV. Accordingly, doses of these drugs (dexamethasone and methylprednisolone) should be reduced.

In addition to affecting CYP3A4, aprepitant can induce CYP2D6, another drug-metabolizing enzyme. As a result, aprepitant can decrease levels of CYP2D6 substrates, including warfarin (an anticoagulant) and ethinyl estradiol (found in oral contraceptives). Patients receiving warfarin should be monitored closely. Patients using oral contraceptives may need an alternative form of birth control.

Preparations, Dosage, and Administration. Aprepitant [Emend] is available in 40-, 80- and 125-mg capsules. Dosing may be done with or without food.

For CINV, dosing is done once a day for 3 days. The first dose (125 mg) is given 1 hour before chemotherapy. The second and third doses (80 mg each) are given early on the following 2 days. As noted, aprepitant should be used in combination with dexamethasone and ondansetron.

For postoperative nausea and vomiting, treatment consists of a single 40-mg dose given within 3 hours of anesthesia induction.

Fosaprepitant. Fosaprepitant [Emend] is an intravenous prodrug that undergoes rapid conversion to aprepitant in the body. Accordingly, the pharmacology of fosaprepitant is nearly identical to that of aprepitant. Fosaprepitant is indicated only for preventing CINV. In contrast, aprepitant is approved for CINV and postoperative nausea and vomiting. For prevention of CINV, fosaprepitant is used as a substitute for aprepitant—but only for the first dose in the three-dose regimen (see above). Because IV fosaprepitant has greater bioavailability than PO aprepitant, the dosage for fosaprepitant is only 115 mg, compared with 125 mg for aprepitant. In addition to causing the same adverse effects as aprepitant, fosaprepitant can cause pain and induration at the infusion site.

Casopitant. Casopitant is a substance P/neurokinin₁ antagonist under study for treatment of CINV. Unlike aprepitant, which must be given in several doses, casopitant appears to be effective in just one dose. Like aprepitant, casopitant is used in combination with a glucocorticoid plus a serotonin antagonist.

Benzodiazepines

Lorazepam [Ativan] is used in combination regimens to suppress CINV. The drug has three principal benefits: sedation, suppression of anticipatory emesis, and production of anterograde amnesia. In addition, lorazepam may help control extrapyramidal reactions caused by phenothiazine antiemetics. The basic pharmacology of lorazepam and other benzodiazepines is discussed in Chapter 34.

Dopamine Antagonists

Phenothiazines. The phenothiazines (eg, prochlorperazine) suppress emesis by blocking dopamine₂ receptors in the CTZ. These drugs can reduce emesis associated with surgery, cancer chemotherapy, and toxins. Side effects include extrapyramidal reactions, anticholinergic effects, hypotension, and sedation. The basic pharmacology of the phenothiazines is discussed in Chapter 31 (Antipsychotic Agents and Their Use in Schizophrenia).

One phenothiazine—*promethazine* [Phenergan]—requires comment. Promethazine is the most widely used antiemetic in young children, despite its dangers (respiratory depression and local tissue injury), and despite the availability of safer alternatives (eg, ondansetron). Respiratory depression from promethazine can be severe. Deaths have occurred. Because of this risk, promethazine is contraindicated in children under the age of 2 years, and should be used with caution in children older than 2. Tissue injury can result in several ways. For example, extravasation of IV promethazine can cause abscess formation, tissue necrosis, and gangrene that requires amputation. Severe injury can also occur with inadvertent perivascular or intra-arterial administration, or with administration into or near a nerve. Risk of local injury is lower with IM dosing than with IV dosing. Accordingly, when parenteral administration is needed, the IM route is preferred. SubQ promethazine is contraindicated. If IV administration *must* be done, promethazine should be given through a large-bore, freely flowing line, in a concentration of 25 mg/mL or less at a rate of 25 mg/min or less. Patients should be advised to report local burning or pain immediately.

Butyrophenones. Two butyrophenones—*haloperidol* [Haldol] and *droperidol* (formerly available as Inapsine)—are used as antiemetics. Like the phenothiazines, the butyrophenones suppress emesis by blocking dopamine₂ receptors in the CTZ. Butyrophenones are effective against postoperative nausea and vomiting, and emesis caused by cancer chemotherapy, radiation therapy, and toxins. Potential side effects are similar to those of the phenothiazines: extrapyramidal reactions, sedation, and hypotension. In addition, droperidol may pose a risk of fatal dys-

TABLE 80-3 ■ Representative Regimens for Preventing Chemotherapy-Induced Nausea and Vomiting

High-Emetogenic-Risk Chemotherapy	
Aprepitant	125 mg PO on day 1, 80 mg PO on days 2 and 3 <i>plus</i>
Dexamethasone	12 mg PO or IV on day 1, 8 mg PO or IV on days 2–4 <i>plus</i>
Ondansetron	8 mg PO twice on day 1 <i>or</i> 8 mg or 1.5 mg/kg IV on day 1
Moderate-Emetogenic-Risk Chemotherapy	
Dexamethasone	8 mg PO or IV <i>plus</i>
Palonosetron	0.25 mg IV or 0.5 mg PO
Low-Emetogenic-Risk Chemotherapy	
Dexamethasone	8 mg PO or IV

Data from Basch E, Prestrud AA, et al. Antiemetics: American Society of Clinical Oncology. Clinical Practice Guideline Update *J Clin Oncol* 29:4189-4198, 2011.

body weight. Fortunately, most cases of NVP abate early in pregnancy: about 60% resolve within 13 weeks, and 90% resolve by the end of 20 weeks. Although NVP is commonly called *morning sickness*, it shouldn't be. Why? Because NVP can occur any time of the day, not just in the morning.

NVP can be managed with drugs and with nondrug measures. Nondrug measures include (1) eating small portions of food throughout the day, (2) avoiding odors, foods, and supplements that can trigger NVP (eg, fatty foods, spicy foods, iron tablets), and (3) use of alternative treatments, such as acupuncture and ginger. Despite use of these nondrug measures, about 10% of women require drug therapy.

First-line therapy consists of a two-drug combination: *doxylamine plus vitamin B₆*. In randomized, controlled trials, the combination reduced NVP by 70%, and showed no evidence of adverse fetal outcomes. In Canada, doxylamine and vitamin B₆ are available in a fixed-dose combination sold as *Diclectin* ♣. In the United States, no fixed-dose combination is available. However, doxylamine is available alone as *Unisom Sleep Tabs*, and vitamin B₆ is readily available as a supplement. When the drugs are taken separately, the dosage of doxylamine is 25 mg at bedtime plus 12.5 mg in the morning and afternoon, and the dosage of vitamin B₆ is 10 to 25 mg every 8 hours.

If doxylamine and vitamin B₆ fail to suppress NVP, alternatives include prochlorperazine, metoclopramide, and ondansetron. Methylprednisolone may be tried as a last resort, but only after 10 weeks of gestation (earlier use greatly increases the risk of cleft lip, with or without cleft palate).

DRUGS FOR MOTION SICKNESS

Motion sickness can be caused by sea, air, automobile, and space travel. Symptoms are nausea, vomiting, pallor, and cold sweats. Drug therapy is most effective when given prophylactically, rather than after symptoms begin.

Scopolamine

Scopolamine, a muscarinic antagonist, is our most effective drug for prevention and treatment of motion sickness. Benefits derive from suppressing nerve traffic in the neuronal pathway that connects the vestibular apparatus of the inner ear to the vomiting center (see Fig. 80-1). The most common side

effects are dry mouth, blurred vision, and drowsiness. More severe but less common effects are urinary retention, constipation, and disorientation.

Scopolamine is available for oral, subcutaneous, and transdermal dosing. The transdermal system [Transderm-Scōp], an adhesive patch that contains scopolamine, is applied behind the ear. Anticholinergic side effects with transdermal administration may be less intense than with oral or subcutaneous dosing.

Antihistamines

The antihistamines used most often for motion sickness are *dimenhydrinate*, *meclizine* [Antivert, others], and *cyclizine* [Marezine]. Because these drugs block receptors for acetylcholine in addition to receptors for histamine, they appear in Table 80-1 as a subclass under *Anticholinergics*. Suppression of motion sickness appears to result from blocking histaminergic (H₁) and muscarinic cholinergic receptors in the neuronal pathway that connects the inner ear to the vomiting center (see Fig. 80-1). The most prominent side effect—sedation—results from blocking H₁ receptors. Other side effects—dry mouth, blurred vision, urinary retention, and constipation—result from blocking muscarinic receptors. Antihistamines are less effective than scopolamine for treating motion sickness, and sedation further limits their utility.

ANTIDIARRHEAL AGENTS

Diarrhea is characterized by stools of excessive volume and fluidity, and by increased frequency of defecation. Diarrhea is a symptom of GI disease and not a disease per se. Causes include infection, maldigestion, inflammation, and functional disorders of the bowel (eg, irritable bowel syndrome). The most serious complications of diarrhea are dehydration and electrolyte depletion. Management is directed at (1) diagnosis and treatment of the underlying disease, (2) replacement of lost water and salts, (3) relief of cramping, and (4) reducing passage of unformed stools.

Antidiarrheal drugs fall into two major groups: (1) specific antidiarrheal drugs and (2) nonspecific antidiarrheal drugs. The specific agents are drugs that treat the underlying cause of diarrhea. Included in this group are anti-infective drugs and drugs used to correct malabsorption syndromes. Nonspecific

TABLE 80-4 ■ Opioids Used to Treat Diarrhea

Generic Name	Trade Name	CSA* Schedule	Antidiarrheal Dosage
Diphenoxylate (plus atropine) [†]	Lomotil, Lonox, Logen, Lomanate	V	Adults: 5 mg, 4 times/day Children (initial dosage): Ages 2–5 yr: 1 mg, 4 times/day Ages 5–8 yr: 1–2 mg, 4 times/day Ages 8–12 yr: 1–2 mg, 4 times/day
Difenoxin (plus atropine) [†]	Motofen	IV	Adults: 2 mg initially, then 1 mg after each loose stool
Loperamide	Imodium, Pepto Diarrhea Control, others	NR [‡]	Adults (initial dose): 4 mg Children (initial dosage): Ages 2–5 yr: 1 mg, 3 times/day Ages 5–8 yr: 2 mg, 2 times/day Ages 8–12 yr: 2 mg, 3 times/day
Paregoric (camphorated tincture of opium; contains 0.4 mg morphine/mL)		III	Adults: 5–10 mL, 1–4 times/day Children: 0.25–0.5 mL/kg, 1–4 times/day
Opium tincture (opioid content equivalent to 10 mg morphine/mL)		II	0.6 mL 4 times/day

*Controlled Substances Act.

[†]Diphenoxylate and difenoxin are available only in combination with atropine. The atropine dose is subtherapeutic and is present to discourage abuse.

[‡]Not regulated under the CSA.

antidiarrheals are agents that act on or within the bowel to provide symptomatic relief; these drugs do not influence the underlying cause.

Nonspecific Antidiarrheal Agents

Opioids

Opioids are our most effective antidiarrheal agents. By activating opioid receptors in the GI tract, these drugs decrease intestinal motility, and thereby slow intestinal transit, which allows more time for absorption of fluid and electrolytes. In addition, activation of opioid receptors decreases secretion of fluid into the small intestine and increases absorption of fluid and salt. The net effect is to present the large intestine with less water. As a result, the fluidity and volume of stools are reduced, as is the frequency of defecation.

At the doses employed to relieve diarrhea, subjective effects and dependence do not occur. However, excessive doses can elicit typical morphine-like subjective effects. If severe overdose occurs, it should be treated with an opioid antagonist (eg, naloxone). In patients with inflammatory bowel disease, opioids may cause toxic megacolon.

Several opioid preparations—diphenoxylate, difenoxin, loperamide, paregoric, and opium tincture—are approved for diarrhea. Of these, diphenoxylate [Lomotil, others] and loperamide [Imodium, others] are the most frequently employed. Pharmacologic properties of these agents are discussed below. Dosages for diarrhea are summarized in Table 80-4.

Diphenoxylate. Diphenoxylate is an opioid used only for diarrhea. The drug is insoluble in water, and hence cannot be abused by parenteral routes. When taken orally in antidiarrheal doses, diphenoxylate has no significant effect on the

CNS. However, if taken in high doses, the drug can elicit typical morphine-like subjective effects.

Diphenoxylate is formulated in combination with atropine. The combination, best known as *Lomotil*, is available in tablets and an oral liquid. Each tablet or 5 mL of liquid contains 2.5 mg of diphenoxylate and 25 mg of atropine sulfate. The atropine is present to discourage diphenoxylate abuse: Doses of the combination that are sufficiently high to produce euphoria from the diphenoxylate would produce unpleasant side effects from the correspondingly high dose of atropine. Accordingly, the combination has a very low potential for abuse and is classified under Schedule V of the Controlled Substances Act (CSA).

Loperamide. Loperamide [Imodium, others] is a structural analog of meperidine. The drug is employed to treat diarrhea and to reduce the volume of discharge from ileostomies. Benefits derive from suppressing bowel motility and from suppressing fluid secretion into the intestinal lumen. The drug is poorly absorbed and does not readily cross the blood-brain barrier. Very large oral doses do not elicit morphine-like subjective effects. Loperamide has little or no potential for abuse, and is not regulated under the CSA. The drug is supplied in 2-mg capsules, in 2-mg tablets, and in two liquid formulations (0.2 and 1 mg/mL).

Difenoxin. Difenoxin is the major active metabolite of diphenoxylate. Like diphenoxylate, difenoxin can elicit morphine-like subjective effects at high doses. To discourage excessive dosing, difenoxin, like diphenoxylate, is formulated in combination with atropine. The combination is marketed as *Motofen*. Because its abuse potential is somewhat greater than that of diphenoxylate plus atropine, Motofen is classified as a Schedule IV product.

Paregoric. Paregoric (camphorated tincture of opium) is a dilute solution of opium, containing morphine (0.4 mg/mL) as its main active ingredient. The primary use is diarrhea, although paregoric has the same approved uses as

morphine. Antidiarrheal doses cause neither euphoria nor analgesia. Very high doses can cause typical morphine-like responses. Paregoric has a moderate potential for abuse and is classified under Schedule III of the CSA.

Opium Tincture. Opium tincture is an alcohol-based solution that contains 10% opium by weight. The principal active ingredient—morphine—is present at 10 mg/mL. The primary indication is diarrhea. In addition, opium tincture (after dilution) may be given to suppress symptoms of withdrawal in opioid-dependent neonates. When administered in antidiarrheal doses, opium tincture does not produce analgesia or euphoria. However, high doses can cause typical opioid agonist effects. Opium tincture has a high potential for abuse and is classified as a Schedule II agent.

Other Nonspecific Antidiarrheals

Bismuth Subsalicylate. Bismuth subsalicylate [Pepto-Bismol, others] is effective for the prevention and treatment of mild diarrhea. For prevention, the dosage is two 262-mg tablets 4 times a day for up to 3 weeks. For treatment, the dosage is 2 tablets every 30 minutes for up to eight doses. Users should be aware that the drug may blacken stools and the tongue.

Bulk-Forming Agents. Paradoxically, methylcellulose, polycarboxophil, and other bulk-forming laxatives can help manage diarrhea. Benefits derive from making stools more firm and less watery. Stool volume is not decreased. The bulk-forming laxatives are discussed in Chapter 79.

Anticholinergic Antispasmodics. Muscarinic antagonists (eg, atropine) can relieve cramping associated with diarrhea, but do not alter fecal consistency or volume. However, owing to undesirable side effects (eg, blurred vision, photophobia, dry mouth, urinary retention, tachycardia), anticholinergic drugs are of limited use. The pharmacology of the muscarinic blockers is discussed in Chapter 14.

Management of Infectious Diarrhea

General Considerations. Infectious diarrhea may be produced by enteric infection with a variety of bacteria and protozoa. These infections are usually self-limited. Mild diarrhea can be managed with nonspecific antidiarrheals. In many cases, no treatment is required at all. Antibiotics should be administered only when clearly indicated. Indiscriminate use of antibiotics is undesirable in that it (1) can promote emergence of antibiotic resistance, and (2) can produce an asymptomatic carrier state by killing most, but not all, of the infectious agents. Conditions that *do* merit antibiotic treatment include severe infections with *Salmonella*, *Shigella*, *Campylobacter*, or *Clostridium*.

Traveler's Diarrhea. Tourists are often plagued by infectious diarrhea. This condition is known variously as Montezuma's revenge, the Aztec two-step, or Rangoon runs. In most cases, the causative organism is *Escherichia coli*. As a rule, treatment is unnecessary: Infection with *E. coli* is self-limited and will run its course in a few days. However, if symptoms are especially severe, treatment with one of the fluoroquinolone antibiotics—*ciprofloxacin* (500 mg twice daily), *levofloxacin* (500 mg once daily), *ofloxacin* (300 mg twice daily), or *norfloxacin* (400 mg twice daily)—is indicated. *Azithromycin* [Zithromax] is preferred for children (10 mg/kg on day 1 and 5 mg/kg on days 2 and 3) and for pregnant women (1000 mg once or 500 mg once daily for 3 days). *Rifaximin* [Xifaxan] (200 mg 3 times a day for 3 days) may also be used, provided the patient is not pregnant or febrile, and that stools are not bloody. For patients with mild symptoms, relief can be achieved with *loperamide*, a nonspecific antidiarrheal. However, by slowing peristalsis, loperamide may delay export of the offending organism, and may thereby prolong the infection.

Several measures can reduce acquisition of traveler's diarrhea. Two measures—avoiding local drinking water and carefully washing foods—are highly effective. Certain drugs—*ciprofloxacin*, *ofloxacin*, and *norfloxacin*—can be taken for prophylaxis. However, because these drugs can cause serious

side effects, prophylaxis is not generally recommended. Lastly, travelers can be vaccinated against some pathogens. Oral vaccination with *Dukoral* protects against diarrhea caused by *E. coli* and *Vibrio cholera*. Oral vaccination with *Mutacol* protects against cholera only.

Clostridium difficile–Associated Diarrhea. *Clostridium difficile* is a gram-positive, anaerobic bacillus that infects the bowel. Injury results from release of bacterial toxins. Symptoms range from relatively mild (abdominal discomfort, nausea, fever, diarrhea) to very severe (toxic megacolon, pseudomembranous colitis, colon perforation, sepsis, and death). *C. difficile* infection and its treatment are discussed at length in Chapter 85 (see Box 85–1).

DRUGS FOR IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is the most common disorder of the GI tract, affecting an estimated 20% of Americans—about 54 million people. The incidence in women is 3 times the incidence in men. IBS is responsible for 12% of all visits to primary care physicians, and 28% of all visits to gastroenterologists. The direct medical costs are estimated at \$8 billion a year; the indirect costs are much higher—about \$25 billion a year. IBS is second only to the common cold as the leading cause of days missed from work.

What is IBS? A GI disorder characterized by crampy abdominal pain—sometimes severe—occurring in association with diarrhea, constipation, or both. Formally, IBS is defined by the presence, for at least 12 weeks in the past year, of abdominal pain or discomfort that cannot be explained by structural or chemical abnormalities and that has at least two of the following features:

- Pain is relieved by defecation.
- Onset of pain occurred in association with development of diarrhea or constipation.
- Onset of pain occurred in association with a change in stool consistency (from normal to loose, watery, or pellet-like).

IBS has three major forms, characterized by either

- Abdominal pain in association with diarrhea (diarrhea-predominant IBS, IBS-D)
- Abdominal pain in association with constipation (constipation-predominant IBS, IBS-C)
- Abdominal pain in association with alternating episodes of diarrhea and constipation

What causes IBS? No one knows. Despite extensive research, no underlying pathophysiologic mechanism has been identified. What we do know is that the bowel appears hypersensitive and hyper-responsive. As a result, mild stimuli that would have no effect on most people can trigger an intense response. In addition, we know that symptoms can be triggered by stress, depression, and dietary factors, including caffeine, alcohol, fried foods, fatty foods, gas-generating vegetables (beans, broccoli, cabbage), and too much sorbitol, a sweetener found in chewing gum and some diet products. Overproduction of gastric acid and excessive bacterial colonization of the small intestine have also been implicated.

Fortunately, many people achieve significant relief with treatment. Nondrug measures and drug therapy are employed. Patients should keep a log to identify foods and stressors that trigger symptoms. Because large meals stretch and stimulate the bowel, switching to smaller, more frequent meals may help. Increasing dietary fluid and fiber may reduce constipation.

Two groups of drugs are used for treatment: nonspecific drugs and drugs specific for IBS. Both groups are discussed below.

Nonspecific Drugs

Four groups of drugs—*antispasmodics* (eg, hyoscyamine, dicyclomine), *bulk-forming agents* (eg, psyllium, polycarbophil), *antidiarrheals* (eg, loperamide), and *tricyclic antidepressants* (TCAs)—have been employed for years to provide symptomatic relief. However, a report from the American College of Gastroenterology (ACG) concluded that, for most of these agents, there is no good proof of clinical benefits. Specifically, after reviewing available data, the authors concluded that loperamide and the bulk-forming agents are no better than placebo at relieving global symptoms of IBS. In contrast, they concluded there is good evidence that TCAs can reduce abdominal pain, and that this benefit is unrelated to relief of depression. Regarding antispasmodic agents, they concluded that the available data are insufficient to make a recommendation for or against use.

Studies suggest that, for some patients, symptoms can be relieved with *antibiotics* or an *acid suppressant*. For example, in one study, researchers observed that many patients with IBS have excessive bacteria in the small intestine. When these people were treated with antibiotics, bacterial colonization was reduced, and so were symptoms of IBS. In a more recent study, treatment with oral rifaximin (a poorly absorbed, broad-spectrum antibiotic) reduced symptoms in some patients with IBS. Another study evaluated the impact of drugs that suppress production of stomach acid in patients who routinely experienced exacerbation of symptoms after eating. Two kinds of acid suppressants were used: proton pump inhibitors (lansoprazole or omeprazole) and histamine₂ receptor blockers (famotidine or ranitidine). In all cases, patients experienced a significant reduction of postprandial urgency and other symptoms. Benefits developed quickly (within days) and reversed when the drugs were stopped.

IBS-Specific Drugs

In this section we discuss the only three drugs approved for IBS. These are alosetron (approved for IBS-D), and lubiprostone and tegaserod (both approved for IBS-C). Owing to a risk of serious cardiovascular events, one of these drugs—tegaserod—is used rarely, and then only in emergency situations.

Alosetron

Alosetron [Lotronex] is a potentially dangerous drug approved for IBS-D in *women*. Safety and efficacy in men have not been demonstrated. Alosetron was first approved on February 9, 2000, and then, in response to reports of severe GI toxicity and several deaths, was withdrawn on November 28, 2000, less than 10 months after being introduced. However, in

2002, alosetron was *reapproved* by the FDA, marking the first time the agency has allowed a drug back on the market after it had been pulled for safety reasons. To reduce risk, prescribers, patients, and pharmacists must adhere to a strict risk management program (see below).

Indications. Alosetron is approved only for treating women with severe IBS-D that has lasted for 6 months or more and has not responded to conventional treatment. IBS-D is considered severe if the patient experiences one or more of the following: (1) frequent and severe abdominal pain or discomfort, (2) frequent bowel urgency or fecal incontinence, and (3) disability or restriction of daily activities because of IBS. Less than 5% of IBS cases qualify as severe.

Mechanism of Action and Clinical Effects. Alosetron causes selective blockade of type 3 serotonin receptors (5-HT₃ receptors), which are found primarily on neurons that innervate the viscera. In patients with IBS-D, alosetron can decrease abdominal pain, increase colonic transit time, reduce intestinal secretions, and increase absorption of water and sodium. As a result, the drug can increase stool firmness and decrease both fecal urgency and frequency. Presumably, all of these effects result from 5-HT₃ blockade. Symptoms decline 1 to 4 weeks after starting the drug, and resume 1 week after stopping the drug.

Pharmacokinetics. Administration is oral, and absorption is rapid but incomplete (50% to 60%). Bioavailability is decreased by food. Plasma levels peak about 1 hour after dosing. Alosetron undergoes extensive metabolism by hepatic cytochrome P450 enzymes, followed by excretion primarily in the urine. The half-life is 1.5 hours.

Drug Interactions. Alosetron has no known adverse interactions with other drugs. It does not interact with theophylline, oral contraceptives, cisapride, ibuprofen, alprazolam, amitriptyline, fluoxetine, or hydrocodone combined with acetaminophen. Because alosetron is metabolized by cytochrome P450 enzymes, drugs that induce these enzymes (eg, carbamazepine, phenobarbital) may decrease alosetron levels.

Adverse Effects and Contraindications. Although alosetron is generally well tolerated, it *can* cause severe adverse effects. Deaths have occurred. The most common problem is constipation (29%), which can be complicated by impaction, bowel obstruction, and perforation. In addition, alosetron can cause *ischemic colitis* (intestinal damage secondary to reduced blood flow). Ischemic colitis and complications of constipation have led to hospitalization, blood transfusion, surgery, and death. Owing to its potential for GI toxicity, alosetron is *contraindicated* for patients with ongoing constipation or a history of

- Chronic constipation, severe constipation, or sequelae from constipation
- Intestinal obstruction or stricture, toxic megacolon, or GI perforation or adhesions
- Ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state
- Crohn's disease or ulcerative colitis
- Diverticulitis

Risk Management Program. To ensure the best possible benefit/risk ratio, the manufacturer and the FDA have established a risk management program that involves active

participation of the patient, prescriber, and pharmacist. The program emphasizes that

- Alosetron can cause potentially fatal GI toxicity.
- Only prescribers enrolled in the program can prescribe the drug.
- Alosetron is indicated only for women with severe, chronic IBS-D that has not responded to conventional therapy.
- Treatment should be discontinued immediately if constipation or signs of ischemic colitis develop.

Each enrolled *prescriber* must attest that he or she

- Is qualified to diagnose and treat IBS
- Is qualified to diagnose and manage ischemic colitis
- Is qualified to diagnose and manage constipation and complications of constipation
- Understands the risks and benefits of alosetron for IBS-D
- Agrees to educate the patient about risks and benefits of alosetron, will confirm that each patient has signed a Patient-Physician Agreement, and will give each patient a copy of that agreement and a copy of an alosetron Medication Guide
- Will report serious adverse events to the manufacturer or the FDA
- Will place a qualification sticker on all prescriptions for alosetron (Pharmacists must not fill prescriptions that lack the sticker.)

Each *patient* must sign a Patient-Physician Agreement indicating that she

- Has been informed about and understands the severity of potential risks of alosetron treatment and understands the balance between risks and benefits
- Agrees to treatment with alosetron
- Will not take alosetron if she is constipated, and will immediately discontinue alosetron and contact the prescriber if she becomes constipated or develops signs of ischemic colitis
- Will stop taking alosetron and call the prescriber if the drug does not control IBS symptoms after 4 weeks

Preparations, Dosage, and Administration. Alosetron [Lotronex] is supplied in 0.5- and 1-mg tablets. The recommended initial dosage is currently 1 mg once a day—one-half the dosage recommended when alosetron was first approved. If, after 4 weeks, the dosage is well tolerated but inadequate, it can be increased to 1 mg twice a day. If, after 4 weeks at the higher dosage, treatment is still inadequate, the drug is not likely to help and should be stopped.

Patients who develop constipation or signs of ischemic colitis (rectal bleeding, bloody diarrhea, new or worsening abdominal pain) should immediately inform the prescriber and discontinue the drug. Those with ischemic colitis should never use alosetron again. Those with constipation may resume treatment, but only after constipation has resolved, and only on the advice of the prescriber. If constipation does not resolve, the prescriber should be seen for evaluation.

Lubiprostone

Lubiprostone [Amitiza] is approved for IBS-C in women age 18 and older. Unfortunately, benefits are modest: The drug can reduce abdominal pain and discomfort, but only in a small percentage of patients. Efficacy against IBS-C in men has not been established. In addition to its use in IBS-C, lubiprostone is used for chronic idiopathic constipation (CIC) in women and men (see Chapter 79). As discussed in Chapter 79, lubiprostone causes selective activation of chloride channels in epithelial cells of the intestine, and thereby (1) promotes secretion of chloride-rich fluid into the intestinal lumen and (2) enhances motility of the small intestine and colon. The dosage for IBS-C is lower than for CIC: 8 mcg twice daily versus 24 mcg twice daily. As a result, compared with patients treated for CIC, patients treated for IBS-C experience less nausea (8% vs. 30%), diarrhea (7% vs. 13%), and chest dis-

comfort (0.4% vs. 2.5%). To reduce the incidence of nausea, all doses should be taken with food and water.

Tegaserod

Therapeutic Use. Tegaserod [Zelnorm] is a serotonin analog approved for short-term therapy of IBS-C and CIC in women under the age of 55, but only if they are free of cardiovascular disease, and then only if there is no alternative treatment. Although tegaserod is approved for these patients, *availability* has been restricted by the manufacturer to emergency situations.

Regulatory History. The regulatory history of tegaserod parallels that of alosetron. Tegaserod was approved in July 2002 for IBS-C and in August 2004 for CIC. On March 30, 2007, the FDA requested that tegaserod be voluntarily withdrawn, owing to reports of serious cardiovascular events. Then, in July 2007, the FDA approved an Investigational New Drug (IND) program that made tegaserod available again, but with restricted access. However, on April 2, 2008, the manufacturer—Novartis—decided to close the restricted access program. Nonetheless, patients who have an emergency situation, defined as one that is immediately life threatening or serious enough to qualify for hospitalization, may still be able to obtain the drug through an emergency IND option. Prescribers may inquire about this option by contacting the FDA CDER Division of Drug Information at 301-796-3400.

Actions. Tegaserod is a partial agonist at type 4 serotonin receptors (5-HT₄ receptors), which are found on neurons that innervate the viscera. By activating these receptors, the drug can decrease visceral sensation and increase GI motility and secretions. As a result, tegaserod can reduce bloating, constipation, and abdominal pain. Unfortunately, benefits are modest and may take a month to develop. Furthermore, some users develop severe diarrhea (see below).

Pharmacokinetics. Tegaserod is rapidly absorbed, but bioavailability is low (about 10% in the absence of food and only 5% in the presence of food). In the blood, the drug is highly bound to plasma proteins. Tegaserod undergoes metabolism to inactive products followed by excretion in the bile.

Adverse Effects and Drug Interactions. The most common adverse effect is *diarrhea*, which has been severe in some patients, leading to dehydration, hypovolemia, and hypotension. Most cases occur during the first week of treatment and resolve despite continued drug use. Furthermore, most patients who experience diarrhea have only one episode. Patients who develop severe diarrhea should discontinue tegaserod. People with ongoing diarrhea, and those who experience frequent diarrhea, should not use the drug.

Postmarketing data indicate that tegaserod can cause serious *cardiovascular events*, namely, myocardial infarction (MI), unstable angina, and stroke. Fortunately, these events are rare, and all have occurred in patients with known cardiovascular disease, cardiovascular risk factors, or both. Patients who experience signs of stroke or MI (eg, severe chest pain, shortness of breath, dizziness) should seek immediate medical attention. Because of the potential for cardiovascular harm, access to tegaserod is restricted.

Rarely, users develop *ischemic colitis*. However, there's no proof that tegaserod is the cause. Patients who develop signs of ischemic colitis (eg, rectal bleeding, bloody diarrhea, new or worsening abdominal pain) should discontinue tegaserod and undergo immediate diagnostic testing.

Tegaserod appears devoid of adverse interactions with other drugs.

Contraindications. Tegaserod is contraindicated for women with known cardiovascular disease, severe renal impairment, moderate or severe hepatic impairment, a history of bowel obstruction, symptomatic gallbladder disease, abdominal adhesions, or sphincter of Oddi dysfunction.

Contrasts with Alosetron. Although tegaserod and alosetron are both used for IBS, the drugs differ with regard to mechanism of action, pharmacologic effects, indications, and adverse effects. Specifically,

- Whereas tegaserod is a partial agonist at 5-HT₄ receptors, alosetron is an antagonist at 5-HT₃ receptors.
- Whereas tegaserod increases intestinal motility and secretions, alosetron decreases motility and secretions.
- Whereas tegaserod is used for constipation-predominant IBS, alosetron is used for diarrhea-predominant IBS.
- Whereas tegaserod can cause diarrhea, stroke, and MI, alosetron can cause constipation and ischemic colitis.

Preparations, Dosage, and Administration. Tegaserod [Zelnorm] is formulated in 2- and 6-mg tablets for oral dosing. When the drug was available for routine use, the recommended initial dosage was 6 mg twice daily (taken at least 30 minutes before meals) for 4 to 6 weeks. If there was a favorable response, treatment could continue for another 4 to 6 weeks.

DRUGS FOR INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) has two forms: *Crohn's disease* and *ulcerative colitis*. Crohn's disease is characterized by transmural inflammation, and usually affects the terminal ileum, but can also affect all other parts of the GI tract. Ulcerative colitis is characterized by inflammation of the mucosa and submucosa of the colon and rectum. Both diseases produce abdominal cramps and diarrhea. Ulcerative colitis may cause rectal bleeding as well. About 15% of patients with ulcerative colitis eventually have an attack severe enough to require hospitalization for IV glucocorticoid therapy, which produces remission in 60% of patients; the remaining 40% usually require total colectomy. In the United States, IBD affects about 1.4 million people.

What causes IBD? There is general agreement that IBD results from an exaggerated immune response directed against normal bowel flora—but only in genetically predisposed people.

Drug therapy of IBD is summarized in Table 80-5. Five types of drugs are employed: *5-aminosalicylates* (eg, sulfasalazine), *glucocorticoids* (eg, hydrocortisone), *immunosuppressants* (eg, azathioprine), *immunomodulators* (eg, infliximab), and *antibiotics* (eg, metronidazole). None of these drugs is curative; at best, drugs may control the disease pro-

cess. Patients frequently require therapy with more than one agent.

5-Aminosalicylates

The 5-aminosalicylates are used to treat mild or moderate ulcerative colitis and Crohn's disease, and to maintain remission after symptoms have subsided. Four aminosalicylates are available: sulfasalazine, mesalamine, olsalazine, and balsalazide.

Sulfasalazine. Sulfasalazine [Azulfidine] belongs to the same chemical family as the sulfonamide antibiotics. However, although similar to the sulfonamides, sulfasalazine is not employed to treat infections. Its only approved indications are IBD and rheumatoid arthritis (see Chapter 73).

Actions. Sulfasalazine is metabolized by intestinal bacteria into two compounds: 5-aminosalicylic acid (5-ASA) and sulfapyridine. 5-ASA is the component responsible for reducing inflammation; sulfapyridine is responsible for adverse effects. Possible mechanisms by which 5-ASA reduces inflammation include suppression of prostaglandin synthesis and suppression of the migration of inflammatory cells into the affected region.

Therapeutic Uses. Sulfasalazine is most effective against acute episodes of mild to moderate ulcerative colitis. Responses are less satisfactory when symptoms are severe. Sulfasalazine can also benefit patients with Crohn's disease.

TABLE 80-5 ■ Therapeutic Options for Inflammatory Bowel Disease

Disease Intensity	Disease Form	
	Ulcerative Colitis	Crohn's Disease
Mild	5-Aminosalicylate: PO or rectal	Mesalamine: PO Metronidazole: PO Budesonide: PO Ciprofloxacin: PO
Moderate	5-Aminosalicylate: PO or rectal Infliximab: IV	Glucocorticoid: PO Azathioprine: PO Mercaptopurine: PO Infliximab: IV Certolizumab: subQ Adalimumab: subQ Natalizumab: IV
Severe	Glucocorticoid: PO or IV Cyclosporine: IV Infliximab: IV	Glucocorticoid: PO or IV Methotrexate: IV or subQ Infliximab: IV Certolizumab: subQ Adalimumab: subQ Natalizumab: IV
Refractory	Glucocorticoid: PO or IV Azathioprine: PO Mercaptopurine: PO	Infliximab: IV Certolizumab: subQ Adalimumab: subQ Natalizumab: IV
Remission	5-Aminosalicylate: PO Azathioprine: PO Mercaptopurine: PO	Mesalamine: PO Azathioprine: PO Metronidazole: PO Mercaptopurine: PO Infliximab: IV Certolizumab: subQ Adalimumab: subQ Natalizumab: IV

Adverse Effects. Nausea, fever, rash, and arthralgia are common. Hematologic disorders (eg, agranulocytosis, hemolytic anemia, macrocytic anemia) may also occur. Accordingly, complete blood counts should be obtained periodically. Sulfasalazine appears safe during pregnancy and lactation.

Preparations, Dosage, and Administration. Sulfasalazine [Azulfidine] is available in 500-mg immediate- and delayed-release oral tablets. The initial adult dosage is 500 mg/day. Maintenance dosages range from 2 to 4 gm/day, given in divided doses.

Mesalamine. Mesalamine [Apriso, Asacol, Canasa, Lialda, Pentasa, Rowasa] is the generic name for 5-ASA, the active component in sulfasalazine. The drug is used for acute treatment of mild to moderate IBD and for maintenance therapy of IBD. Mesalamine can be administered by retention enema, by rectal suppository, or by mouth (in tablets and capsules that dissolve when they reach the terminal ileum). Adverse effects are milder than with sulfasalazine. The most common side effects of oral therapy are headache and GI upset. The adult oral dosage is 800 mg 3 times a day (for Asacol tablets) or 1 gm 4 times a day (for Pentasa capsules) or 1.5 gm once a day (for Apriso) or 2.4 to 4.8 gm once a day (for Lialda tablets). The 1000-mg rectal suppositories [Canasa] are administered once daily at bedtime. The retention enema [Rowasa] is administered once daily (4 gm in 60 mL).

Olsalazine. Olsalazine [Dipentum] is a dimer composed of two molecules of 5-ASA, the active component of sulfasalazine. Olsalazine is approved for maintenance therapy of ulcerative colitis in patients who can't tolerate sulfasalazine. The most common adverse effect is watery diarrhea, which occurs in 17% of patients. Other adverse effects include abdominal pain, cramps, acne, rash, and joint pain. Olsalazine is supplied in 250-mg oral capsules. The adult dosage is 500 mg twice daily with food.

Balsalazide. Balsalazide [Colozal] is an aminosalicilate indicated for mildly to moderately active ulcerative colitis. As with sulfasalazine, colonic bacteria act on balsalazide to release 5-ASA, the active portion of the molecule. Nearly all of the drug remains in the intestine; less than 1% is absorbed. As a result, balsalazide is well tolerated. The most common adverse effects are headache (8%), abdominal pain (6%), and diarrhea and nausea (5%). Balsalazide is available in 750-mg oral capsules. The recommended dosage is 3 capsules 3 times a day for 8 to 12 weeks. This dosage delivers 2.4 gm of free 5-ASA to the colon daily.

Glucocorticoids

The basic pharmacology of the glucocorticoids is presented in Chapters 60 and 72; discussion here is limited to their use in IBD. Glucocorticoids (eg, dexamethasone, budesonide) can relieve symptoms of ulcerative colitis and Crohn's disease. Benefits derive from anti-inflammatory actions. Glucocorticoids are indicated primarily for induction of remission—not for long-term maintenance. Why? Because prolonged use can cause severe adverse effects, including adrenal suppression, osteoporosis, increased susceptibility to infection, and a cushingoid syndrome. Administration is IV or PO.

Oral *budesonide* [Entocort EC] is approved for mild to moderate Crohn's disease that involves the ileum and ascending colon. Entocort EC capsules are formulated to release budesonide when it reaches the ileum and ascending colon. As a result, high local concentrations are produced. Systemic effects are lower than with other glucocorticoids because absorbed budesonide undergoes extensive first-pass metabolism.

Immunosuppressants

Immunosuppressants are used for long-term therapy of selected patients with ulcerative colitis and Crohn's disease. Clinical experience is greatest with azathioprine and mercaptopurine.

Thiopurines: Azathioprine and Mercaptopurine. These drugs are discussed together because one is the active form of the other. (Mercaptopurine is the active drug; azathioprine is a prodrug that undergoes conversion to mercaptopurine in the body.)

Although not approved for IBD, azathioprine [Imuran] and mercaptopurine [Purinethol] have been employed with success to induce and maintain remission in both ulcerative colitis and Crohn's disease. Because onset of effects may be delayed for up to 6 months, these agents cannot be used for acute monotherapy. Furthermore, because these drugs are more toxic than aminosaliclates or glucocorticoids, they are generally reserved for patients who have not responded to traditional therapy. Major adverse effects are pancreatitis and neutropenia (secondary to bone marrow suppression). At the doses used for IBD, these drugs are neither carcinogenic nor teratogenic. The basic pharmacology of azathioprine and mercaptopurine is discussed in Chapters 69 and 102, respectively.

Cyclosporine. Cyclosporine [Sandimmune, Neoral, Graf] is a stronger immunosuppressant than azathioprine or mercaptopurine, and acts faster too. When used for IBD, the drug is generally reserved for patients with acute, severe ulcerative colitis or Crohn's disease that has not responded to glucocorticoids. For these patients, continuous IV infusion can rapidly induce remission. In addition to IV administration, the drug has been administered orally in low doses to maintain remission, but results have been inconsistent. Cyclosporine is a toxic compound that can cause renal impairment, neurotoxicity, and generalized suppression of the immune system. The basic pharmacology of cyclosporine is discussed in Chapter 69.

Methotrexate. In patients with Crohn's disease, methotrexate can promote short-term remission, and thereby reduce the need for glucocorticoids. Because the doses employed are low (25 mg once a week), the toxicity associated with high-dose therapy in cancer patients is avoided. The basic pharmacology of methotrexate is discussed in Chapter 102.

Immunomodulators

The drugs discussed in this section are monoclonal antibody products that modulate immune responses. Three of these drugs—infliximab, certolizumab, and adalimumab—are inhibitors of *tumor necrosis factor-alpha* (TNF). The fourth drug—natalizumab—interferes with α_4 integrin. These drugs are generally considered second-line agents. However, some authorities now recommend their use early in treatment, with the hope of inducing remission quickly and maintaining remission longer.

Infliximab. Infliximab [Remicade] is a monoclonal antibody designed to neutralize TNF, a key immunoinflammatory modulator. The drug is indicated for moderate to severe Crohn's disease and ulcerative colitis. In clinical trials, infliximab reduced symptoms in 65% of patients with moderate to severe Crohn's disease and produced clinical remission in 33%. Good responses are also seen in ulcerative colitis. As discussed in Chapter 73, infliximab is also used for rheumatoid arthritis.

During clinical trials, 5% of patients dropped out because of serious adverse effects. Infections (21%) and infusion reactions (16%) are most common. Tuberculosis (TB) and opportunistic infections are of particular concern (see Chapter 73). Infusion reactions include fever, chills, pruritus, urticaria, and cardiopulmonary reactions (chest pain, hypotension, hypertension, dyspnea). Infliximab may also increase the risk of lymphoma, especially among patients with highly active disease or those on long-term immunosuppressive therapy.

Infliximab is supplied as a powder to be reconstituted for IV infusion. For patients with Crohn's disease or ulcerative

colitis, treatment consists of an induction regimen (5 mg/kg infused at 0, 2, and 6 weeks) followed by maintenance infusions of 5 mg/kg every 8 weeks thereafter.

The basic pharmacology of infliximab is discussed in Chapter 73 (Drug Therapy of Rheumatoid Arthritis).

Certolizumab Pegol. Like infliximab, certolizumab pegol [Cimzia] is a monoclonal antibody derivative designed to neutralize TNF. The drug is approved for reducing signs and symptoms of Crohn's disease in patients who have not responded adequately to conventional therapy. Certolizumab is also approved for rheumatoid arthritis (see Chapter 73).

A single dose consists of two subQ injections (200 mg each, 400 mg total) made at separate sites on the abdomen or thigh. To initiate treatment, the patient is given a 400-mg dose at weeks 0, 2, and 4. If there is a clinical response, 400-mg maintenance doses are given every 4 weeks.

The basic pharmacology of certolizumab is discussed in Chapter 73 (Drug Therapy of Rheumatoid Arthritis).

Adalimumab. Like infliximab and certolizumab, adalimumab [Humira] is a monoclonal antibody product that neutralizes TNF. The drug is approved for Crohn's disease, rheumatoid arthritis, psoriasis, and other inflammatory disorders. The pharmacology of adalimumab, including its dosage for Crohn's disease, is presented in Chapter 73 (Drug Therapy of Rheumatoid Arthritis).

Natalizumab. Natalizumab [Tysabri] is monoclonal antibody that interferes with alpha₄ integrin, and thereby impedes migration of leukocytes from the vasculature into areas of inflammation. The drug is approved for Crohn's disease and multiple sclerosis. The pharmacology of natalizumab, including its dosage for Crohn's disease, is presented in Chapter 23 (Drugs for Multiple Sclerosis).

Antibiotics

Antibiotics, such as metronidazole and ciprofloxacin, can help control symptoms in patients with mild or moderate Crohn's disease. In contrast, antibiotics are largely ineffective against ulcerative colitis.

Metronidazole. In patients with mild or moderate Crohn's disease, metronidazole [Flagyl, Protostat] is as effective as sulfasalazine. The dosages employed—up to 750 mg 3 times a day—are high. Furthermore, because relapse is likely if metronidazole is discontinued, long-term therapy is required. Unfortunately, prolonged use of high-dose metronidazole poses a risk of peripheral neuropathy. Although metronidazole can help patients with Crohn's disease, benefits are minimal in those with ulcerative colitis. The pharmacology of metronidazole is presented in Chapter 91.

Ciprofloxacin. Like metronidazole, ciprofloxacin [Cipro] is highly effective in patients with mild or moderate Crohn's disease. A typical dosage is 500 mg twice daily. In one study, ciprofloxacin produced complete or partial remission in 72% of those treated. Combining ciprofloxacin with infliximab is superior to either drug used alone. Like metronidazole, ciprofloxacin is of little benefit in ulcerative colitis. The pharmacology of ciprofloxacin is presented in Chapter 91.

Nicotine

Observational and experimental evidence indicate that nicotine can help protect against ulcerative colitis. It is well known that ulcerative colitis occurs mainly in nonsmokers. Furthermore, the disease frequently develops soon after smoking cessation, and smoking resumption can help reduce symptoms. These observations in smokers have been reinforced by controlled experiments, which have shown that transdermal nicotine (nicotine patches) and a nicotine enema can reduce symptoms in patients with mild to moderate ulcerative colitis. However, until more information is available, nicotine cannot be recommended for routine treatment.

PROKINETIC AGENTS

Prokinetic drugs increase the tone and motility of the GI tract. Indications include gastroesophageal reflux disease (GERD), chemotherapy-induced nausea and vomiting (CINV), and diabetic gastroparesis.

Metoclopramide

Actions. Metoclopramide [Reglan, Metozolv ODT] has two beneficial actions: it (1) suppresses emesis (by blocking receptors for dopamine and serotonin in the CTZ); and

(2) increases upper GI motility (by enhancing the actions of acetylcholine).

Therapeutic Uses. Indications depend on the route (oral or IV). Oral metoclopramide has two approved uses: diabetic gastroparesis and suppression of gastroesophageal reflux. Intravenous metoclopramide has four approved uses: suppression of postoperative nausea and vomiting, suppression of CINV, facilitation of small bowel intubation, and facilitation of radiologic examination of the GI tract. Off-label uses include hiccups, and nausea and vomiting of early pregnancy.

Adverse Effects. With high-dose therapy, sedation and diarrhea are common. Long-term high-dose therapy can cause irreversible *tardive dyskinesia* (TD), characterized by repetitive, involuntary movements of the arms, legs, and facial muscles. The elderly are especially vulnerable. To reduce the risk of TD, treatment should be as brief as possible using the lowest effective dose. Owing to its ability to increase gastric and intestinal motility, metoclopramide is contraindicated in patients with GI obstruction, perforation, or hemorrhage. Of note, exposure to metoclopramide during the first trimester of pregnancy is not associated with an excess risk of congenital malformations.

Preparations, Dosage, and Administration. Metoclopramide is available in four formulations: standard tablets (5 and 10 mg) sold as Reglan, orally disintegrating tablets (5 and 10 mg) sold as Metozolv ODT, an oral syrup (1 mg/mL) sold generically, and a solution for injection (5 mg/mL) sold as Reglan. Dosages are as follows.

Diabetic Gastroparesis. The adult dosage is 10 mg PO 30 minutes before each meal and at bedtime for 2 to 8 weeks. The maximum duration is 12 weeks.

Symptomatic Gastroesophageal Reflux. The usual adult dosage is 10 to 15 mg PO 30 minutes before each meal and at bedtime, for a maximum of 12 weeks. If symptoms are sporadic, a single dose can be taken as needed (up to 20 mg PO 30 minutes before the precipitating situation).

Chemotherapy-Induced Nausea and Vomiting. For prophylaxis of CINV, metoclopramide is given IV, starting 30 minutes before chemotherapy. The initial dose is 1 to 2 mg/kg infused over 15 minutes or more. Additional doses of 1 to 2 mg/kg are administered 2, 4, 7, 10, and 13 hours after the first dose.

Cisapride

Therapeutic Use. Cisapride [Propulsid] is a dangerous drug that can cause fatal cardiac dysrhythmias. In July of 2000, it was voluntarily withdrawn from the U.S. market. Today, it is once again available—but only through an investigational, limited-access program sponsored by Janssen Pharmaceutical. Four indications are recognized: GERD, gastroparesis, pseudo-GI obstruction, and severe chronic constipation. In all cases, cisapride is considered a drug of last resort, reserved for patients who have not responded to standard therapy.

Mechanism of Action. Cisapride increases the tone and motility of GI smooth muscle by promoting release of acetylcholine from neurons of the myenteric plexus. In patients with GERD, the drug reduces symptoms by accelerating gastric emptying, increasing esophageal peristalsis, and increasing tone in the lower esophageal sphincter.

Pharmacokinetics. Cisapride is rapidly absorbed after oral dosing. Blood levels peak within 1.5 hours. The drug is highly (98%) bound to plasma proteins. Cisapride undergoes extensive hepatic metabolism—primarily by CYP3A4—followed by excretion in the urine.

Adverse Effects: Cardiac Dysrhythmias. Cisapride prolongs the QT interval, posing a risk of fatal dysrhythmias. At least 80 patients have died. The risk is greatest among patients with disorders that predispose to dysrhythmias. Accordingly, cisapride is contraindicated for patients with ischemic heart disease, heart failure, prolonged QT interval at baseline, history of torsades de pointes, sinus node dysfunction, second- or third-degree atrioventricular block, or a history of ventricular dysrhythmias. Prior to receiving cisapride, patients should undergo electrocardiographic evaluation.

Drug Interactions. A variety of drugs can increase the risk of cisapride-induced dysrhythmias. Several mechanisms are involved. Some drugs (eg, erythromycin, ketoconazole) inhibit CYP3A4, and thereby increase cisapride levels. Other drugs (eg, quinidine, bepridil) prolong the QT

TABLE 80-6 ■ Drugs That Can Increase the Risk of Cisapride-Induced Dysrhythmias

Drugs That Inhibit the CYP3A4 Enzyme System		
Anastrozole	Fluconazole	Norfloxacin
Cimetidine	Fluoxetine	Paroxetine
Clarithromycin	Fluvoxamine	Propranolol
Clotrimazole	Indinavir	Quinidine
Danazol	Itraconazole	Quinine
Delavirdine	Ketoconazole	Ranitidine
Diethylthiocarbamate	Metronidazole	Ritonavir
Diltiazem	Mirtazapine	Saquinavir
Efavirenz	Nelfinavir	Sertraline
Erythromycin	Nevirapine	Zafirlukast

Drugs That Prolong the QT Interval and Promote Dysrhythmias		
Class I Antidysrhythmics (some)	Beta Agonists	Tricyclic Antidepressants
Quinidine	Albuterol	Amitriptyline
Procainamide	Terbutaline	Imipramine
Flecainide	others	others
others		
Class II Antidysrhythmics	Antimicrobials	Antipsychotic Drugs (some)
Amiodarone	Chloroquine	Chlorpromazine
Dronedarone	Erythromycin	Pimozide
Sotalol	Halofantrine	others
Bepridil	others	

Diuretics That Promote Hypokalemia	
Loop Diuretics	Thiazide Diuretics
Furosemide	Chlorothiazide
Torsemide	Hydrochlorothiazide
others	others

interval. And still others (eg, loop diuretics, thiazide diuretics) promote hypokalemia. Table 80-6 lists many of the drugs that can interact adversely with cisapride. All of them should be avoided.

Preparations, Dosage, and Administration. Cisapride [Propulsid] is formulated in tablets (10 and 20 mg) and an oral suspension (10 mg/mL). The recommended dosage is 10 mg 4 times a day. Dosing is done at least 15 minutes before meals and at bedtime. Some patients may need 20-mg doses. To reduce the risk of adverse effects, the lowest effective dosage should be used. Dosage should be reduced by 50% in patients with liver impairment. If nocturnal heartburn continues, cisapride should be stopped.

PALIFERMIN

Palifermin [Kepivance] is the first drug to be approved for decreasing oral mucositis (OM), a serious and painful complication of cancer chemoradiotherapy. For reasons discussed below, palifermin is currently indicated only for patients with hematologic malignancies. Side effects of the drug are generally mild.

Mechanism of Action

Palifermin is a synthetic form of human keratinocyte growth factor (KGF), a naturally occurring compound. Commercial production is by recombinant DNA technology. Palifermin acts through KGF receptors, which are found on epithelial cells in many structures, including the tongue, buccal mucosa, esophagus, stomach, intestine, salivary gland, liver, lung, pancreas, kidney, bladder, mammary glands, skin (hair follicles and sebaceous glands), and lens of the eye. Importantly, KGF receptors are *not* found on cells of hematopoi-

etic origin. When palifermin binds with KGF receptors, it stimulates proliferation, differentiation, and migration of epithelial cells. In mice and rats, KGF increased the thickness of epithelial tissue in the tongue, buccal mucosa, and GI tract. Similarly, in healthy human volunteers, palifermin produced dose-dependent proliferation of epithelial cells in the buccal mucosa.

Indications and Clinical Benefits

Palifermin is approved for decreasing the incidence and duration of severe OM—but only in patients with *hematologic malignancies*, and then only in those receiving high-dose chemotherapy and whole-body irradiation (to eradicate cancer cells prior to a hematopoietic stem cell transplant). In one trial, palifermin reduced the incidence of OM (67% with palifermin vs. 80% with placebo) as well as the duration (4 days vs. 6 days with placebo). In a second trial, the results were similar: palifermin again reduced both the incidence of OM (63% vs. 98% with placebo) and the duration (6 days vs. 9 days with placebo). In both trials, palifermin reduced the need for pain relief with opioid analgesics, and the need for supplemental parenteral nutrition.

At this time, palifermin therapy is restricted to patients with hematologic malignancies. Why? Because, in experimental models, palifermin can stimulate proliferation of certain malignant cells of nonhematologic origin—specifically, malignant epithelial cells that bear KGF receptors. Palifermin is safe for patients with hematologic cancers because these cancers do not have KGF receptors. As we learn more about

the safety of palifermin in nonhematologic cancers, indications for the drug may expand.

Pharmacokinetics

Information on the kinetics of palifermin is limited. Plasma levels of the drug decline by 95% within 30 minutes of IV dosing, and decline at a slower rate thereafter. The terminal half-life is about 4.5 hours. Giving single doses on 3 consecutive days does result in drug accumulation.

Adverse Effects

Palifermin is generally well tolerated. The most common reactions concern the skin and mouth. Among these are rash, erythema, edema, pruritus, distortion of taste, thickening and/or discoloration of the tongue, and oral or perioral dysesthesias (unpleasant sensations produced by ordinary stimuli). The most serious reaction is skin rash, which develops in less than 1% of patients. In some patients, serum levels of amylase and lipase rise, suggesting possible injury to the pancreas. Because palifermin can stimulate epithelial growth in the lens, there is concern that it might affect vision.

Drug Interactions

Palifermin binds with *heparin*. Accordingly, before giving palifermin through an IV line, any heparin that might be present should be flushed out with saline.

If the interval between giving palifermin and anticancer drugs is too small, palifermin may *increase* the severity and duration of oral mucositis. Accordingly, dosing with palifermin should cease at least 24 hours before giving chemotherapy, and should not resume for at least 24 hours after.

Preparations, Dosage, and Administration

Palifermin [Kepivance] is supplied as a powder (6.25 mg in single-dose vials) for reconstitution with 1.2 mL of sterile water for injection. Administration is by IV bolus. Dosing is done once daily on 3 consecutive days before chemotherapy and on 3 consecutive days after, for a total of six doses. Each dose is 60 mcg/kg. The first dose is given 3 to 4 days before chemotherapy (so that the third dose can be given 1 to 2 days before chemotherapy). The fourth is given at least 4 days after the third dose of palifermin, and at least 1 day after stem cell infusion. Palifermin should be stored under refrigeration, protected from light, and used immediately after reconstitution. Palifermin is expensive: A six-dose course costs about \$10,000.

PANCREATIC ENZYMES

The pancreas produces three types of digestive enzymes: *lipases*, *amylases*, and *proteases*. These enzymes are secreted into the duodenum, where they help digest fats, carbohydrates, and proteins. To protect the enzymes from stomach acid and pepsin, the pancreas secretes bicarbonate. The bicarbonate neutralizes acid in the duodenum, and the resulting elevation in pH inactivates pepsin.

Deficiency of pancreatic enzymes can compromise digestion, especially digestion of fats. Fatty stools are characteristic of the deficiency. When secretion of pancreatic enzymes is reduced, replacement therapy is needed. Causes of deficiency include cystic fibrosis (CF), pancreatotomy, pancreatitis, and obstruction of the pancreatic duct.

Pancreatic enzymes for clinical use are available as *pancrelipase*, a mixture of lipases, amylases, and proteases prepared from hog pancreas. Trade names are *Creon*, *Pancreaze*, and *Zenpep*. All three are supplied in delayed-release capsules designed to dissolve in the duodenum and upper jejunum. The capsules should not be crushed, chewed, or retained in the mouth, owing to a risk of irritating the oral mucosa.

Pancrelipase is generally well tolerated. The most common adverse effects are abdominal discomfort, flatulence, headache, and cough. Large doses can cause diarrhea, nausea, and cramping. The most serious concern is *fibrosing colonopathy*, seen rarely during high-dose therapy in patients with CF. Porcine pancrelipase contains high levels of purines, and hence may pose a risk to patients with gout or hyperuricemia. Allergic reactions occur occasionally.

Acid suppressants (eg, histamine₂ receptor blockers, proton pump inhibitors) may be employed as adjuvants to pancreatic enzyme therapy. The objective is to reduce gastric pH, thereby protecting the enzymes from inactivation. However, acid suppressants are beneficial only when acid secretion is excessive.

Dosage is adjusted on an individual basis. Determining factors include the extent of enzyme deficiency, dietary fat content, and enzyme activity of the preparation selected. The efficacy of therapy can be evaluated by measuring the reduction in 24-hour fat excretion. Pancreatic enzymes should be taken with every meal and snack.

DRUGS USED TO DISSOLVE GALLSTONES

The gallbladder serves as a repository for bile, a fluid composed of cholesterol, bile acids, and other substances. Following production in the liver, bile may be secreted directly into the small intestine or it may be transferred to the gallbladder, where it is concentrated and stored.

Bile has two principal functions: it (1) aids in the digestion of fats, and (2) serves as the only medium by which cholesterol is excreted from the body. The acids in bile facilitate the absorption of fats. In addition, bile acids help solubilize cholesterol.

Cholelithiasis—development of gallstones—is the most common form of gallbladder disease. Most stones are formed from cholesterol. Stones made of cholesterol alone cannot be detected with x-rays, and hence are said to be *radiolucent*. In contrast, stones that contain calcium (in addition to cholesterol) are *radiopaque* (ie, they absorb x-rays and therefore can be seen in a radiograph). Risk factors for cholelithiasis include obesity and high plasma cholesterol.

For many people, gallstones can be present for years without causing symptoms. When symptoms do develop, they can be much like those of indigestion (bloating, abdominal discomfort, gassiness). If a stone becomes lodged in the bile duct, severe pain and jaundice can result.

Cholelithiasis may be treated by cholecystectomy (surgical removal of the gallbladder) or with drugs. As a rule, when intervention is required, cholecystectomy is preferred. In asymptomatic patients, more conservative measures (weight loss and reduced fat intake) may be indicated. Medications employed to dissolve gallstones are discussed below.

Chenodiol (Chenodeoxycholic Acid)

Actions. Chenodiol [Chenodal, Chenix], is a naturally occurring bile acid that reduces hepatic production of cholesterol. Reduced cholesterol production lowers the cholesterol content of bile, which in turn facilitates the gradual dissolution of cholesterol gallstones. Chenodiol may also increase the amount of bile acid in bile, and may thereby enhance cholesterol solubility. It should be noted that chenodiol is useful only for dissolving radiolucent stones. Radiopaque stones (stones with significant calcium content) are not affected.

Therapeutic Use. Chenodiol is given to promote dissolution of cholesterol gallstones, but only in carefully selected patients. Success is most likely in women who have low cholesterol levels, stones of small size, and the ability to tolerate high doses of the drug. Complete disappearance of stones occurs in only 20% to 40% of patients. Therapy is usually prolonged; 2 years is common.

Adverse Effects. Dose-dependent diarrhea occurs in 30% to 40% of patients. Of greater concern, chenodiol can injure the liver. Hence, patients must undergo periodic tests of liver function. Because chenodiol is hepatotoxic, the drug is contraindicated for patients with pre-existing liver disease. Chenodiol is also contraindicated during pregnancy (FDA Pregnancy Risk Category X).

Ursodiol (Ursodeoxycholic Acid)

Ursodiol [Actigall, URSO 250, URSO forte] is an analog of chenodiol. Like chenodiol, ursodiol reduces the cholesterol content of bile, thereby facilitating the gradual dissolution of cholesterol gallstones. In contrast to chenodiol, ursodiol does not increase production of bile acids. Like chenodiol, ursodiol promotes dissolution of *radiolucent* gallstones but not *radiopaque* gallstones. Ursodiol is indicated for dissolution of cholesterol gallstones in carefully selected patients.

Ursodiol is well tolerated. Significant adverse effects are rare. The drug is classified in FDA Pregnancy Risk Category B.

Ursodiol is formulated in capsules (300 mg) and tablets (250 and 500 mg). The usual adult dosage for dissolving gallstones is 4 to 5 mg/kg twice daily (1 capsule or tablet in the morning and 1 in the evening). Treatment lasts for months.

ANORECTAL PREPARATIONS

Nitroglycerin for Anal Fissures

In 2011, the FDA approved a 0.4% nitroglycerin ointment, sold as *Rectogesic*, for relief of moderate to severe pain caused by chronic anal fissures (small tears in the skin that lines the anus). These fissures afflict about 700,000 Americans every year, often causing unrelenting and debilitating pain. Topical nitroglycerin relieves pain and promotes healing by relaxing the internal anal sphincter. Nitroglycerin ointment has been used in other countries for years, and is considered by many experts to be a first-line therapy. The principal adverse effect is headache, which develops in 25% of patients.

Other Anorectal Preparations

Various preparations can help relieve discomfort from hemorrhoids and other anorectal disorders. *Local anesthetics* (eg, benzocaine, dibucaine) and *hydrocortisone* (a glucocorticoid) are common ingredients. Hydrocortisone suppresses inflammation, itching, and swelling. Local anesthetics reduce itching and pain. Anorectal preparations may also contain *emollients* (eg, mineral oil, lanolin), whose lubricant properties reduce irritation, and *astringents* (eg, bismuth subgallate, witch hazel, zinc oxide), which reduce irritation and inflammation. Anorectal preparations are available in multiple formulations: suppositories, creams, ointments, lotions, foams, tissues, and pads. Trade names include *Preparation H*, *Rectagene*, and *Anusol*.

KEY POINTS

- Emesis results from activation of the vomiting center, which receives its principal stimulatory inputs from the chemoreceptor trigger zone (CTZ), cerebral cortex, and inner ear.
- Serotonin antagonists, such as ondansetron [Zofran], are the most effective antiemetics available.
- Aprepitant (an antiemetic) is the first member of a new class of drugs: the substance P/neurokinin₁ receptor antagonists. Unlike most antiemetics, aprepitant can prevent *delayed* chemotherapy-induced nausea and vomiting (CINV) as well as *acute* CINV.
- To suppress CINV, a combination of drugs is more effective than monotherapy.
- For patients receiving highly emetogenic chemotherapy, the preferred antiemetic regimen consists of three drugs: aprepitant, a glucocorticoid (eg, dexamethasone), and a serotonin antagonist (eg, ondansetron).
- For management of CINV, antiemetics are more effective when given before chemotherapy (to prevent emesis) than when given after chemotherapy (in an effort to stop ongoing emesis).
- Nausea and vomiting develop in about 75% of pregnant women, especially during the first trimester.
- First-line therapy for pregnancy-related nausea and vomiting consists of two drugs: doxylamine plus vitamin B₆ (pyridoxine).
- Opioids (eg, diphenoxylate) are the most effective antidiarrheal agents available.
- Traveler's diarrhea can be treated with loperamide (a nonspecific antidiarrheal drug), a fluoroquinolone antibiotic (eg, ciprofloxacin), or azithromycin (for children and pregnant women).
- Irritable bowel syndrome (IBS) is the most common disorder of the GI tract.
- Although three drugs are FDA approved for IBS, only two of them—alosetron and lubiprostone—are generally available.
- Alosetron is approved for IBS-D in women. Benefits derive from blocking 5-HT₃ receptors on neurons that innervate the viscera.
- Alosetron can cause ischemic colitis and severe constipation. Colitis and complications of constipation have led to hospitalization, blood transfusion, surgery, and death.
- Lubiprostone is approved for IBS-C in women. Benefits derive from activating (opening) chloride channels in the intestine.
- Inflammatory bowel disease—ulcerative colitis and Crohn's disease—is treated with 5-aminosalicylates (eg, sulfasalazine, mesalamine), glucocorticoids (eg, dexamethasone, budesonide), immunosuppressants (eg, azathioprine, mercaptopurine), immunomodulators (eg, infliximab, certolizumab), and antibiotics (eg, metronidazole, ciprofloxacin).
- Metoclopramide, a prokinetic agent, has two beneficial actions: It increases upper GI motility and suppresses emesis.
- Palifermin is used to reduce the intensity and duration of oral mucositis in patients with hematologic malignancy undergoing intensive radiochemotherapy.

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Basic Considerations

Dietary Reference Intakes

Classification of Vitamins

Should We Take Multivitamin Supplements?

Fat-Soluble Vitamins

Vitamin A (Retinol)

Vitamin D

Vitamin E (Alpha-Tocopherol)

Vitamin K

Water-Soluble Vitamins

Vitamin C (Ascorbic Acid)

Niacin (Nicotinic Acid)

Riboflavin (Vitamin B₂)Thiamin (Vitamin B₁)Pyridoxine (Vitamin B₆)Cyanocobalamin (Vitamin B₁₂) and Folic Acid

Pantothenic Acid

Biotin

Box 81-1. The Increasingly Strong Case Against Antioxidants

Vitamins have the following defining characteristics: (1) they are *organic compounds*, (2) they are required in *minute amounts* for growth and maintenance of health, and (3) they do not serve as a source of energy (in contrast to fats, carbohydrates, and proteins), but rather are *essential for energy transformation and regulation of metabolic processes*. Several vitamins are inactive in their native form and must be converted to active compounds in the body.

BASIC CONSIDERATIONS**Dietary Reference Intakes**

Reference values on dietary vitamin intake, as set by the Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences, were established to provide a standard for good nutrition. In a 1998 report—*Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline*—the Food and Nutrition Board defined four reference values: *recommended dietary allowance* (RDA), *Adequate Intake* (AI), *Tolerable Upper Intake Level* (UL), and *Estimated Average Requirement* (EAR). Collectively, these four values are referred to as *Dietary Reference Intakes* (DRIs).

Recommended Dietary Allowance. The RDA is the average daily dietary intake sufficient to meet the nutrient requirements of nearly all (97% to 98%) healthy individuals. RDAs are based on extensive experimental data. Because RDAs represent *average* daily intakes, low intake on one day can be compensated for by high intake on another day. RDAs change as we grow older. In addition, they often differ for males and females, and typically increase for women who are pregnant or breast-feeding. You should appreciate that RDAs apply only to individuals in good health. Vitamin requirements can be increased by illness, and therefore published RDA values may not be appropriate for sick people. RDAs are revised periodically as new information becomes available. Table 81-1 summarizes when the most recent revisions were made.

Adequate Intake. The AI is an *estimate* of the average daily intake required to meet nutritional needs. AIs are employed when experimental evidence is not strong enough to establish an RDA. AIs are set with the expectation that they will meet the needs of all individuals. However, because AIs are only estimates, there is no guarantee they are adequate.

Tolerable Upper Intake Level. The UL is the highest average daily intake that can be consumed by nearly everyone without a significant risk of adverse effects. Please note that the UL is not a *recommended* upper limit for intake. It is simply an index of safety. There is no known benefit to exceeding the RDA.

Estimated Average Requirement. The EAR is the level of intake that will meet nutrition requirements for 50% of the healthy individuals in any life-stage or gender group. By definition, the EAR will be insufficient for the other 50%. The EAR for a vitamin is based on extensive experimental data, and serves as the basis for establishing an RDA. If there is not enough information to establish an EAR, no RDA can be set. Instead, an AI is assigned, using the limited data on hand.

Classification of Vitamins

The vitamins are divided into two major groups: *fat-soluble vitamins* and *water-soluble vitamins*. In the fat-soluble group are vitamins A, D, E, and K. The water-soluble group consists of vitamin C and members of the vitamin B complex (thiamin, riboflavin, niacin, pyridoxine, pantothenic acid, biotin, folic acid, and cyanocobalamin). Except for vitamin B₁₂, water-soluble vitamins undergo minimal storage in the body, and hence frequent ingestion is needed to replenish supplies. In contrast, fat-soluble vitamins can be stored in massive amounts, which is good news and bad news. The good news is that extensive storage minimizes the risk of deficiency. The bad news is that extensive storage greatly increases the potential for toxicity if intake is excessive.

TABLE 81-1 ■ Where to Find Food and Nutrition Board Updates for Specific Vitamins*

Vitamin	Publication	Date
Biotin, folate, niacin, pantothenic acid, riboflavin, thiamin, and vitamins B ₆ and B ₁₂	Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B ₆ , Folate, Vitamin B ₁₂ , Pantothenic Acid, Biotin, and Choline	1998
Vitamins C and E	Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids	2000
Vitamins A and K	Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc	2002
Vitamin D	Dietary Reference Intakes for Calcium and Vitamin D	2010

*All publications are from the Food and Nutrition Board, Institute of Medicine, and published by the National Academy Press, Washington, DC.

Should We Take Multivitamin Supplements?

In the United States, we spend about \$3.5 billion a year on multivitamin and multiminerals supplements—with the hope of preventing cancer, heart disease, bone loss, and other chronic disorders. Is the money well spent? Maybe. Maybe not. According to an expert panel—convened by the Office of Dietary Supplements at the National Institutes of Health—there is insufficient evidence to recommend either for or against the use of multivitamins by Americans to prevent chronic disease. Hence, as one official put it, “If you’re taking a multivitamin, there’s no reason to stop—but if you’re not taking a multivitamin, there’s no reason to start, either.” The panel’s findings were published in a January 2007 supplement to the *American Journal of Clinical Nutrition*.

For people who *do* take a multivitamin supplement, the dosage should be moderate. Why? Because excessive doses can cause harm. For example, too much vitamin A increases the risk of osteoporosis in postmenopausal women, and can cause birth defects when taken early in pregnancy. In people who smoke, too much beta-carotene (a precursor of vitamin A), increases the risk of lung cancer. And in older people with chronic health problems, too much vitamin E increases the risk of death. Because of these and other concerns, high-dose multivitamin supplements should be avoided. Instead, supplements that supply 100% or *less* of the RDA should be used.

Although research supporting the use of multivitamin supplements is inconclusive, we do have solid data supporting the use of three *individual* vitamins—namely, vitamin B₁₂, folic acid, and vitamin D. Who should take these vitamins? Nutrition experts recommend vitamin B₁₂ for all people over age 50, folic acid for all women of child-bearing age, and vitamin D (plus calcium) for postmenopausal women and other people at risk of fractures.

FAT-SOLUBLE VITAMINS

Vitamin A (Retinol)

Actions. Vitamin A, also known as retinol, has multiple functions. In the eye, vitamin A plays an important role in adaptation to dim light. The vitamin also has a role in embryo-

genesis, spermatogenesis, immunity, growth, and maintaining the structural and functional integrity of the skin and mucous membranes.

Sources. Requirements for vitamin A can be met by (1) consuming foods that contain *preformed vitamin A* (retinol) and (2) consuming foods that contain *provitamin A carotenoids* (beta-carotene, alpha-carotene, beta-cryptoxanthin), which are converted to retinol by cells of the intestinal mucosa. Preformed vitamin A is present only in foods of animal origin. Good sources are dairy products, meat, fish oil, and fish. Provitamin A carotenoids are found in darkly colored, carotene-rich fruits and vegetables. Especially rich sources are carrots, cantaloupe, mangoes, spinach, tomatoes, pumpkins, and sweet potatoes.

Units. The unit employed to measure vitamin A activity is called the *retinol activity equivalent* (RAE). By definition, 1 RAE equals 1 mcg of retinol, 12 mcg of beta-carotene, 24 mcg of alpha-carotene, or 24 mcg of beta-cryptoxanthin. Why are the RAEs for the provitamin A carotenoids 12 to 24 times higher than the RAE for retinol? Because dietary carotenoids are poorly absorbed and incompletely converted into retinol. Hence, to produce the nutritional equivalent of retinol, we need to ingest much higher amounts of the carotenoids. In the past, vitamin A activity was measured in international units (IU). One IU is equal to 0.3 RAEs.

Requirements. Current RDAs for vitamin A, set in 2002, are slightly lower than the previous RDAs. The new RDA for adult males is 900 RAEs, and the RDA for adult females is 700 RAEs. RDAs for individuals in other life-stage groups are shown in Table 81-2.

Pharmacokinetics. Under normal conditions, dietary vitamin A is readily absorbed and then stored in the liver. As a rule, liver reserves of vitamin A are large and will last for months if intake of retinol ceases. Normal plasma levels for retinol range between 30 and 70 mcg/dL. In the absence of vitamin A intake, levels are maintained through mobilization of liver reserves. As liver stores approach depletion, plasma levels begin to decline. Signs and symptoms of deficiency appear when plasma levels fall below 20 mcg/dL.

Deficiency. Because vitamin A is needed for dark adaptation, night blindness is often the first indication of deficiency. With time, vitamin A deficiency may lead to *xerophthalmia* (a dry, thickened condition of the conjunctiva) and *keratomalacia* (degeneration of the cornea with keratinization of the corneal epithelium). When vitamin A deficiency is severe, blindness may occur. In addition to effects on the eye, deficiency can produce skin lesions and dysfunction of mucous membranes.

Toxicity. In high doses, vitamin A can cause birth defects, liver injury, and bone-related disorders. To reduce risk, the Food and Nutrition Board has set the UL for vitamin A at 3000 mcg/day.

Vitamin A is highly *teratogenic*. Excessive intake during pregnancy can cause malformation of the fetal heart, skull, and other structures of cranial–neural crest origin. Risk is highest among women taking vitamin A supplements. Pregnant women should definitely not exceed the UL for vitamin A, and should probably not exceed the RDA.

Excessive doses can cause a toxic state, referred to as *hypervitaminosis A*. Chronic intoxication affects multiple organ systems, especially the liver. Symptoms are diverse and may include vomiting, jaundice, hepatosplenomegaly, skin changes, hypomenorrhea, and elevation of intracranial pressure. Most symptoms disappear following vitamin A withdrawal.

Vitamin A excess can damage bone. In infants and young children, vitamin A can cause bulging of the skull at sites where bone has not yet formed. In adult females, too much vitamin A can increase the risk of hip fracture—apparently by blocking the ability of vitamin D to enhance calcium absorption.

Therapeutic Uses. The only indication for vitamin A is prevention or correction of vitamin A deficiency. Contrary to earlier hopes, it is now clear that vitamin A, in the form of beta-carotene supplements, does not decrease the risk of cancer or cardiovascular disease. In fact, in a study comparing placebo with dietary supplements (beta-carotene plus vitamin A), subjects taking the supplements had a significantly *increased* risk of lung cancer and overall mortality. As discussed in Chapter 105, certain derivatives of vitamin A (eg, isotretinoin, tretinoin) are used to treat acne and other dermatologic disorders.

Preparations, Dosage, and Administration. Vitamin A (retinol) is available in drops, tablets, and capsules for oral dosing and in solution for IM injection. Oral dosing is generally preferred. To *prevent* deficiency, dietary plus supplemental vitamin A should add up to the RDA (see Table 81–2). To *treat* deficiency, doses up to 100 times the RDA may be required.

Vitamin D

Vitamin D plays a critical role in calcium metabolism and maintenance of bone health. The classic effects of deficiency are *rickets* (in children) and *osteomalacia* (in adults). Does vitamin D offer health benefits beyond bone health? Possibly. Studies suggest that vitamin D may protect against arthritis, diabetes, heart disease, autoimmune disorders, and cancers of the colon, breast, and prostate. However, in a 2010 report—*Dietary Reference Intakes for Calcium and Vitamin D*—an expert panel concluded that, although such claims might eventually prove true, the current evidence does not prove any benefits beyond bone health. The pharmacology and physiology of vitamin D are discussed at length in Chapter 75. Values for RDAs and adequate intake are summarized in Table 81–2.

Vitamin E (Alpha-Tocopherol)

Vitamin E (alpha-tocopherol) is essential to the health of many animal species, but has no clearly established role in human nutrition. Unlike other vitamins, vitamin E has no known role in metabolism. Deficiency, which is rare, can result in neurologic deficits.

Vitamin E helps maintain health primarily through antioxidant actions. Specifically, the vitamin helps protect against peroxidation of lipids. Observational studies suggest that vita-

min E may protect against cardiovascular disease, Alzheimer's disease, and cancer. However, more rigorous studies have failed to show any such benefits (Box 81–1). Moreover, there is evidence that high-dose vitamin E may actually increase the risk of heart failure, cancer progression, and all-cause mortality.

Forms of Vitamin E. Vitamin E exists in a variety of forms (eg, alpha-tocopherol, beta-tocopherol, alpha-tocotrienol), each of which has multiple stereoisomers. However, only four stereoisomers are found in our blood, all of them variants of *alpha-tocopherol*. These isomers are designated *RRR-*, *RRS-*, *RSS-*, and *RSS-alpha-tocopherol*. Of the four, only *RRR-alpha-tocopherol* occurs naturally in foods. However, all four can be found in fortified foods and dietary supplements. Why are other forms of vitamin E absent from blood? Because they are unable to bind to *alpha-tocopherol transfer protein* (alpha-TTP), the hepatic protein required for secretion of vitamin E from the liver and subsequent transport throughout the body.

Sources. Most dietary vitamin E comes from vegetable oils (eg, corn oil, olive oil, cottonseed oil, safflower oil, canola oil). The vitamin is also found in nuts, wheat germ, whole-grain products, and mustard greens.

Requirements. Current RDAs for vitamin E were set in 2000 (see Table 81–2). For men and women, the RDA is 15 mg/day (22.5 IU). RDAs increase for women who are breast-feeding, but not for those who are pregnant. Taking more than 200 mg/day increases the risk of hemorrhagic stroke. Accordingly, this limit should be exceeded only when there is a need to manage a specific disorder (eg, advanced macular degeneration), and only when advised by a healthcare professional.

Deficiency. Vitamin E deficiency is rare. In the United States, deficiency is limited primarily to people with an inborn deficiency of alpha-TTP and to those who have fat malabsorption syndromes, and hence cannot absorb fat-soluble vitamins. Symptoms of deficiency include ataxia, sensory neuropathy, areflexia, and muscle hypertrophy.

Potential Benefits. There is evidence that 200 IU of vitamin E daily may reduce the risk of colds in the elderly, and 400 IU daily (in combination with vitamin C, beta-carotene, zinc, and copper) may delay progression of age-related macular degeneration. Vitamin E does not prevent Alzheimer's disease or age-related wrinkles and, as discussed in Box 81–1, does not protect against cardiovascular disease or cancer.

Potential Risks. High-dose vitamin E appears to increase the risk of *hemorrhagic stroke*. How? By inhibiting platelet aggregation. According to a 2010 report, for every 10,000 people taking over 200 IU of vitamin E daily for 1 year, there would be 8 additional cases of hemorrhagic stroke. Accordingly, doses above 200 IU/day should generally be avoided.

A study published in 2005 showed that, in patients with head and neck cancer, vitamin E (400 IU daily) was associated with a *decrease* in cancer-free survival. Similarly, a study published in 2011 showed that vitamin E (400 IU daily) significantly increased the risk of prostate cancer among healthy men. These results are consistent with the theory that antioxidants may cause cancer or accelerate cancer progression.

A study published in 2004 concluded that doses of vitamin E only 9 times the RDA may increase the risk of *death*, especially in older people with additional risk factors. The study, a meta-analysis of 19 clinical trials, indicated that the risk of all-cause mortality was increased by long-term therapy with daily doses of 400 IU (266 mg) or higher. There was no increased risk at daily doses below 200 IU (133 mg). The authors recommend that the UL for vitamin E—currently set at 1500 IU daily—be reduced.

A study published in 2009 showed that high-dose vitamin E (in combination with vitamin C) can blunt the beneficial effects of exercise on insulin sensitivity. Under normal conditions, exercising enhances cellular responses to insulin. However, among subjects who took vitamin E (400 IU/day) plus vitamin C (500 mg twice daily), exercising failed to yield this benefit.

TABLE 81-2 • Recommended Vitamin Intakes for Individuals

Life-Stage Group	Recommended Vitamin Intake Per Day												
	Vitamin A (mcg) ^a	Vitamin C (mg)	Vitamin D (IU) ^{b,c}	Vitamin E (mg) ^d	Vitamin K (mcg)	Thiamin (mg)	Riboflavin (mg)	Niacin (mg) ^e	Vitamin B ₆ (mg)	Folate (mcg) ^f	Vitamin B ₁₂ (mcg)	Pantothenic Acid (mg)	Biotin (mcg)
Infants													
0-6 mo	400*	40*	400*	4*	2*	0.2*	0.3*	2*	0.1*	65*	0.4*	1.7*	5*
7-12 mo	500*	50*	400*	5*	2.5*	0.3*	0.4*	4*	0.3*	80*	0.5*	1.8*	6*
Children													
1-3 yr	300	15	600	6	30*	0.5	0.5	6	0.5	150	0.9	2*	8*
4-8 yr	400	25	600	7	55*	0.6	0.6	8	0.6	200	1.2	3*	12*
Male													
9-13 yr	600	45	600	11	60*	0.9	0.9	12	1	300	1.8	4*	20*
14-18 yr	900	75	600	15	75*	1.2	1.3	16	1.3	400	2.4	5*	25*
19-30 yr	900	90	600	15	120*	1.2	1.3	16	1.3	400	2.4	5*	30*
31-50 yr	900	90	600	15	120*	1.2	1.3	16	1.3	400	2.4	5*	30*
51-70 yr	900	90	600	15	120*	1.2	1.3	16	1.7	400	2.4 ^g	5*	30*
>70 yr	900	90	800	15	120*	1.2	1.3	16	1.7	400	2.4 ^g	5*	30*
Female													
9-13 yr	600	45	600	11	60*	0.9	0.9	12	1	300	1.8	4*	20*
14-18 yr	700	65	600	15	75*	1	1	14	1.2	400 ^h	2.4	5*	25*
19-30 yr	700	75	600	15	90*	1.1	1.1	14	1.3	400 ^h	2.4	5*	30*
31-50 yr	700	75	600	15	90*	1.1	1.1	14	1.3	400 ^h	2.4	5*	30*
51-70 yr	700	75	600	15	90*	1.1	1.1	14	1.5	400	2.4 ^g	5*	30*
>70 yr	700	75	800	15	90*	1.1	1.1	14	1.5	400	2.4 ^g	5*	30*
Pregnancy													
≤18 yr	750	80	600	15	75*	1.4	1.4	18	1.9	600 ⁱ	2.6	6*	30*
19-30 yr	770	85	600	15	90*	1.4	1.4	18	1.9	600 ⁱ	2.6	6*	30*
31-50 yr	770	85	600	15	90*	1.4	1.4	18	1.9	600 ⁱ	2.6	6*	30*
Lactation													
≤18 yr	1200	115	600	19	75*	1.4	1.6	17	2	500	2.8	7*	35*
19-30 yr	1300	120	600	19	90*	1.4	1.6	17	2	500	2.8	7*	35*
31-50 yr	1300	120	600	19	90*	1.4	1.6	17	2	500	2.8	7*	35*

NOTE: This table presents recommended dietary allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs are based on the needs of all individuals in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life-stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

^aAs retinol activity equivalents (RAEs): 1 RAE = 1 mcg retinol, 12 mcg beta-carotene, or 24 mcg alpha-carotene, 24 mcg alpha-carotene, or 24 mcg beta-cryptoxanthin. To calculate RAEs from retinol equivalents (REs) of provitamin A carotenoids in foods, divide the REs by 2. For preformed vitamin A in foods or supplements and for provitamin A carotenoids in supplements, 1 RE = 1 RAE.

^bThese new RDAs and AIs were issued by the Institute of Medicine on November 30, 2010.

^cIn the absence of adequate exposure to sunlight.

^dAs alpha-tocopherol. Alpha-tocopherol includes *RRR*-alpha-tocopherol, the only form of alpha-tocopherol that occurs naturally in foods, and the 2*R*-stereoisomeric forms of alpha-tocopherol (*RRR*-, *RSS*-, *RRS*-, and *RSS*-alpha-tocopherol) that occur in fortified foods and supplements. It does not include the 2*S*-stereoisomeric forms of alpha-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-alpha-tocopherol), also found in fortified foods and supplements.

^eAs niacin equivalents (NE): 1 mg of niacin = 60 mg of tryptophan; 0–6 months = preformed niacin (not NE).

^fAs dietary folate equivalents (DFEs): 1 DFE = 1 mcg food folate = 0.6 mcg of folic acid from fortified food or as a supplement consumed with food = 0.5 mcg of a supplement taken on an empty stomach.

^gBecause 10% to 30% of older people may absorb food-bound B₁₂ poorly, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with B₁₂ or by consuming a supplement containing B₁₂.

^hIn view of evidence linking folate deficiency with neural tube defects in the fetus, the USPSTF recommends that all women capable of becoming pregnant consume 400 to 800 mcg from supplements in addition to intake of food folate from a varied diet.

ⁱIt is assumed that women will continue consuming 400 mcg from supplements or fortified food until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube.

Data from a summary table in Food and Nutrition Board, Institute of Medicine: Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press, 2002:770–771. However, except for the information on vitamins A and K, all of the information in this table was first released in the earlier publications listed in Table 81–1.

THE INCREASINGLY STRONG CASE AGAINST ANTIOXIDANTS

Do megadoses of antioxidants protect against chronic disease? Probably not. Despite early encouraging studies, and despite plausible theories for protective effects, more recent and more rigorous trials have failed to show protection against heart disease, cancer, or any other long-term illness. Worse yet, these trials suggest that high-dose antioxidants may actually *increase* the risk of certain diseases and death.

What are antioxidants? Dietary antioxidants are defined as substances present in food that can significantly decrease cellular and tissue injury caused by highly reactive forms of oxygen and nitrogen, known as “free radicals.” These free radicals, which are normal by-products of metabolism, readily react with other molecules. The result is tissue injury known as “oxidative stress.” Antioxidants help reduce oxidative stress by neutralizing free radicals before they can cause harm. There is no question that dietary antioxidants can decrease injury. However, we have no solid data showing that large doses can reduce the risk of chronic disease.

Which dietary constituents function as antioxidants? There is good evidence that three compounds—selenium, vitamin C, and vitamin E—exert significant antioxidant actions. Data for beta-carotene (a precursor of vitamin A) are less clear: Although beta-carotene has antioxidant activity *in vitro*, convincing evidence of *in vivo* antioxidant activity is lacking.

How might antioxidants protect against chronic disease? By reducing oxidative damage to DNA, they could reduce the risk of cancer. By reducing oxidation of LDL cholesterol, a critical step in the formation of atherosclerotic plaque, they could protect against heart disease. Reducing oxidation of other biologic molecules could explain protection against other diseases.

When evaluating antioxidants for clinical effects, scientists have conducted two kinds of studies: *observational studies* and *randomized controlled trials* (RCTs). Observational studies are based on patient histories: for example, what did patients eat, and what was their medical status? In contrast, RCTs are rigorous, prospective studies in which patients are randomly assigned to either an experimental group or a placebo group; conclusions are based on differences between the two. The results of RCTs are much more reliable than are the results of observational studies.

Nearly all of the early studies on antioxidants were observational. These studies indicated that daily consumption of vegetables rich in antioxidants is associated with a reduced risk of heart disease and several types of cancer. The problem is, these results have more than one interpretation. Yes, they may mean that antioxidant vitamins protected against heart disease and cancer. However, they may also mean that protection was conferred by some other component of the diet (eg, high fiber content and/or low content of cholesterol and saturated fat). Or, perhaps diet had nothing to do with it: Maybe protection resulted from a generally healthy lifestyle, and not from a healthy diet. Hence, although observational studies suggest that antioxidants may protect against heart disease and cancer, they certainly don't prove it.

To establish definitive proof of cardiovascular benefits, scientists have conducted large RCTs. The outcomes have been

both unexpected and discouraging. Results of several major RCTs are summarized below.

- Two large RCTs—the *Heart Outcomes Prevention Evaluation (HOPE) Study* and the *GISSI-Prevenzione trial*—examined the impact of vitamin E on cardiovascular health. Results of HOPE were reported in the January 20, 2000, issue of the *New England Journal of Medicine*. This trial enrolled 9541 patients ages 55 and older, of whom 80% had cardiovascular disease and 40% had diabetes. Half the patients were given 400 IU of vitamin E daily, and half received a placebo. In addition, the patients were randomly assigned to receive either ramipril (an angiotensin-converting enzyme inhibitor) or a second placebo. After 4.5 years, the results were conclusive: Ramipril provided clear protection against cardiovascular events, whereas vitamin E provided none. A 2.5-year extension of the HOPE trial, known as *HOPE-TOO* (for HOPE—The Ongoing Outcomes) reinforced the original data: Over a median interval of 7 years, vitamin E was no better than placebo at preventing cancer, cancer deaths, or the combined endpoint of stroke, myocardial infarction (MI), or cardiovascular death. In August 1999, an Italian group reported similar results in the British journal *Lancet*. Their study, the GISSI-Prevenzione trial, involved 11,000 patients who had suffered an MI. Half were randomly assigned treatment with vitamin E (300 IU daily) and half were given placebo. After 3.5 years, the incidence of nonfatal MI and death from coronary heart disease was the same for both groups, indicating no protection from vitamin E. Not only did vitamin E fail to protect against cardiovascular disease, in the HOPE trial, vitamin E appeared to *increase* the risk of heart failure.
- A study in the January 4, 2005, issue of the *Annals of Internal Medicine* reported on the impact of vitamin E on mortality. The authors of the study, titled *Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality*, analyzed the results of 19 clinical trials involving 135,967 subjects, and concluded that high-dose vitamin E (400 IU a day or more) may increase all-cause mortality and should be avoided.
- In the February 28, 2007, issue of *JAMA*, a study titled *Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention* asked the question: What is the impact of antioxidants on mortality? To get their answer, the authors analyzed the results of 68 randomized trials conducted before 2005. All told, these trials involved over 232,000 patients who were given either antioxidants or placebo. What did the results show? Treatment with three antioxidants—beta-carotene, vitamin A, and vitamin E—may *increase* mortality, not decrease it. For two other antioxidants—vitamin C and selenium—the data were insufficient to determine an impact on mortality, and hence additional studies are needed.
- Two large RCTs, reported in the January 7, 2009, issue of *JAMA* concluded that antioxidants do not protect against cancer of the prostate and any other tissue. The first study—

BOX 81-1 ■ SPECIAL INTEREST TOPIC—cont'd

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Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT)—enrolled 35,533 men and randomized them to either daily selenium (200 mcg), vitamin E (400 IU), both antioxidants, or neither. After 5.5 years, there was no significant difference among the four groups regarding rates of prostate cancer or all-cause mortality. The second study—*Vitamins E and C in the Prevention of Prostate and Total Cancer in Men: The Physicians' Health Study II Randomized Controlled Trial*—enrolled 14,461 male physicians and randomized them to either vitamin E (400 IU every other day), vitamin C (500 mg daily), both antioxidants, or neither. After 8 years, there was no difference among the four groups regarding risk of prostate cancer, other cancers, or cancer-specific mortality.

- Two RCTs, reported in 2007 and 2009, examined the impact of antioxidants on cardiovascular events and cancer in a large group of women. The first study—*A Randomized Factorial Trial of Vitamins C and E and Beta Carotene in the Secondary Prevention of Cardiovascular Events in Women: Results from the Women's Antioxidant Cardiovascular Study*—randomized 8187 women to receive either vitamin C (500 mg daily), vitamin E (600 IU every other day), beta-carotene (50 mg every other day), a combination of these

antioxidants, or placebo. After 9 years of treatment, the antioxidants failed to lower the incidence of cardiovascular events. The second study—*Vitamins C and E and Beta-Carotene Supplementation and Cancer Risk: A Randomized Controlled Trial*—which involved 7627 women from the first study, reported that none of the antioxidants, taken alone or in combinations, lowered the risk for cancer or cancer-related mortality.

What's the bottom line? In 2000, years before most of the above studies were completed, the National Academy of Sciences issued a report stating there is no conclusive evidence that megadoses of dietary antioxidants can protect against cancer, heart disease, Alzheimer's disease, or any other chronic disorder. Furthermore, they noted that excessive doses can cause harm. Accordingly, they recommended limiting intake of antioxidants to amounts that will prevent nutritional deficiency, and recommended avoiding doses that are potentially harmful. The report, titled *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*, is available from the National Academy Press. All of the major studies completed after this 2000 report strongly reinforce its conclusions: High-dose antioxidants do not prevent heart disease or cancer, do not prolong life, and may actually increase the risk of mortality.

Vitamin K

Action. Vitamin K is required for synthesis of prothrombin and three other clotting factors: VII, IX, and X. All of these vitamin K–dependent factors are needed for coagulation of blood.

Forms and Sources of Vitamin K. Vitamin K occurs in nature in two forms: (1) vitamin K₁, or phytonadione (phylloquinone); and (2) vitamin K₂. Phytonadione is present in a wide variety of foods. Vitamin K₂ is synthesized by the normal flora of the gut. Two other forms—vitamin K₄ (menadiol) and vitamin K₃ (menadione)—are produced synthetically. At this time, phytonadione is the only form of vitamin K available for therapeutic use.

Requirements. Human requirements for vitamin K have not been precisely defined. In 2002, the Food and Nutrition Board set the AI for adult males at 120 mcg, and the AI for adult females at 90 mcg. AIs for other life-stage groups are shown in Table 81-2. For most individuals, vitamin K requirements are readily met through dietary sources, and through vitamin K synthesized by intestinal bacteria. Since bacterial colonization of the gut is not complete until several days after birth, levels of vitamin K may be low in newborns.

Pharmacokinetics. Intestinal absorption of the natural forms of vitamin K (phytonadione and vitamin K₂) is adequate only in the presence of bile salts. Menadione and menadiol do not require bile salts for absorption. Following absorption, vitamin K is concentrated in the liver. Metabolism and secretion occur rapidly. Very little is stored.

Deficiency. Vitamin K deficiency produces bleeding tendencies. If the deficiency is severe, spontaneous hemorrhage may occur. In newborns, intracranial hemorrhage is of particular concern.

An important cause of deficiency is reduced absorption. Since the natural forms of vitamin K require bile salts for their uptake, any condition that decreases availability of these

salts (eg, obstructive jaundice) can lead to deficiency. Malabsorption syndromes (sprue, celiac disease, cystic fibrosis of the pancreas) can also decrease vitamin K uptake. Other potential causes of impaired absorption are ulcerative colitis, regional enteritis, and surgical resection of the intestine.

Disruption of intestinal flora may result in deficiency by eliminating vitamin K–synthesizing bacteria. Hence, deficiency may occur secondary to use of antibiotics. In infants, diarrhea may cause bacterial losses sufficient to result in deficiency.

The normal infant is born vitamin K deficient. Consequently, in order to rapidly elevate prothrombin levels, and thereby reduce the risk of neonatal hemorrhage, it is recommended that all infants receive a single injection of phytonadione (vitamin K₁) immediately after delivery.

As discussed in Chapter 52, the anticoagulant warfarin acts as an antagonist of vitamin K, and thereby decreases synthesis of vitamin K–dependent clotting factors. As a result, warfarin produces a state that is functionally equivalent to vitamin K deficiency. If the dosage of warfarin is excessive, hemorrhage can occur secondary to lack of prothrombin.

Adverse Effects. Severe Hypersensitivity Reactions. Intravenous phytonadione can cause serious reactions (shock, respiratory arrest, cardiac arrest) that resemble anaphylaxis or hypersensitivity reactions. Death has occurred. Consequently, phytonadione should not be administered IV unless other routes are not feasible, and then only if the potential benefits clearly outweigh the risks.

Hyperbilirubinemia. When administered *parenterally* to newborns, vitamin K derivatives can elevate plasma levels of bilirubin, thereby posing a risk of *kernicterus*. The incidence of hyperbilirubinemia is greater in premature infants than in

full-term infants. Although all forms of vitamin K can raise bilirubin levels, the risk is higher with menadione and menadiol than with phytonadione.

Therapeutic Uses and Dosage. Vitamin K has two major applications: (1) correction or prevention of hypoprothrombinemia and bleeding caused by vitamin K deficiency, and (2) control of hemorrhage caused by overdose with warfarin.

Vitamin K Deficiency. As discussed, vitamin K deficiency can result from impaired absorption and from insufficient synthesis of vitamin K by intestinal flora. Rarely, deficiency results from inadequate diet. For children and adults, the usual dosage for correction of vitamin K deficiency ranges between 5 and 15 mg/day.

As noted, infants are born vitamin K deficient. To prevent hemorrhagic disease in neonates, it is recommended that all newborns be given an injection of phytonadione (0.5 to 1 mg) immediately after delivery.

Warfarin Overdose. Vitamin K reverses hypoprothrombinemia and bleeding caused by excessive dosing with warfarin, an oral anticoagulant. Bleeding is controlled within hours of vitamin K administration (see Chapter 52 for dosage).

Preparations and Routes of Administration. Phytonadione (vitamin K₁) is available in 5-mg tablets, marketed as Mephyton, and in parenteral formulations (2 and 10 mg/mL) sold generically. Parenteral phytonadione may be administered IM, subQ, and IV. However, since IV administration is dangerous, this route should be used only when other routes are not feasible, and only if the perceived benefits outweigh the substantial risks.

WATER-SOLUBLE VITAMINS

The group of water-soluble vitamins consists of vitamin C and members of the vitamin B complex: thiamin, riboflavin, niacin, pyridoxine, pantothenic acid, biotin, folic acid, and cyanocobalamin. The B vitamins differ widely from one another in structure and function. They are grouped together because they were first isolated from the same sources (yeast and liver). Vitamin C is not found in the same foods as the B vitamins, and hence is classified by itself. DRIs for the B vitamins were revised in 1998. DRIs for vitamin C were revised in 2000.

Two compounds—*pangamic acid* and *laetrile*—have been falsely promoted as B vitamins. Pangamic acid has been marketed as “vitamin B₁₅” and laetrile as “vitamin B₁₇.” There is no proof these compounds act as vitamins or have any other role in human nutrition.

Vitamin C (Ascorbic Acid)

Actions. Vitamin C participates in multiple biochemical reactions. Among these are synthesis of adrenal steroids, conversion of folic acid to folinic acid, and regulation of the respiratory cycle in mitochondria. At the tissue level, vitamin C is required for production of collagen and other compounds that comprise the intercellular matrix that binds cells together. In addition, vitamin C has antioxidant activity (see Box 81-1) and facilitates absorption of dietary iron.

Sources. The main dietary sources of ascorbic acid are citrus fruits and juices, tomatoes, potatoes, strawberries, melons, spinach, and broccoli. Orange juice and lemon juice are especially rich sources.

Requirements. Current RDAs for vitamin C, set in 2000, are higher than the previous RDAs. As in the past, RDAs increase for women who are pregnant or breast-feeding. For smokers, the RDA is increased by 35 mg/day.

Deficiency. Deficiency of vitamin C can lead to *scurvy*, a disease rarely seen in the United States. Symptoms include faulty bone and tooth development, loosening of the teeth, gingivitis, bleeding gums, poor wound healing, hemorrhage into muscles and joints, and ecchymoses (skin discoloration caused by leakage of blood into subcutaneous tissues). Many of these symptoms result from disruption of the intercellular matrix of capillaries and other tissues.

Adverse Effects. Excessive doses can cause *nausea*, *abdominal cramps*, and *diarrhea*. The mechanism is direct irritation of the intestinal mucosa. To protect against GI disturbances, the Food and Nutrition Board has set 2 gm/day as the adult UL for vitamin C.

Therapeutic Use. The only established indication for vitamin C is prevention and treatment of scurvy. For severe acute deficiency, parenteral administration is recommended. The usual adult dosage is 0.3 to 1 gm/day.

Vitamin C has been advocated for therapy of many conditions unrelated to deficiency, including cancers, asthma, osteoporosis, and the common cold. Claims of efficacy for several of these conditions have been definitively disproved. Other claims remain unproved. Studies have shown that large doses do not reduce the incidence of colds, although the intensity or duration of illness may be reduced slightly. Research has failed to show any benefit of vitamin C therapy for patients with advanced cancer, atherosclerosis, or schizophrenia. Vitamin C does not promote healing of wounds.

Preparations and Routes of Administration. Vitamin C is available in formulations for oral and parenteral administration. Oral products include tablets (ranging from 25 to 1500 mg), timed-release capsules (500 mg), and syrups (20 and 100 mg/mL). For parenteral use, vitamin C is available as ascorbic acid, sodium ascorbate, and calcium ascorbate. Administration may be subQ, IM, or IV.

Niacin (Nicotinic Acid)

Niacin has a role as both a vitamin and a medicine. In its medicinal role, niacin is used to reduce cholesterol levels; the doses required are much higher than those used to correct or prevent nutritional deficiency. Discussion in this chapter focuses on niacin as a vitamin. Use of nicotinic acid to reduce cholesterol levels is discussed in Chapter 50.

Physiologic Actions. Before it can exert physiologic effects, niacin must first be converted into nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP). NAD and NADP then act as coenzymes in oxidation-reduction reactions essential for cellular respiration.

Sources. Nicotinic acid (or its nutritional equivalent, nicotinamide) is present in many foods of plant and animal origin. Particularly rich sources are liver, poultry, fish, potatoes, peanuts, cereal bran, and cereal germ.

In humans, the amino acid tryptophan can be converted to nicotinic acid. Hence, proteins can be a source of the vitamin. About 60 mg of dietary tryptophan is required to produce 1 mg of nicotinic acid.

Requirements. RDAs for nicotinic acid are stated as niacin equivalents (NEs). By definition, 1 NE is equal to 1 mg of niacin (nicotinic acid) or 60 mg of tryptophan. Current RDAs for niacin (see Table 81-2) were set in 1998.

Deficiency. The syndrome caused by niacin deficiency is called *pellagra*, a term that is a condensation of the Italian words *pelle agra*, meaning “rough skin.” As suggested by

this name, a prominent symptom of pellagra is dermatitis, characterized by scaling and cracking of the skin in areas exposed to the sun. Other symptoms involve the GI tract (abdominal pain, diarrhea, soreness of the tongue and mouth) and central nervous system (irritability, insomnia, memory loss, anxiety, dementia). All symptoms reverse with niacin replacement therapy.

Adverse Effects. Nicotinic acid has very low toxicity. Small doses are completely devoid of adverse effects. When taken in large doses, nicotinic acid can cause vasodilation with resultant *flushing*, *dizziness*, and *nausea*. Using flushing as an index of excess niacin consumption, the Food and Nutrition Board has set 50 mg as the adult UL. Toxicity associated with high-dose therapy is discussed in Chapter 50.

Nicotinamide, a compound that can substitute for nicotinic acid in the treatment of pellagra, is not a vasodilator, and hence does not produce the adverse effects associated with large doses of nicotinic acid. Accordingly, nicotinamide is often preferred to nicotinic acid for treating pellagra.

Therapeutic Uses. In its capacity as a vitamin, nicotinic acid is indicated only for the prevention or treatment of niacin deficiency. As noted, high-dose nicotinic acid may be used to lower cholesterol levels (see Chapter 50).

Preparations, Dosage, and Administration. *Nicotinic acid* (niacin) is available in immediate-release tablets (50 to 500 mg), controlled-release tablets (250 to 1000 mg), and extended-release capsules (125 to 500 mg). Dosages for mild deficiency range from 10 to 20 mg/day. For treatment of pellagra, daily doses may be as high as 500 mg. Dosages for hyperlipidemia are given in Chapter 50.

Nicotinamide (niacinamide) is available in 100- and 500-mg tablets. For treatment or prevention of pellagra, dosages range from 150 to 500 mg/day. Unlike nicotinic acid, nicotinamide has no effect on plasma lipoproteins, and hence is not used to treat hyperlipidemias.

Riboflavin (Vitamin B₂)

Actions. Riboflavin participates in numerous enzymatic reactions. However, in order to do so, the vitamin must first be converted into one of two active forms: flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN). In the form of FAD or FMN, riboflavin acts as a coenzyme for multiple oxidative reactions.

Sources and Requirements. In the United States, most dietary riboflavin comes from milk, yogurt, cheese, bread products, and fortified cereals. Organ meats are also rich sources. Current RDAs for riboflavin (see Table 81-2) were established in 1998.

Toxicity. Riboflavin appears devoid of toxicity to humans. When large doses are administered, the excess is rapidly excreted in the urine. Because large doses are harmless, no UL has been set.

Use in Riboflavin Deficiency. Riboflavin is indicated only for prevention and correction of riboflavin deficiency, which usually occurs in conjunction with deficiency of other B vitamins. In its early state, riboflavin deficiency manifests as sore throat and angular stomatitis (cracks in the skin at the corners of the mouth). Later symptoms include cheilosis (painful cracks in the lips), glossitis (inflammation of the tongue), vascularization of the cornea, and itchy dermatitis of the scrotum or vulva. Oral riboflavin is used for treatment. The dosage is 10 to 15 mg/day.

Use in Migraine Headache. As discussed in Chapter 30, riboflavin can help prevent migraine headaches. The daily dosage is 400 mg—much higher than the dosage for riboflavin deficiency.

Thiamin (Vitamin B₁)

Actions and Requirements. The active form of thiamin (thiamin pyrophosphate) is an essential coenzyme for carbohydrate metabolism. Thiamin requirements are related to car-

bohydrate intake, and are greatest when carbohydrates are the primary source of calories. For maintenance of good health, thiamin consumption should be at least 0.3 mg/1000 kcal in the diet. Current RDAs for thiamin, set in 1998, appear in Table 81-2. As indicated, thiamin requirements increase significantly during pregnancy and lactation.

Sources. In the United States, the principal dietary sources of thiamin are enriched, fortified, or whole-grain products, especially breads and ready-to-eat cereals. The richest source of the natural vitamin is pork.

Deficiency. Severe thiamin deficiency produces *beriberi*, a disorder having two distinct forms: *wet beriberi* and *dry beriberi*. *Wet beriberi* is so named because its primary symptom is fluid accumulation in the legs. Cardiovascular complications (palpitations, electrocardiogram abnormalities, high-output heart failure) are common and may progress rapidly to circulatory collapse and death. *Dry beriberi* is characterized by neurologic and motor deficits (eg, anesthesia of the feet, ataxic gait, footdrop, wristdrop); edema and cardiovascular symptoms are absent. *Wet beriberi* responds rapidly and dramatically to replacement therapy. In contrast, recovery from *dry beriberi* can be very slow.

In the United States, thiamin deficiency occurs most commonly among alcoholics. In this population, deficiency manifests as *Wernicke-Korsakoff syndrome* rather than frank beriberi. This syndrome is a serious disorder of the central nervous system, having neurologic and psychologic manifestations. Symptoms include nystagmus, diplopia, ataxia, and an inability to remember the recent past. Failure to correct the deficit may result in irreversible brain damage. Accordingly, if Wernicke-Korsakoff syndrome is suspected, parenteral thiamin should be administered immediately.

Adverse Effects. When taken orally, thiamin is devoid of adverse effects. Accordingly, no UL for the vitamin has been established.

Therapeutic Use. The only indication for thiamin is treatment and prevention of thiamin deficiency.

Preparations, Dosage, and Administration. Thiamin is available in standard tablets (50, 100, and 250 mg) and enteric-coated tablets (20 mg) for oral use, and in solution (100 mg/mL) for IM or IV administration. For mild deficiency, oral thiamin is preferred. Parenteral administration is reserved for severe deficiency states (*wet* or *dry beriberi*, *Wernicke-Korsakoff syndrome*). The dosage for beriberi is 50 to 100 mg IM daily for 1 to 2 weeks, followed by 2.5 to 10 mg PO daily until recovery is complete.

Pyridoxine (Vitamin B₆)

Actions. Pyridoxine functions as a coenzyme in the metabolism of amino acids and proteins. However, before it can do so, pyridoxine must first be converted to its active form: pyridoxal phosphate.

Requirements. Current RDAs for pyridoxine were set in 1998. For most people, and especially young people, the RDAs (see Table 81-2) are considerably lower than the RDAs set previously. As in the past, RDAs increase significantly for women who are pregnant or breast-feeding.

Sources. In the United States, the principal dietary sources of pyridoxine are fortified, ready-to-eat cereals; meat, fish, and poultry; white potatoes and other starchy vegetables; and noncitrus fruits. Especially rich sources are organ meats (eg, beef liver) and cereals or soy-based products that have been highly fortified.

Deficiency. Pyridoxine deficiency may result from poor diet, use of isoniazid, and inborn errors of metabolism. Symptoms include seborrheic dermatitis, microcytic anemia, peripheral neuritis, convulsions, depression, and confusion.

In the United States, dietary deficiency of vitamin B₆ is rare, except among alcoholics. Within the alcoholic population, vitamin B₆ deficiency is estimated at 20% to 30%, and occurs in combination with deficiency of other B vitamins.

Isoniazid (a drug for tuberculosis) prevents conversion of vitamin B₆ to its active form, and may thereby induce symptoms of deficiency (peripheral neuritis). Patients who are predisposed to this neuropathy (eg, alcoholics, diabetics) should receive daily pyridoxine supplements.

Inborn errors of metabolism can prevent efficient utilization of vitamin B₆, resulting in greatly increased pyridoxine requirements. Among infants, symptoms include irritability, convulsions, and anemia. Unless treatment with vitamin B₆ is initiated early, permanent retardation may result.

Adverse Effects. At low doses, pyridoxine is devoid of adverse effects. However, if extremely large doses are taken, neurologic injury may result. Symptoms include ataxia and numbness of the feet and hands. To minimize risk, adults should not consume more than 100 mg/day, the UL for this vitamin.

Drug Interactions. Vitamin B₆ interferes with the utilization of levodopa, a drug for Parkinson's disease. Accordingly, patients receiving levodopa should be advised against taking the vitamin.

Therapeutic Uses. Pyridoxine is indicated for prevention and treatment of all vitamin B₆ deficiency states (dietary deficiency, isoniazid-induced deficiency, pyridoxine dependency syndrome).

Preparations, Dosage, and Administration. Pyridoxine is available in standard tablets (25 to 500 mg) and enteric-coated tablets (25 mg) for oral use, and in solution (100 mg/mL) for IM or IV administration. To correct dietary deficiency, the dosage is 10 to 20 mg/day for 3 weeks followed by 1.5 to 2.5 mg/day thereafter for maintenance. To treat deficiency induced by isoniazid, the dosage is 50 to 200 mg/day. To protect against developing isoniazid-induced deficiency, the dosage is 25 to 50 mg/day. Pyridoxine dependency syndrome may require initial doses up to 600 mg/day followed by 25 to 50 mg/day for life.

Cyanocobalamin (Vitamin B₁₂) and Folic Acid

Cyanocobalamin (vitamin B₁₂) and folic acid (folacin) are essential factors in the synthesis of DNA. Deficiency of either vitamin manifests as megaloblastic anemia. Cyanocobalamin deficiency produces neurologic damage as well. Because deficiency presents as anemia, folic acid and cyanocobalamin are discussed at length in Chapter 55 (Drugs for Deficiency Anemias).

RDAs and ULs. Revised RDAs for vitamin B₁₂ and folate (see Table 81-2) were published in 1998. The revised adult RDA for B₁₂ (2.4 mcg) is about 20% higher than the RDA established in 1989, and the revised adult RDA for folic acid (400 mcg) is 100% higher than the old one. Because adults over age 50 often have difficulty absorbing dietary vitamin B₁₂, they should ingest at least 2.4 mcg/day in the form of a supplement. A UL of 1000 mcg/day has been set for folic acid. Owing to insufficient data, no UL has been set for B₁₂.

Food Folate Versus Synthetic Folate. The form of folate that occurs naturally (food folate) has a different chemical structure than synthetic folate (pteroylglutamic acid). Synthetic folate is more stable than food folate, and has greater bioavailability. In the presence of food, the bioavailability of synthetic folate is at least 85%. In contrast, bioavailability of food folate is less than 50%.

To increase folate in the American diet, the Food and Drug Administration issued the following order: Beginning January 1, 1998, all enriched grain products (eg, enriched bread, pasta, flour, breakfast cereal, grits, rice) must be fortified with syn-

thetic folate—specifically, 140 mcg/100 gm of grain. As a result of grain fortification, the incidence of folic acid deficiency in the United States has declined dramatically. Unfortunately, the incidence of birth defects from folate deficiency (see below) has only dropped by 32%.

Folic Acid Deficiency and Fetal Development. Deficiency of folic acid during pregnancy can impair development of the central nervous system, resulting in *neural tube defects* (NTDs), manifesting as *anencephaly* or *spina bifida*. Anencephaly (failure of the brain to develop) is uniformly fatal. Spina bifida, a condition characterized by defective development of the bony encasement of the spinal cord, can result in nerve damage, paralysis, and other complications. The time of vulnerability for NTDs is days 21 through 28 after conception. As a result, damage can occur before a woman recognizes her pregnancy by missing a period. Because NTDs occur very early in pregnancy, it is essential that adequate levels of folic acid be present *when pregnancy begins*; women cannot wait until pregnancy is confirmed before establishing adequate intake. To ensure sufficient folate at the onset of pregnancy, the U. S. Preventive Services Task Force (USPSTF) now recommends that *all women who may become pregnant consume 400 to 800 mcg of supplemental folic acid each day—in addition to the folate they get from food*. Since pregnancy can occur despite birth control measures, this recommendation applies even to women who don't intend to become pregnant.

Folic Acid and Cancer Risk. There is evidence that folic acid in *low* doses may *reduce* cancer risk, whereas folic acid in *higher* doses may *increase* cancer risk—suggesting that cancer risk is increased by having either *too little* folic acid (folic acid deficiency) or by having *too much* folic acid (folic acid excess). In the Nurses' Health Study, women who took a vitamin supplement containing 400 mcg of folate every day for 15 or more years reduced their risk of colon cancer by 75%, suggesting that that low-dose folic acid may be protective. By contrast, in the Aspirin/Folate Polyp Prevention Study, not only did high-dose folic acid (1000 mcg/day for up to 6 years) fail to protect against colorectal cancer, it was actually associated with an increased risk of having three or more colon polyps. Other studies have shown an association between high-dose folic acid and increased risk of lung and prostate cancers. The bottom line? Taking high-dose folic acid to reduce cancer risk is ineffective and should be discouraged. Women who might become pregnant should continue taking at least 400 mcg of folic acid every day to prevent neural tube defects.

Pantothenic Acid

Pantothenic acid is an essential component of two biologically important molecules: *coenzyme A* and *acyl carrier protein*. Coenzyme A is an essential factor in multiple biochemical processes, including gluconeogenesis, intermediary metabolism of carbohydrates, and biosynthesis of steroid hormones, porphyrins, and acetylcholine. Acyl carrier protein is required for synthesis of fatty acids. Pantothenic acid is present in virtually all foods. As a result, spontaneous deficiency has not been reported. There are insufficient data to establish RDAs for pantothenic acid. However, the Food and Nutrition Board has assigned AIs (see Table 81-2). There are no reports of toxicity from pantothenic acid. Accordingly, no UL has been set. Pantothenic acid is available in single-ingredient tablets and in multivitamin preparations. However, because deficiency does not occur, there is no reason to take supplements.

Biotin

Biotin is an essential cofactor for several reactions involved in the metabolism of carbohydrates and fats. The vitamin is found in a wide variety of foods, although the exact amount in most foods has not been determined. In

In addition to being available in foods, biotin is synthesized by intestinal bacteria. Biotin deficiency is extremely rare. In fact, in order to determine the effects of deficiency, scientists had to induce it experimentally. When this was done, subjects experienced dermatitis, conjunctivitis, hair loss, muscle pain, peripheral paresthesias, and psychologic effects (lethargy, hallucinations,

depression). At this time, the data are insufficient to establish RDAs for biotin. However, as with pantothenic acid, the Food and Nutrition Board has assigned AIs (see Table 81-2). Biotin appears devoid of toxicity: Subjects given large doses experienced no adverse effects. Accordingly, no UL has been set.

KEY POINTS

- Vitamins can be defined as organic compounds, required in minute amounts, that promote growth and health maintenance by participating in energy transformation and regulation of metabolic processes.
- Recommended dietary allowances (RDAs) for vitamins, which are set by the Food and Nutrition Board of the National Academy of Sciences, represent the average daily dietary intake sufficient to meet the nutrient requirements of nearly all (97% to 98%) healthy individuals in a particular life-stage or gender group.
- The Tolerable Upper Intake Limit (UL) for a vitamin is the highest average daily intake that can be consumed by nearly everyone without a significant risk of adverse effects. The UL is simply an index of safety—not a recommendation to exceed the RDA.
- There is no evidence that taking daily *multivitamin* supplements can decrease the risk of chronic disease. However, there *is* evidence that taking supplements of vitamin B₁₂, folic acid, and vitamin D (plus calcium) can benefit certain individuals.
- Vitamins are divided into two major groups: fat-soluble vitamins (A, D, E, and K) and water-soluble vitamins (vitamin C and members of the vitamin B complex).
- Vitamin A deficiency can cause night blindness, xerophthalmia (a dry, thickened condition of the conjunctiva), and keratomalacia (degeneration of the cornea with keratinization of the corneal epithelium).
- Too much vitamin A can cause birth defects, liver injury, and bone abnormalities. Accordingly, vitamin A intake should not exceed the UL, set at 3000 mcg/day.
- Vitamin D plays a critical role in the regulation of calcium and phosphorus metabolism, and may help protect against breast cancer, colorectal cancer, type 1 diabetes, and overall mortality.
- In children, vitamin D deficiency causes rickets. In adults, deficiency causes osteomalacia.
- High-dose vitamin E (more than 200 IU/day) increases the risk of hemorrhagic stroke.
- Vitamin K is required for synthesis of prothrombin and other clotting factors.
- Vitamin K deficiency causes bleeding tendencies. Severe deficiency can cause spontaneous hemorrhage.
- Vitamin K is used to treat vitamin K deficiency (including neonatal deficiency) as well as overdose with warfarin (an anticoagulant).
- Vitamin C deficiency can cause scurvy.
- Niacin (nicotinic acid) is both a vitamin and a drug.
- When niacin is used as a drug (to reduce cholesterol levels), doses are much higher than when niacin is used to prevent or correct deficiency.
- Niacin deficiency results in pellagra.
- Severe thiamin deficiency produces beriberi.
- In the United States, thiamin deficiency occurs most commonly among alcoholics. In this population, deficiency manifests as Wernicke-Korsakoff syndrome rather than beriberi.
- Pyridoxine (vitamin B₆) deficiency can cause peripheral neuritis and other symptoms.
- Isoniazid, a drug for tuberculosis, prevents conversion of pyridoxine to its active form, and can thereby induce deficiency.
- Folic acid deficiency during early pregnancy can cause neural tube defects (anencephaly and spina bifida). To ensure folic acid sufficiency at the start of pregnancy, all women with the potential for becoming pregnant should consume 400 to 800 mcg of supplemental folic acid every day (in addition to food folate).
- Taking high doses of folic acid (more than 800 mcg/day) is associated with an increased risk of certain cancers, and hence should be discouraged.
- High-dose antioxidants do not prevent heart disease or cancer, do not prolong life, and may actually increase the risk of mortality.

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- Assessment of Weight-Related Health Risk
- Overview of Obesity Treatment
- Weight-Loss Drugs for Long-Term Use
 - Orlistat, a Lipase Inhibitor
 - Investigational Drugs for Long-Term Use
- Weight-Loss Drugs for Short-Term Use:
 - Sympathomimetic Amines
- Discontinued Weight-Loss Drugs
- Calorie-Saving Foods
 - Sugar Substitutes
 - Olestra, a Fat Substitute

Excessive body weight is a public health epidemic. In the United States, 33.8% of adults are obese, and another 34.2% are overweight (although not obese). Worse yet, if the current trend continues, fully half of us will be obese by 2030. Excessive body fat increases the risk of morbidity from hypertension, coronary heart disease, ischemic stroke, type 2 diabetes, gallbladder disease, liver disease, kidney stones, osteoarthritis, sleep apnea, dementia, and certain cancers. Among women, obesity also increases the risk of menstrual irregularities, amenorrhea, urinary incontinence, and polycystic ovary syndrome. And during pregnancy, obesity increases the risk of morbidity and mortality for both the mother and child. In young men, obesity reduces the quality and quantity of sperm. Estimates of how many Americans die from obesity-related illnesses vary widely—from 120,000 a year to over 300,000. Regardless of which estimate is more accurate, obesity is second only to smoking as the leading preventable cause of death.

Pediatric obesity is a special concern. One-third of American children and adolescents are overweight or obese. Since 1963, the average weight of 10-year-old children has increased by 11 pounds. Among children ages 6 to 11, the prevalence of obesity has tripled since 1980. This extra weight is exacting a profound toll on health—increasing the risk of hypertension, heart disease, and asthma. In addition, type 2 diabetes, formerly seen almost exclusively in adults, has increased 10-fold among children and teens, and gallbladder disease has tripled. Because of obesity, and for the first time in history, American children could have a shorter life span than their parents.

Obesity is now viewed as a chronic disease, much like hypertension and diabetes. Despite intensive research, the underlying cause remains incompletely understood. Contributing factors include genetics, metabolism, and appetite regulation, along with environmental, psychosocial, and cultural factors. Although obese people can lose weight, the tendency to regain weight cannot be eliminated. Put another way,

obesity cannot yet be cured. Accordingly, for most patients, lifelong management is indicated.

Several important guidelines on obesity management have been published. In 1998, the National Heart, Lung, and Blood Institute (NHLBI), in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases, released the first federal clinical guidelines on obesity, titled *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report*. Two years later, the NHLBI, in cooperation with the North American Association for the Study of Obesity, released a companion document—*The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*—to give clinicians specific tools to help their patients lose weight and keep it off. In 2005, the American College of Physicians (ACP) released a new guideline—*Pharmacologic and Surgical Management of Obesity in Primary Care*—which addresses evidence-based treatments for obesity. Pediatric obesity is addressed in several guidelines, including *Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity*, released in 2007 by the Childhood Obesity Action Network, and *Prevention and Treatment of Pediatric Obesity: An Endocrine Society Clinical Practice Guideline Based on Expert Opinion*, released in 2008.

ASSESSMENT OF WEIGHT-RELATED HEALTH RISK

Health risk is determined by (1) the degree of obesity (as reflected in the body mass index), (2) the pattern of fat distribution (as reflected in the waist circumference measurement), and (3) the presence of obesity-related diseases and/or cardiovascular risk factors. Accordingly, all three factors must be assessed when establishing a treatment plan.

Body Mass Index. The body mass index (BMI), which is derived from the patient's weight and height, is a simple way to estimate body fat content. Studies indicate a close correlation between BMI and total body fat. The BMI is calculated by dividing a patient's weight (in kilograms) by the square of the patient's height (in meters). Hence, BMI is expressed in units of kg/m^2 . BMI can also be calculated using the patient's weight in *pounds* and height in *inches* (Fig. 82-1). According to the federal guidelines, a BMI of 30 or higher indicates obesity. Individuals with a BMI of 25 to 29.9 are considered overweight, but not obese. There is good evidence that the risk of cardiovascular disease and other disorders rises significantly when the BMI exceeds 25. When the BMI exceeds 30, there is an increased risk of death. These specific associations between BMI and health risk do not apply to elderly adults, growing children, or

BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Height	Weight in Pounds																													
4'10"	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215	220	224	229
4'11"	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	217	222	227	232	237
5'	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184	189	194	199	204	209	215	220	225	230	235	240	245
5'1"	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238	243	248	254
5'2"	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196	202	207	213	218	224	229	235	240	246	251	256	262
5'3"	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197	203	208	214	220	225	231	237	242	248	254	259	265	270
5'4"	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209	215	221	227	232	238	244	250	256	262	267	273	279
5'5"	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240	246	252	258	264	270	276	282	288
5'6"	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223	229	235	241	247	253	260	266	272	278	284	291	297
5'7"	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223	230	236	242	249	255	261	268	274	280	287	293	299	306
5'8"	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236	243	249	256	262	269	276	282	289	295	302	308	315
5'9"	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243	250	257	263	270	277	284	291	297	304	311	318	324
5'10"	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250	257	264	271	278	285	292	299	306	313	320	327	334
5'11"	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257	265	272	279	286	293	301	308	315	322	329	336	343
6'	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258	265	272	279	287	294	302	309	316	324	331	338	346	353
6'1"	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272	280	288	295	302	310	318	325	333	340	348	355	363
6'2"	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280	287	295	303	311	319	326	334	342	350	358	365	373
6'3"	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287	295	303	311	319	327	335	343	351	359	367	375	383
6'4"	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295	304	312	320	328	336	344	353	361	369	377	385	394

- = Healthy weight: BMI 18.5 to 24.9
- = Overweight: BMI 25 to 29.9
- = Obese: BMI 30 to 39.9
- = Severely obese: BMI 40 and higher

Figure 82-1 ■ Adult weight classification based on body mass index (BMI).

Adapted from National Heart, Lung, and Blood Institute: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report. Bethesda, MD: National Institutes of Health, 1998.

TABLE 82-1 ■ Disease Risk Based on BMI and WC

BMI (kg/m ²)	Weight Class	Obesity Class	Disease Risk*	
			Nonexcessive WC [†]	Excessive WC [‡]
Below 18.5	Underweight	—	—	—
18.5–24.9	Normal	—	—	—
25–29.9	Overweight	—	Increased	High
30–34.9	Obesity	I	High	Very high
35–39.9	Obesity	II	Very high	Very high
40 or more	Extreme obesity	III	Extremely high	Extremely high

*Risk for hypertension, cardiovascular disease, and type 2 diabetes, relative to individuals of normal weight.

[†]Nonexcessive WC = waist circumference of 40 inches or less for men, and 35 inches or less for women.

[‡]Excessive WC = waist circumference above 40 inches for men, and above 35 inches for women.

Adapted from National Heart, Lung, and Blood Institute: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report. Bethesda, MD: National Institutes of Health, 1998.

women who are pregnant or lactating. Nor do they apply to competitive athletes or bodybuilders, who are heavy because of muscle mass rather than excess fat. Table 82-1 summarizes weight classifications based on BMI.

Waist Circumference. Waist circumference (WC) is an indicator of abdominal fat content, an independent risk factor for obesity-related diseases. Accumulation of fat in the upper body, and especially within the abdominal cavity, poses a greater risk to health than does accumulation of fat in the lower body (hips and thighs). People with too much abdomi-

nal fat are at increased risk of insulin resistance, diabetes, hypertension, coronary atherosclerosis, ischemic stroke, and dementia. Fat distribution can be estimated simply by looking in the mirror: an apple shape indicates too much abdominal fat, whereas a pear shape indicates fat on the hips and thighs. Measurement of WC provides a quantitative estimate of abdominal fat. A WC exceeding 40 inches (102 cm) in men or 35 inches (88 cm) in women signifies an increased health risk—but only for people with a BMI between 25 and 34.9 (see Table 82-1).

Risk Status. Overall weight-related health risk is determined by BMI, WC, and the presence of weight-related diseases and cardiovascular risk factors. Certain weight-related diseases—established coronary heart disease, other atherosclerotic diseases, type 2 diabetes, and sleep apnea—confer a very high risk for complications and mortality. Other weight-related diseases—gynecologic abnormalities, osteoarthritis, gallstones, and stress incontinence—confer less risk. Cardiovascular risk factors—smoking, hypertension, high levels of low-density lipoprotein (LDL) cholesterol, low levels of high-density lipoprotein (HDL) cholesterol, high fasting glucose, family history of premature coronary heart disease, physical inactivity, and advancing age—confer a high risk when three or more of these factors are present.

Not surprisingly, health risk rises as BMI gets larger (see Table 82-1). In addition, the risk is increased by the presence of an excessive WC. The risk is further increased by weight-related diseases and cardiovascular risk factors. In the absence of an excessive WC and other risk factors, health risk is minimal with a BMI below 25, and relatively low with a BMI below 30. Conversely, a BMI of 30 or more indicates significant risk. In the presence of an excessive WC, health risk is high for all individuals with a BMI above 25.

OVERVIEW OF OBESITY TREATMENT

The strategy for losing weight is simple: take in fewer calories per day than are burned. Of course, implementation is tough. The key components of a weight-loss program are diet and exercise. Drugs and other measures are employed only as adjuncts.

Who Should Be Treated?

According to the federal guidelines, weight-loss therapy is indicated for people with

- A BMI of 30 or more
- A BMI of 25 to 29.9 *plus* two risk factors
- A WC greater than 40 inches (in men) or greater than 35 inches (in women) *plus* two risk factors

Benefits of Treatment

It is well established that obesity increases morbidity and mortality. It is also well established that weight reduction reduces morbidity, and probably mortality. In overweight and obese people, weight reduction confers these proven benefits:

- Reduction of high blood pressure in patients with hypertension
- Improvement of blood lipid status (elevation of HDL cholesterol and reduction of LDL cholesterol, total cholesterol, and triglycerides)
- Reduction of elevated blood glucose in patients with type 2 diabetes
- Reduced mortality

Treatment Goal

The goal of treatment is to promote and maintain weight loss. The initial objective is to reduce weight by 10% over 6 months. For patients with a BMI of 27 to 35, this can usually be achieved by reducing energy intake by 300 to 500 kcal/day,

which should allow a loss of 0.5 to 1 pound a week—or 13 to 26 pounds in 6 months. More severely obese people (BMI above 35) require greater caloric restriction (500 to 1000 kcal/day) to lose 10% of their weight in 6 months. After 6 months, the goal for all patients is to prevent lost weight from returning. This can be accomplished by a combination of diet, physical activity, and behavioral therapy. If appropriate, additional weight reduction can be attempted.

Treatment Modalities

Weight loss can be accomplished with five treatment modalities: caloric restriction, physical activity, behavior therapy, drug therapy, and surgery. For any individual, the treatment mode is determined by the degree of obesity and personal preference.

Caloric Restriction. A reduced-calorie diet is central to any weight-loss program. As noted, the only way to lose weight is to take in fewer calories than we burn. Depending on the individual, the caloric deficit should range from 300 to 1000 kcal/day. Because fats contain more calories than either carbohydrates or proteins (on an ounce-for-ounce basis), reducing dietary fat is the easiest way to reduce calorie intake.

What's the best diet for losing weight? Answer: The one that you actually stick to. In one study, 160 overweight subjects were randomized to follow one of four popular diet plans: Atkins (low-carbohydrate), Ornish (fat-restricted), Weight Watchers (portion- and calorie-restricted), and Zone (low-glycemic-index). Mean weight loss after 1 year was modest—ranging from 4.6 to 7.3 pounds—and did not differ significantly between the plans. However, what did matter was adherence: There was a direct correlation between weight lost and adherence to the plan, regardless of which plan was followed.

To succeed at losing weight, it helps to know just how many calories you take in each day and how many you burn. The following web sites, which are free, have databases on foods and physical activities, along with tools to calculate and log calories taken in and calories burned:

- MyPyramid—www.mypyramidtracker.gov
- Fitday—www.fitday.com
- Sparkpeople—www.sparkpeople.com
- NutritionData—www.nutritiondata.com

Exercise. Physical activity should be a component of all weight-loss and weight-maintenance programs. Exercise makes a modest contribution to weight loss by increasing energy expenditure. In addition, exercise can help reduce abdominal fat, increase cardiorespiratory fitness, and maintain weight once loss has occurred. According to 2009 guidelines from the American College of Sports Medicine, people trying to *lose* weight should exercise at least 150 minutes per week (and preferably more), and those trying to *maintain* weight loss should exercise 200 to 300 minutes per week.

Behavior Modification. Behavior therapy is directed at modifying eating and exercise habits. As such, behavior therapy can strengthen a program of diet and exercise. In the absence of continuing behavior therapy, most patients regain lost weight when treatment stops. Techniques of behavior therapy include self-monitoring of eating and exercise habits, stress management (because stress can trigger eating), and stimulus control (limiting exposure to stimuli that promote eating). There is no evidence that any one of these techniques is superior to others.

TABLE 82-2 • Drugs Approved for Weight Loss in the United States

Drug	FDA-Approved Indications	Mechanism	Weight Loss Beyond That with Placebo	Adverse Effects	Schedule IV Controlled Substance
Orlistat [Alli, Xenical]	Weight loss: long term	Reduces fat absorption; inhibits lipase	3%	Oily spotting, flatulence, diarrhea, fecal urgency	No
Phentermine [Adipex-P, Ionamin]	Weight loss: short term	Suppresses appetite; sympathomimetic amine	4%	Nervousness, insomnia, palpitations, tachycardia, mild increase in blood pressure	Yes
Diethylpropion (generic only)	Weight loss: short term	Suppresses appetite; sympathomimetic amine	3%	Same as phentermine	Yes

Drug Therapy. Drugs can be used as an adjunct to diet and exercise—but only for people at increased health risk, and only after a 6-month program of diet and exercise has failed. Drugs should never be used alone. Rather, they should be part of a comprehensive weight-reduction program—one that includes exercise, behavior modification, and a reduced-calorie diet.

Candidates for drug therapy should be at increased health risk owing to excessive body fat. Specifically, drugs should be reserved for patients whose BMI is 30 or greater (in the absence of additional risk factors), or 27 or greater (in the presence of additional risk factors). Drugs are not appropriate for patients whose BMI is relatively low.

Benefits of drugs are usually modest. Weight loss attributable to drugs generally ranges between 4.4 and 22 pounds, although some people lose significantly more. As a rule, the majority of weight loss occurs during the first 6 months of treatment.

Expert opinion regarding duration of therapy has changed. In the past, drug therapy was limited to a few months. Today, long-term treatment is recommended. Why? Because we now know that, when drugs are discontinued, most patients regain lost weight. This is similar to the return of high blood pressure when antihypertensive drugs are withdrawn. Accordingly, when treatment has been effective and well tolerated, it should continue indefinitely. At this time, only one drug—*orlistat*—is approved for long-term use, and hence is preferred to other agents.

Not everyone responds to drugs, and hence regular assessment is required. Patients should lose at least 4 pounds during the first 4 weeks of drug treatment. If this initial response is absent, further drug use should be questioned. For patients who *do* respond, ongoing assessment must show that (1) the drug is effective at *maintaining* weight loss, and that (2) serious adverse effects are absent. Otherwise, drug therapy should cease.

In theory, drugs can promote weight loss in three ways: They can suppress appetite, reduce absorption of nutrients, or increase metabolic rate. With one exception—*orlistat*—all of the drugs used for obesity work by suppressing appetite. *Orlistat* works by reducing absorption of fat. None of the available drugs increases metabolic rate.

Table 82-2 lists Food and Drug Administration (FDA)-approved drugs for obesity, and summarizes their approved

indications, mechanism of action, major side effects, and status under the Controlled Substances Act (CSA).

Bariatric Surgery. Surgical procedures can produce significant weight loss. However, they are indicated only for severely obese patients—that is, people with a BMI of 40 or more (in the absence of severe comorbidity). Furthermore, surgery should be reserved for patients who have failed to respond to less invasive therapies and who are at high risk for obesity-related morbidity or mortality. The two most widely used procedures are *gastric bypass surgery* (Roux-en-Y procedure) and laparoscopic implantation of an *adjustable gastric band*, which reduces the effective volume of the upper part of the stomach. Unlike surgeries used in the past, which were designed to reduce nutrient absorption, these procedures are designed to reduce food intake. Surgery is highly effective: In 6 months to a year, patients can lose between 110 and 220 pounds. Furthermore, benefits are sustained. Unfortunately, although surgery is very effective, it can carry significant risk: In one study, mortality rates at 30 days, 90 days, and 1 year after gastric surgery were 2%, 2.8%, and 4.6%, respectively.

WEIGHT-LOSS DRUGS FOR LONG-TERM USE

For treatment of obesity, we need drugs that can be used long term. Unfortunately, such drugs are rare. In fact, at this time, only one drug—*orlistat*—is approved for long-term use. As discussed below, additional drugs for long-term use are in development.

Orlistat, a Lipase Inhibitor Actions and Use

Orlistat [Xenical, Alli] is a novel drug approved for promoting and maintaining weight loss in obese patients age 12 years and older. Unlike most other weight-loss drugs, which act in the brain to curb appetite, *orlistat* acts in the GI tract to reduce absorption of fat. Specifically, the drug acts in the stomach and small intestine to cause irreversible inhibition of gastric and pancreatic lipases, enzymes that break down triglycerides into monoglycerides and free fatty acids. If triglycerides are

not broken down, they can't be absorbed. In patients taking orlistat, absorption of dietary fat is reduced about 30%. Orlistat should be reserved for patients with a BMI of at least 30—or 27 in the presence of other risk factors (eg, diabetes, hypertension, hyperlipidemia). Patients must adopt a reduced-calorie diet in which 30% of calories come from fat.

In clinical trials, orlistat produced modest but sustained benefits. When taken for 2 years, the drug enhanced weight loss, reduced regain of lost weight, and improved some obesity-related risk factors. Patients treated for 2 years lost an average of 19 pounds, compared with 12 pounds for those taking placebo. In addition, treatment reduced total and LDL cholesterol, raised HDL cholesterol, reduced fasting blood glucose, and lowered systolic and diastolic blood pressure. Safety and efficacy beyond 2 years of treatment have not been evaluated.

Adverse Effects

Gastrointestinal Effects. Orlistat undergoes less than 1% absorption, and hence systemic effects are absent. In contrast, GI effects are common. Patients frequently experience oily spotting (27%), flatulence with discharge (24%), fecal urgency (22%), fatty or oily stools (20%), oily evacuation (12%), increased defecation (11%), and fecal incontinence (8%). All of these are the direct result of reduced fat absorption, and all can be minimized by reducing fat intake. For many patients, these unpleasant effects provide strong motivation for adhering to a low-fat diet, and hence may be viewed as beneficial as well as adverse. Dosing with psyllium [Metamucil, others], a bulk-forming laxative, can greatly reduce GI effects. The underlying mechanism is adsorption of dietary fat by psyllium.

Possible Liver Damage. Orlistat has been associated with very rare cases of severe liver damage, although a causal relationship has not been established. Signs and symptoms include itching, vomiting, jaundice, anorexia, fatigue, dark urine, and light-colored stools. Patients who experience these signs and symptoms should report them immediately. Orlistat should be discontinued until liver injury has been ruled out.

Other Adverse Effects. Rarely, orlistat has been associated with *acute pancreatitis* and *kidney stones*, although a causal relationship has not been established.

Contraindications. Orlistat is contraindicated for patients with malabsorption syndrome or cholestasis.

Drug and Nutrient Interactions

Reduced Absorption of Vitamins. By reducing fat absorption, orlistat can reduce absorption of fat-soluble vitamins (vitamins A, D, E, and K). To avoid deficiency, patients should take a daily multivitamin supplement. Administration should be done 2 hours before or 2 hours after taking orlistat.

Warfarin. Vitamin K deficiency can intensify the effects of *warfarin*, an anticoagulant. In patients taking *warfarin*, anticoagulant effects should be monitored closely.

Levothyroxine. Orlistat may cause hypothyroidism in patients taking *levothyroxine* (thyroid hormone). To minimize this effect, *levothyroxine* and orlistat should be administered at least 4 hours apart.

Preparations, Dosage, and Administration

Orlistat is available in two strengths: 60-mg capsules sold as *Alli*, and 120-mg capsules sold as *Xenical*. *Xenical* requires a prescription; *Alli* does not. Of note, the efficacy and side effects of both products are nearly identical, even though one is twice the strength of the other. With either product, patients should take

1 capsule 3 times a day. Each dose should be administered during a major meal or up to 1 hour after. There is no benefit to exceeding three daily doses. Orlistat dosing can be omitted if a meal is missed, or if a meal has little or no fat.

Investigational Drugs for Long-Term Use

Locaserin

Locaserin [Lorcress] is a selective serotonin_{2C} (5-HT_{2C}) agonist that suppresses appetite and creates a sense of satiety. Benefits derive from activating hypothalamic and mesolimbic pathways that control appetite. Weight loss efficacy was first shown in the BLOOM (Behavioral Modification and Locaserin for Obesity and Overweight Management) study, which randomized patients to treatment with locaserin (10 mg twice daily) or placebo. The result? After 1 year, patients taking locaserin lost an average of 5.8% of their baseline weight, compared with 2.2% in those taking placebo. In addition, locaserin reduced BMI, waist circumference, fasting glucose, insulin, total cholesterol, LDL cholesterol, and triglycerides. The principal adverse effects were headache (18% vs. 11% with placebo), dizziness (8.2% vs. 3.8%), nausea (7.5% vs. 5.4%), constipation (6.7% vs. 4%), fatigue (6% vs. 3%), and dry mouth (5.2% vs. 2.3%). Locaserin has a small potential for abuse and, if approved, will be classified as a Schedule IV substance.

In 2010, locaserin was denied FDA approval owing to concern about (1) brain and breast tumors and (2) valvular heart disease. Although tumors have not been seen in humans, they have been seen in rats. The FDA has requested more data to determine if the cancer risk in rats applies to us. Concern about heart valve disease is based on experience with two similar drugs—fenfluramine and dexfenfluramine—that were withdrawn because they damaged the heart. The mechanism involved activation of 5-HT_{2B} receptors on cardiac valves. In theory, since locaserin is highly selective for 5-HT_{2C} receptors (rather than 5-HT_{2B} receptors), it should not pose similar risk. Indeed, in the BLOOM study, no evidence of valvulopathy was found. However, in a companion trial, known as BLOOM-DM, valve damage, although uncommon, did occur more often with locaserin than with placebo. The FDA has requested more data to determine if the risk of valvulopathy is real.

Bupropion/Naltrexone [Contrave]

Contrave is the trade name for a combination of bupropion and naltrexone. Bupropion is currently approved for depression (see Chapter 32) and smoking cessation (see Chapter 39). Naltrexone is currently approved for alcohol dependence (see Chapter 38) and opioid addiction (see Chapter 40). When used for weight loss, both drugs work together to suppress food intake. Bupropion blocks reuptake of dopamine, and thereby increases dopamine availability at synapses that control appetite. Naltrexone blocks receptors for beta-endorphin, a transmitter that stimulates appetite. The result is a reduction in appetite, food craving, and food intake. In one large trial, treatment for 56 weeks with sustained-release bupropion (360 mg) plus sustained-release naltrexone (either 16 or 32 mg) produced, on average, an 8.3% reduction in body weight, compared with 1.3% in subjects taking placebo. Also, subjects reported less difficulty resisting food, less food craving, and greater control over eating. Principal adverse effects are nausea (27.2% vs. 5.3% with placebo), headache (16% vs. 9.3%), constipation (15.8% vs. 5.6%), dizziness (7.7% vs. 2.6%), dry mouth (7.4% vs. 1.9%), and vomiting (6.3% vs. 5.2%). Of concern, bupropion/naltrexone failed to improve blood pressure and heart rate in most patients. In fact, many experienced a small increase in both parameters. In 2010, the FDA denied approval of *Contrave*, arguing that weight loss with the drug is only modest, and hence may not translate into morbidity and mortality benefits that are big enough to offset potential risks. A final decision won't be made until the manufacturer submits additional data on cardiovascular effects.

Phentermine/Topiramate [Qnexa]

Qnexa is the trade name for a combination of phentermine and topiramate. Phentermine is a sympathomimetic agent already approved for short-term management of obesity (see below). Topiramate is currently approved for seizure disorders (see Chapter 24) and prophylaxis of migraine (see Chapter 30). In overweight patients, phentermine suppresses appetite, and topiramate induces a sense of satiety. Possible mechanisms for topiramate include antagonism of glutamate (an excitatory neurotransmitter), modulation of receptors for gamma-aminobutyric acid (GABA), and inhibition of carbonic anhydrase. In a 56-week trial, phentermine/topiramate produced a 10% reduction in weight, and a significant decrease in systolic blood pressure. The most common adverse effects were dry mouth, constipation, altered taste, nausea, blurred vision, dizziness, insomnia, and numbness and tingling in the limbs. The most serious effects were memory impairment, difficulty concentrating, birth defects, metabolic acidosis, and increased

heart rate. In 2010, the FDA denied approval of Qnexa, citing the need for more evidence of safety, especially regarding cognitive disorders and birth defects. If Qnexa is approved, it will be classified as a Schedule IV substance, owing to its phentermine content.

Leptin

In 1994, Jeffrey Friedman of Rockefeller University announced the discovery of leptin, a hormone that helps regulate appetite and energy metabolism. In addition, leptin participates in sexual development. The name *leptin* derives from *leptos*, the Greek word for *thin*. Mice and humans who lack the gene for leptin are obese. For this reason, leptin is also known as the *antiobesity hormone*.

The physiology of leptin is only partly understood. The hormone is released by adipocytes (fat cells) when they fill with fat. Leptin then acts in the hypothalamus to reduce appetite, increase physical activity, and increase fat metabolism. These actions serve to halt further fat accumulation. Hence, the leptin system behaves like a typical feedback loop: When fat storage climbs too high, leptin is released and suppresses further storage; when fat storage falls too low, leptin release is suppressed, allowing more fat to accumulate. The evolutionary purpose of this system is unknown, although there are two obvious possibilities: it may serve to protect against storing too much fat, or it may serve to ensure storage of sufficient fat.

Genetic deficiency of leptin causes extreme obesity. Congenital deficiency is characterized by hyperphagia (overeating), excessive weight gain early in life, and severe obesity. In addition, sexual development is delayed. In 1999, English researchers described the effects of leptin deficiency and leptin replacement therapy in a young girl. The child had a normal weight at birth, but began gaining excessive weight after 4 months. She was constantly hungry (despite hyperphagia), demanded food continuously, and expressed great discontent when food was denied. By age 6, she weighed 125 pounds and needed leg liposuction to improve mobility. By age 9, she weighed 208 pounds. At that time, she began daily subQ injections of leptin. Within a week, her appetite subsided. After 1 year, she had lost 36 pounds, almost all of it fat. Interestingly, she also showed signs of early puberty. (As noted, leptin stimulates sexual development.) This was the first report that leptin replacement is effective in a leptin-deficient person.

Can exogenous leptin help obese people lose weight? Yes—but only if they are like the girl just described. That is, for leptin to work, patients must be unable to make leptin themselves. However, the vast majority of obese people have no problem making leptin. In fact, their leptin levels are usually high—not low, as might be expected. High levels suggest leptin resistance. Possible causes include failure to produce enough leptin receptors or production of receptors that are faulty. When tested in such people, leptin did not induce significant loss of weight.

Other Investigational Long-Term Drugs

Cetilistat. Cetilistat is a lipase inhibitor similar to orlistat. In clinical trials, weight loss was equal to that achieved with orlistat, and tolerability was better. Principal side effects are fecal urgency, diarrhea, and abdominal discomfort. As with orlistat, absorption is minimal, and hence systemic side effects are absent.

Tesofensine. Tesofensine, originally developed to treat neurodegenerative disorders, is under study for treating obesity. The drug blocks reuptake of three neurotransmitters: dopamine, norepinephrine, and 5-hydroxytryptamine (5-HT). Weight loss results from appetite suppression and increased expenditure of energy. In a Phase II trial, the drug produced a dose-dependent decrease in weight, body fat, and waist circumference. The highest dose increased blood pressure. Principal side effects are gastrointestinal.

Exenatide and Liraglutide. Exenatide [Byetta] and liraglutide [Victoza] are long-acting incretin mimetics currently approved for type 2 diabetes (see Chapter 57). Dosing is by subQ injection. In patients with diabetes, these drugs slow gastric emptying, stimulate insulin release, inhibit glucagon release, and suppress appetite. Weight reduction probably results from decreasing appetite. The most common adverse effects are nausea, vomiting, and diarrhea. The most serious adverse effects are renal impairment and pancreatitis.

Bupropion/Zonisamide [Empatic]. *Empatic* is the trade name for a combination of bupropion and zonisamide. As noted above, bupropion is currently approved for depression and smoking cessation. Zonisamide is currently approved for seizure disorders (see Chapter 24). Both drugs suppress appetite, but through different mechanisms. As a result, they reinforce each other's effects. In overweight patients, zonisamide is more effective than placebo, and the combination of zonisamide plus bupropion is more effective than zonisamide alone. In a 24-week trial, patients taking bupropion/zonisamide lost 9.9% of their weight, compared with 1.7% among those taking placebo. Furthermore, the combination reduced waist circumference, triglycerides, fasting insulin, and blood pressure. Side effects of zonisamide

include nausea, drowsiness, fatigue, decreased concentration, and problems with memory, speech, and language.

Pramlintide/Metreleptin. Pramlintide/metreleptin, administered by subQ injection, is a novel combination for promoting weight loss. Pramlintide [Symlin], currently approved for type 2 diabetes (see Chapter 57), is a synthetic analog of amylin, a neurohormone that helps modulate appetite, food intake, and postprandial glucose levels. Metreleptin is an analog of leptin (see above), a neurohormone that helps regulate fat metabolism, glucose metabolism, energy use, and body weight. In a preliminary trial, patients receiving pramlintide/metreleptin lost, on average, 12.7% of their weight (about 25 pounds) over 24 weeks. In a separate trial, patients who used the combination continuously for 52 weeks experienced sustained weight loss, whereas those switched to placebo after 28 weeks regained nearly all of the weight they had lost. The most common adverse effects— injection-site reactions and nausea—were mostly mild to moderate and decreased with continued dosing.

WEIGHT-LOSS DRUGS FOR SHORT-TERM USE: SYMPATHOMIMETIC AMINES

The sympathomimetic amines promote weight loss by decreasing appetite. In contrast to orlistat, these drugs should only be used short term (for 3 months or less). The sympathomimetics fall into two groups: amphetamines and nonamphetamines. The amphetamines have a much higher abuse potential than the nonamphetamines, and hence should be avoided.

Nonamphetamines: Diethylpropion and Phentermine

The sympathomimetic amines suppress appetite by increasing the availability of NE at receptors in the brain. This same mechanism underlies their stimulant effects and potential for abuse (see below). As with orlistat, weight loss is modest: about 7 to 8 pounds.

Currently, four nonamphetamines are approved for weight loss. However, only two—*diethylpropion* and *phentermine* [Adipex-P, Ionamin]—should be used. Why? Because the other two—*benzphetamine* and *phendimetrazine*—have a higher potential for abuse.

Diethylpropion and phentermine are CNS stimulants. Consequently, like the amphetamines, they can increase alertness, decrease fatigue, and induce nervousness and insomnia. Because they can interfere with sleep, these drugs should be administered no later than 4:00 PM. Following drug withdrawal, fatigue and depression may replace CNS stimulation.

Like the amphetamines, the nonamphetamines have effects in the periphery as well as the CNS. Peripheral effects of greatest concern are tachycardia, anginal pain, and hypertension. Accordingly, these drugs should be used with caution in patients with cardiovascular disease.

Although the risk of abuse with the nonamphetamine anorexiant is lower than with the amphetamines, abuse can nonetheless occur. Both diethylpropion and phentermine are regulated under Schedule IV of the CSA (benzphetamine and phendimetrazine are regulated under Schedule III). To reduce the risk of abuse, try to identify abuse-prone patients prior to treatment.

Tolerance is common and may be seen in 6 to 12 weeks. If tolerance develops, the appropriate response is to discontinue the drug rather than increase the dosage.

For two reasons, these drugs are not recommended during pregnancy. First, they are not very effective during pregnancy, and hence there is little point in taking them. Second, *in utero* exposure to these drugs poses an increased risk of cleft palate and congenital heart defects.

Both diethylpropion and phentermine require a prescription. For diethylpropion, the recommended dosage is 25 mg 3 times a day taken 1 hour before meals (using immediate-release tablets) or 75 mg once a day in midmorning (using sustained-release tablets). For phentermine, dosing options include 8 mg 3 times a day before meals or 18.75 to 37.5 mg once daily before breakfast.

Amphetamines

Because of their ability to suppress appetite, the amphetamines have been employed as adjunctive aids in programs for weight loss. However, because of their high abuse potential, and because they offer no advantages over less dangerous sympathomimetics, amphetamines are not recommended—nor are they approved by the FDA for either short-term or long-term weight-loss therapy.

DISCONTINUED WEIGHT-LOSS DRUGS

Weight-loss drugs frequently share a disturbing history: They receive regulatory approval, undergo widespread use, and then are withdrawn owing to discovery of serious adverse effects. Some drugs that have been withdrawn are discussed below.

Sibutramine

Sibutramine [Meridia] was approved in 1997 and then withdrawn in 2010. The drug reduces appetite by blocking reuptake of norepinephrine and 5-HT in the CNS. Prior to being withdrawn, sibutramine had been the only appetite suppressant approved for long-term use. Withdrawal was based on data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT), which showed an increased risk of serious, nonfatal cardiovascular events, including stroke and myocardial infarction. The FDA concluded that the modest weight-loss benefits of sibutramine were far outweighed by the cardiovascular risks.

Rimonabant

Rimonabant, a highly effective weight-loss drug, has been withdrawn in Europe and was never approved in the United States. Owing to its unique mechanism—selective blockade of cannabinoid receptors (the same receptors that marijuana works through)—rimonabant produces multiple beneficial effects: It works in the brain to reduce food intake and nicotine craving, and it works in the periphery to decrease insulin resistance, improve glucose tolerance, reduce triglyceride levels, increase HDL cholesterol (good cholesterol), and increase levels of adiponectin, a cardioprotective molecule. Unfortunately, postmarketing data revealed an increased risk of anxiety, depression, and suicidality. In 2007, an FDA panel recommended unanimously against approving the drug, primarily due to concerns about depression and other psychiatric effects. Rimonabant was approved in Europe for treating obesity in 2006, but was then withdrawn in 2008.

Dexfenfluramine and Fenfluramine

Dexfenfluramine and fenfluramine—two highly effective appetite suppressants—can damage valves of the heart, and can thereby cause cardiac regurgitation. Accordingly, in 1997, both drugs were voluntarily withdrawn from the market. Prior to being withdrawn, fenfluramine was the “fen” in the widely used combination known as “fen-phen” (fenfluramine plus phenter-

mine). For more information on fenfluramine, dexfenfluramine, and “fen-phen,” refer to the fifth edition of this text.

CALORIE-SAVING FOODS

Sugar Substitutes

Calorie-Free Sweeteners

Six calorie-free sweeteners are available: *saccharin* [Sweet 'N Low], *aspartame* [NutraSweet, Equal], *sucralose* [NutraTaste Gold, Splenda], *acesulfame* [Sunett, Sweet One], *rebaudioside A (rebiana)* [Truvia, PureVia], and *neotame* (no trade name yet). Their calorie content is negligible. As indicated in Table 82-3, all six are much sweeter than sucrose (table sugar), when compared ounce-for-ounce. With the exception of aspartame, which is unstable at high heat, all can be used for cooking. These sweeteners are present in literally thousands of commercial food products, including soft drinks, alcoholic beverages, canned goods, baked goods, candies, and various desserts. For people trying to lose pounds or keep them off, switching to foods made with these sweeteners may help.

Calorie-free sweeteners have been used extensively for years, and have proved very safe. At very high doses, saccharin can cause bladder cancer in rats. However, at the doses consumed in the diet, there is no evidence that it causes cancer in humans. Aspartame contains phenylalanine, and hence can harm people with phenylketonuria. All of these sweeteners are safe for people with diabetes. There is no evidence to support rumors that aspartame contributes to multiple sclerosis, systemic lupus erythematosus, Alzheimer's disease, and other disorders.

Reduced-Calorie Sweetener: Tagatose

Tagatose [Slimsweet, Nutratose], an isomer of fructose, is a naturally occurring sugar with properties much like those of sucrose—but with only 38% of the calories. Tagatose tastes like sucrose and, unlike saccharin, has

TABLE 82-3 ■ Sugar Substitutes

Generic Name	Trade Name	Relative Sweetness*	Heat Stability	Comments
Calorie-Free Sweeteners				
Aspartame	NutraSweet, Equal	180	Poor	No aftertaste. Made of two amino acids: aspartate and phenylalanine. Phenylalanine makes it dangerous for phenylketonurics. Because of poor heat stability, it is not good for cooking.
Acesulfame	Sunett, Sweet One	200	Good	No aftertaste. Derived from acetoacetic acid. OK for cooking.
Rebaudioside A (rebiana, reb A)	Truvia, PureVia	200	Good	No aftertaste. Rebaudioside A, also known as rebiana or reb A, is an extract of <i>stevia leaf</i> . OK for cooking.
Saccharin	Sweet 'N Low	300	Good	Bitter aftertaste. High doses cause bladder cancer in rats, but there is no evidence of cancer in humans. OK for cooking.
Sucralose	NutraTaste Gold, Splenda	600	Very good	No aftertaste. The only low-calorie sweetener derived from sucrose. Very heat stable, and hence excellent for cooking.
Neotame		8000	Good	No aftertaste. OK for cooking.
Reduced-Calorie Sweetener				
Tagatose	Slimsweet, Nutratose	1	Good	An isomer of fructose with 38% of the calories of sucrose. No aftertaste. OK for cooking.

*Intensity of sweetness relative to sucrose (eg, saccharin is 300 times sweeter than sucrose).

no bitter aftertaste. When used for cooking and baking, tagatose behaves the same as sucrose.

Olestra, a Fat Substitute

Olestra (Olean) is a nonabsorbable, calorie-free fat substitute used to make potato chips, corn chips, crackers, and other snack foods. Olestra cannot be broken down by pancreatic enzymes, and hence cannot be absorbed. As a result, it provides no dietary fat or calories.

Olestra is very well tolerated. Two randomized, double-blind trials failed to support anecdotal reports of olestra-induced GI symptoms. In one trial, subjects were given a large bag of potato chips—fried in olestra or a traditional fat—to eat while watching a movie. Later, 563 subjects were inter-

viewed. The result? Olestra produced virtually no increase in gas, diarrhea, or abdominal cramping—although the participants did rate the olestra chips as less tasty (5.6 vs. 6.4 on a 9-point scale). In the second study, 3182 subjects ate traditional potato chips or olestra potato chips over 6 weeks. Again, olestra caused no increase in GI symptoms (heartburn, nausea, vomiting, gas, bloating, cramping, frequency of bowel movements, or loose stools).

Olestra can reduce the absorption of fat-soluble vitamins (A, D, E, and K). When these vitamins are ingested at the same time as olestra, they can dissolve in the olestra, and then pass through the intestine without being absorbed. To compensate for this action, snack foods made with olestra are fortified with fat-soluble vitamins. Hence, there is no risk of vitamin deficiency.

KEY POINTS

- Obesity increases the risk of morbidity and mortality.
- Obesity is a chronic disease that requires lifelong treatment.
- The body mass index (BMI) is a measure of body fat content.
- A BMI of 25 to 29.9 indicates overweight, and a BMI of 30 or more indicates obesity.
- Waist circumference (WC) is an index of abdominal fat. Accumulation of abdominal fat is believed to pose a greater risk to health than does accumulation of fat in the hips and thighs.
- Obesity-related health risk is determined by the degree of obesity, excessive abdominal fat, and the presence of obesity-related diseases (eg, type 2 diabetes, sleep apnea) and cardiovascular risk factors (eg, smoking, hypertension, high LDL cholesterol).
- Weight reduction reduces morbidity and probably mortality.
- Weight reduction can be accomplished with caloric restriction, physical activity, behavior therapy, drug therapy, and surgery.
- Antiobesity drugs should be used only as adjuncts to a comprehensive weight-loss program that includes exercise, behavior modification, and a reduced-calorie diet.
- Antiobesity drugs are indicated for patients with a BMI of 30 or more (in the absence of other risk factors) or 27 or more (in the presence of other risk factors).
- Most patients regain lost weight when antiobesity drugs are discontinued. Hence, to remain effective, these drugs must be taken indefinitely.
- Only one drug—orlistat—is approved for long-term therapy of obesity.
- Orlistat promotes weight loss by decreasing absorption of dietary fat. The underlying mechanism is inhibition of gastric and pancreatic lipases.
- Orlistat frequently causes GI symptoms (oily spotting, fecal urgency, oily stools, and fecal incontinence). These symptoms, which are a direct result of reduced fat absorption, can be minimized by reducing fat intake, and by taking the bulk-forming laxative psyllium [Metamucil, others].
- Orlistat can reduce absorption of fat-soluble vitamins (vitamins A, D, E, and K). To avoid deficiency, patients should take a daily multivitamin supplement.

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Basic Principles of Antimicrobial Therapy

Selective Toxicity

Classification of Antimicrobial Drugs

Acquired Resistance to Antimicrobial Drugs

Microbial Mechanisms of Drug Resistance

Mechanisms by Which Resistance Is Acquired

Relationships Between Antibiotic Use and Emergence of Drug-Resistant Microbes

Suprainfection (Superinfection)

Delaying the Emergence of Resistance in Hospitals

Selection of Antibiotics

Empiric Therapy Prior to Completion of Laboratory Tests

Identifying the Infecting Organism

Determining Drug Susceptibility

Host Factors That Modify Drug Choice, Route of Administration, or Dosage

Host Defenses

Site of Infection

Other Host Factors

Dosage Size and Duration of Treatment

Therapy with Antibiotic Combinations

Antimicrobial Effects of Antibiotic Combinations

Indications for Antibiotic Combinations

Disadvantages of Antibiotic Combinations

Prophylactic Use of Antimicrobial Drugs

Misuses of Antimicrobial Drugs

Monitoring Antimicrobial Therapy

si Box 83–1. Antibiotics in Animal Feed: Dying for a Big Mac and Chicken McNuggets

With this chapter we begin our study of drugs used to treat infectious diseases. These drugs are given to about 30% of all hospitalized patients, and constitute one of our most widely used groups of medicines.

Modern antimicrobial agents had their debut in the 1930s and 1940s, and have greatly reduced morbidity and mortality from infection. As newer drugs are introduced, our ability to fight infections increases even more. However, despite impressive advances, continued progress is needed. Why? Because there are organisms that respond poorly to available drugs; there are effective drugs whose use is limited by toxicity; and there is, because of evolving microbial resistance, the

constant threat that currently effective antibiotics will be rendered useless.

In this introductory chapter, we focus on two principal themes. The first is microbial susceptibility to drugs, with special emphasis on resistance. The second is clinical usage of antimicrobials. Topics addressed include criteria for drug selection, host factors that modify drug use, use of antimicrobial combinations, and use of antimicrobial agents for prophylaxis.

Before going further, we need to consider three terms: *chemotherapy*, *antibiotic*, and *antimicrobial agent*. Although we often think of *chemotherapy* as the use of drugs to kill or suppress cancer cells, this term was first defined as *the use of chemicals against invading organisms* (eg, bacteria, viruses, fungi). Today, the word is applied to the treatment of both cancer and infection. Hence, not only do we speak of cancer chemotherapy, we also speak of chemotherapy of infectious diseases.

In common practice, the terms *antibiotic* and *antimicrobial drug* are used interchangeably, as they are in this book. However, be aware that the formal definitions of these words are not identical. Strictly speaking, an *antibiotic* is a chemical that is produced by one microbe and has the ability to harm other microbes. Under this definition, only those compounds that are actually made by microorganisms qualify as antibiotics. Drugs such as the sulfonamides, which are produced in the laboratory, would not be considered antibiotics under the strict definition. In contrast, an *antimicrobial drug* is defined as any agent, natural or synthetic, that has the ability to kill or suppress microorganisms. Under this definition, no distinction is made between compounds produced by microbes and those made by chemists. From the perspective of therapeutics, there is no benefit to distinguishing between drugs made by microorganisms and drugs made by chemists. Hence, the current practice is to use the terms *antibiotic* and *antimicrobial drug* interchangeably.

SELECTIVE TOXICITY

What Is Selective Toxicity?

The term *selective toxicity* is defined as the ability of a drug to injure a target cell or target organism without injuring other cells or organisms that are in intimate contact with the target. As applied to antimicrobial drugs, selective toxicity indicates the ability of an antibiotic to kill or suppress microbial pathogens without causing injury to the host. Selective toxicity is the property that makes antibiotics valuable. If it weren't for selective toxicity—that is, if antibiotics were as harmful to the host as they are to infecting organisms—these drugs would have no therapeutic utility.

How Is Selective Toxicity Achieved?

How can a drug be highly toxic to microbes but harmless to the host? The answer lies with differences in the cellular chemistry of mammals and microbes. There are biochemical processes critical to microbial well-being that do not take place in mammalian cells. Hence, drugs that selectively interfere with these unique microbial processes can cause serious injury to microorganisms while leaving mammalian cells intact. Three examples of how we achieve selective toxicity are discussed below.

Disruption of the Bacterial Cell Wall. Unlike mammalian cells, bacteria are encased in a rigid cell wall. The protoplasm within this wall has a high concentration of solutes, making osmotic pressure within the bacterium high. If it were not for the cell wall, bacteria would absorb water, swell, and then burst. Several families of drugs (eg, penicillins, cephalosporins) weaken the cell wall and thereby promote bacterial lysis. Because mammalian cells have no cell wall, drugs directed at this structure do not affect us.

Inhibition of an Enzyme Unique to Bacteria. The sulfonamides represent antibiotics that are selectively toxic because they inhibit an enzyme critical to bacterial survival but not to our survival. Specifically, sulfonamides inhibit an enzyme needed to make folic acid, a compound required by all cells, both mammalian and bacterial. If we need folic acid, why don't sulfonamides hurt us? Because we can use folic acid from dietary sources. In contrast, bacteria must synthesize folic acid themselves (because, unlike us, they can't take up folic acid from the environment). Hence, to meet their needs, bacteria first take up *para*-aminobenzoic acid (PABA), a precursor of folic acid, and then convert the PABA into folic acid. Sulfonamides block this conversion. Since mammalian cells do not make their own folic acid, sulfonamide toxicity is limited to microbes.

Disruption of Bacterial Protein Synthesis. In bacteria as in mammalian cells, protein synthesis is done by ribosomes. However, bacterial and mammalian ribosomes are not identical, and hence we can make drugs that disrupt function of one but not the other. As a result, we can impair protein synthesis in bacteria while leaving mammalian protein synthesis untouched.

CLASSIFICATION OF ANTIMICROBIAL DRUGS

Various schemes are employed to classify antimicrobial drugs. The two schemes most suited to our objectives are considered below.

Classification by Susceptible Organism

Antibiotics differ widely in their antimicrobial activity. Some agents, called *narrow-spectrum antibiotics*, are active against only a few species of microorganisms. In contrast, *broad-spectrum antibiotics* are active against a wide variety of microbes. As discussed below, *narrow-spectrum drugs are generally preferred to broad-spectrum drugs*.

Table 83-1 classifies the major antimicrobial drugs according to susceptible organisms. The table shows three major groups: *antibacterial drugs*, *antifungal drugs*, and *antiviral drugs*. In addition, the table subdivides the antibacterial drugs into narrow-spectrum and broad-spectrum agents, and indicates the principal classes of bacteria against which they are active.

TABLE 83-1 ■ Classification of Antimicrobial Drugs by Susceptible Organisms

ANTIBACTERIAL DRUGS

Narrow Spectrum

Gram-Positive Cocci and Gram-Positive Bacilli

Penicillin G and V
Penicillinase-resistant penicillins: methicillin, nafcillin
Vancomycin
Erythromycin
Clindamycin

Gram-Negative Aerobes

Aminoglycosides: gentamicin, others
Cephalosporins (first and second generations)

Mycobacterium tuberculosis

Isoniazid
Rifampin
Ethambutol
Pyrazinamide

Broad Spectrum

Gram-Positive Cocci and Gram-Negative Bacilli

Broad-spectrum penicillins: ampicillin, others
Extended-spectrum penicillins: carbenicillin, others
Cephalosporins (third generation)
Tetracyclines: tetracycline, others
Carbapenems: imipenem, others
Trimethoprim
Sulfonamides: sulfisoxazole, others
Fluoroquinolones: ciprofloxacin, others

ANTIVIRAL DRUGS

Drugs for HIV Infection

Reverse transcriptase inhibitors: zidovudine, others
Protease inhibitors: ritonavir, others
Fusion inhibitors: enfuvirtide
Integrase inhibitors: raltegravir
CCR5 antagonists: maraviroc

Drugs for Influenza

Adamantanes: amantadine, others
Neuraminidase inhibitors: oseltamivir, others

Other Antiviral Drugs

Acyclovir
Ribavirin
Interferon alfa

ANTIFUNGAL DRUGS

Polyene antibiotics: amphotericin B, others
Azoles: itraconazole, others
Echinocandins: caspofungin, others

Classification by Mechanism of Action

The antimicrobial drugs fall into seven major groups based on mechanism of action. This classification is summarized in Table 83-2. Properties of the seven major classes are discussed briefly below.

- *Drugs that inhibit bacterial cell wall synthesis or activate enzymes that disrupt the cell wall*—These drugs (eg, penicillins, cephalosporins) weaken the cell wall and thereby promote bacterial lysis and death.
- *Drugs that increase cell membrane permeability*—Drugs in this group (eg, amphotericin B) increase the permeability

TABLE 83-2 ■ Classification of Antimicrobial Drugs by Mechanism of Action

Drug Class	Representative Antibiotics
Inhibitors of cell wall synthesis	Penicillins Cephalosporins Imipenem Vancomycin Caspofungin
Drugs that disrupt the cell membrane	Amphotericin B Daptomycin Itraconazole
Bactericidal inhibitors of protein synthesis	Aminoglycosides
Bacteriostatic inhibitors of protein synthesis	Clindamycin Erythromycin Linezolid Tetracyclines
Drugs that interfere with synthesis or integrity of bacterial DNA and RNA	Fluoroquinolones Metronidazole Rifampin
Antimetabolites	Flucytosine Sulfonamides Trimethoprim
Drugs that suppress viral replication	
Viral DNA polymerase inhibitors	Acyclovir Ganciclovir
HIV reverse transcriptase inhibitors	Zidovudine Lamivudine
HIV protease inhibitors	Ritonavir Saquinavir
HIV fusion inhibitors	Enfuvirtide
HIV integrase inhibitors	Raltegravir
HIV CCR5 antagonists	Maraviroc
Influenza neuraminidase inhibitors	Oseltamivir Zanamivir

of cell membranes, causing leakage of intracellular material.

- **Drugs that cause lethal inhibition of bacterial protein synthesis**—The aminoglycosides (eg, gentamicin) are the only drugs in this group. We do not know why inhibition of protein synthesis by these agents results in cell death.
- **Drugs that cause nonlethal inhibition of protein synthesis**—Like the aminoglycosides, these drugs (eg, tetracyclines) inhibit bacterial protein synthesis. However, in contrast to the aminoglycosides, these agents only slow microbial growth; they do not kill bacteria at clinically achievable concentrations.
- **Drugs that inhibit bacterial synthesis of DNA and RNA or disrupt DNA function**—These drugs inhibit synthesis of DNA or RNA by binding directly to nucleic acids or by interacting with enzymes required for nucleic acid synthesis. They may also bind with DNA and disrupt its function. Members of this group include rifampin, metronidazole, and the fluoroquinolones (eg, ciprofloxacin).
- **Antimetabolites**—These drugs disrupt specific biochemical reactions. The result is either a decrease in the synthesis of essential cell constituents or synthesis of nonfunctional

analogs of normal metabolites. Examples of antimetabolites include trimethoprim and the sulfonamides.

- **Drugs that suppress viral replication**—Most of these drugs inhibit specific enzymes—DNA polymerase, reverse transcriptase, protease, integrase, or neuraminidase—required for viral replication and infectivity.

When considering the *antibacterial* drugs, it is useful to distinguish between agents that are *bactericidal* and agents that are *bacteriostatic*. *Bactericidal* drugs are directly lethal to bacteria at clinically achievable concentrations. In contrast, *bacteriostatic* drugs can slow bacterial growth but do not cause cell death. When a bacteriostatic drug is used, elimination of bacteria must ultimately be accomplished by host defenses (ie, the immune system working in concert with phagocytic cells).

ACQUIRED RESISTANCE TO ANTIMICROBIAL DRUGS

In this section, we discuss bacterial resistance to antibiotics, which may be *innate* (natural, inborn), or *acquired* over time. Discussion here is limited to acquired resistance, which is a much greater clinical concern than innate resistance.

Over time, an organism that had once been highly sensitive to an antibiotic may become less susceptible, or it may lose drug sensitivity entirely. In some cases, resistance develops to several drugs. Acquired resistance is of great concern in that it can render currently effective drugs useless, thereby creating a clinical crisis and a constant need for new antimicrobial agents. As a rule, antibiotic resistance is associated with extended hospitalization, significant morbidity, and excess mortality. Organisms for which drug resistance is now a serious problem include *Enterococcus faecium*, *Staphylococcus aureus*, *Enterobacter* species, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella* species, and *Clostridium difficile* (Table 83-3). Two of these resistant bacteria—methicillin-resistant *Staph. aureus* and *C. difficile*—are discussed at length in Chapter 84 (Box 84-1) and Chapter 85 (Box 85-1), respectively.

In the discussion that follows, we examine the mechanisms by which microbial drug resistance is acquired and the measures by which emergence of resistance can be delayed. As you read this section, keep in mind that it is the *microbe* that becomes drug resistant, *not the patient*.

Microbial Mechanisms of Drug Resistance

Microbes have four basic mechanisms for resisting drugs. They can (1) decrease the concentration of a drug at its site of action, (2) alter the structure of drug target molecules, (3) produce a drug antagonist, and (4) cause drug inactivation.

Reduction of Drug Concentration at Its Site of Action. For most antimicrobial drugs, the site of action is intracellular. Accordingly, if a bug can reduce the intracellular concentration of a drug, it can resist harm. Two basic mechanisms are involved. First, microbes can *cease active uptake* of certain drugs—tetracyclines and gentamicin, for example. Second, microbes can *increase active export* of certain drugs—tetracyclines, fluoroquinolones, and macrolides, for example.

TABLE 83-3 ■ Drugs for Some Highly Resistant Bacteria

Bacterium	Resistance	Resistance Mechanism	Alternative Treatments
<i>Enterococcus faecium</i>	Ampicillin	Mutation and overexpression of PBPs	Quinupristin/dalfopristin, daptomycin, tigecycline, linezolid
	Linezolid	Production of altered 23S ribosomes	Quinupristin/dalfopristin, daptomycin, tigecycline
	Daptomycin	Unknown	Quinupristin/dalfopristin
	Quinupristin/dalfopristin	Production of enzymes that inactivate quinupristin/dalfopristin, altered drug target	Daptomycin, tigecycline, linezolid
	Aminoglycosides	Production of aminoglycoside-modifying enzymes, ribosomal mutations	No reliable alternative available
<i>Staphylococcus aureus</i> *	Vancomycin	Thickening of cell wall and altered structure of cell wall precursor molecules	Quinupristin/dalfopristin, daptomycin, tigecycline, linezolid, telavancin, ceftobiprole
	Daptomycin	Altered structure of cell wall and cell membrane	Quinupristin/dalfopristin, tigecycline, linezolid, telavancin, ceftobiprole
	Linezolid	Production of altered 23S ribosomes	Quinupristin/dalfopristin, daptomycin, tigecycline, telavancin, ceftobiprole, ceftaroline
<i>Enterobacter</i> species	Ceftriaxone, cefotaxime, ceftazidime, cefepime	Production of extended-spectrum beta-lactamases	Carbapenems, tigecycline
	Carbapenems	Production of carbapenemases, decreased permeability	Polymyxins, tigecycline
<i>Klebsiella</i> species	Ceftriaxone, cefotaxime, ceftazidime, cefepime	Production of extended-spectrum beta-lactamases	Carbapenems, tigecycline
	Carbapenems	Production of carbapenemases, decreased permeability	Polymyxins, tigecycline
<i>Pseudomonas aeruginosa</i>	Carbapenems	Decreased permeability, increased drug efflux, production of carbapenemases	Polymyxins
<i>Acinetobacter baumannii</i>	Carbapenems	Decreased permeability, increased drug efflux, production of carbapenemases	Polymyxins
<i>Clostridium difficile</i> [†]	Metronidazole	Reduced drug activation, increased drug efflux, increased repair of drug-induced DNA damage	Vancomycin, rifaximin

PBP5 = penicillin-binding protein 5.

*Methicillin-resistant *Staphylococcus aureus* is discussed at length in Chapter 84 (see Box 84-1).

[†]*Clostridium difficile* infection is discussed at length in Chapter 85 (see Box 85-1).

Alteration of Drug Target Molecules. Most antibiotics, like most other drugs, must interact with target molecules (receptors) to produce their effects. Hence, if the structure of the target molecule is altered, resistance can result. For example, some bacteria are now resistant to streptomycin because of structural changes in bacterial ribosomes, the sites at which streptomycin acts to inhibit protein synthesis.

Antagonist Production. In rare cases, a microbe can synthesize a compound that antagonizes drug actions. For example, by acquiring the ability to synthesize increased quantities of PABA, some bacteria have developed resistance to sulfonamides.

Drug Inactivation. Microbes can resist harm by producing drug-metabolizing enzymes. For example, many bacteria are resistant to penicillin G because of increased production of penicillinase, an enzyme that inactivates penicillin. In addition to penicillins, bacterial enzymes can inactivate other antibiotics, including cephalosporins, carbapenems, and fluoroquinolones.

New Delhi Metallo-Beta-Lactamase 1 (NDM-1) Gene.

Extensive drug resistance is conferred by the NDM-1 gene, which codes for a powerful form of beta-lactamase. As discussed in Chapters 84 and 85, beta-lactamases are enzymes that can inactivate drugs that have a beta-lactam ring. The form of beta-lactamase encoded by NDM-1 is both unusual and troubling in that it can inactivate essentially all beta-lactam antibiotics, a group that includes penicillins, cephalosporins, and carbapenems. Worse yet, the DNA segment that contains the NDM-1 gene also contains genes that code for additional resistance determinants, including drug efflux pumps, and enzymes that can inactivate other important antibiotics, including erythromycin, rifampicin, chloramphenicol, and fluoroquinolones. Furthermore, all of these genes are present on a plasmid, a piece of DNA that can be easily transferred from one bacterium to another (see below). Of note, bacteria that have the NDM-1 gene are resistant to nearly all antibiotics, except for tigecycline and colistin. Since its

discovery in *Klebsiella pneumoniae* in 2008, NDM-1 has been found in other common enteric bacteria, including *Escherichia coli*, *Enterobacter*, *Salmonella*, *Citrobacter freundii*, *Providencia rettgeri*, and *Morganella morganii*. To date, only a few cases of NDM-1 infection have been reported in the United States and Canada.

Mechanisms by Which Resistance Is Acquired

How do microbes acquire mechanisms of resistance? Ultimately, all of the alterations in structure and function discussed above result from changes in the microbial genome. These genetic changes may result either from spontaneous mutation or from acquisition of DNA from an external source. One important mechanism of DNA acquisition is conjugation with other bacteria.

Spontaneous Mutation. Spontaneous mutations produce random changes in a microbe's DNA. The result is a gradual increase in resistance. Low-level resistance develops first. With additional mutations, resistance becomes greater. As a rule, spontaneous mutations confer resistance to *only one drug*.

Conjugation. Conjugation is a process by which extrachromosomal DNA is transferred from one bacterium to another. In order to transfer resistance by conjugation, the donor organism must possess two unique DNA segments, one that codes for the mechanisms of drug resistance and one that codes for the "sexual" apparatus required for DNA transfer. Together, these two DNA segments constitute an *R factor* (resistance factor).

Conjugation takes place primarily among *gram-negative* bacteria. Genetic material may be transferred between members of the same species or between members of different species. Because transfer of R factors is not species specific, it is possible for pathogenic bacteria to acquire R factors from the normal flora of the body. Because R factors are becoming common in normal flora, the possibility of transferring resistance from normal flora to pathogens is a significant clinical concern.

In contrast to spontaneous mutation, conjugation frequently confers *multiple drug resistance*. This can be achieved, for example, by transferring DNA that codes for several different drug-metabolizing enzymes. Hence, in a single event, a drug-sensitive bacterium can become highly drug resistant.

Relationships Between Antibiotic Use and Emergence of Drug-Resistant Microbes

Use of antibiotics promotes the emergence of drug-resistant microbes. Please note, however, that although antibiotics promote drug resistance, they are not mutagenic and do not directly cause the genetic changes that underlie reduced drug sensitivity. Spontaneous mutation and conjugation are random events whose incidence is independent of drug use. Drugs simply make conditions favorable for overgrowth of microbes that have acquired mechanisms for resistance.

How Do Antibiotics Promote Resistance? To answer this question, we need to recall two aspects of microbial ecology: (1) microbes secrete compounds that are toxic to other microbes, and (2) microbes within a given ecologic niche (eg,

large intestine, urogenital tract, skin) compete with each other for available nutrients. Under drug-free conditions, the various microbes in a given niche keep each other in check. Furthermore, if none of these organisms is drug resistant, introduction of antibiotics will be equally detrimental to all members of the population, and therefore will not promote the growth of any individual. However, *if a drug-resistant organism is present, antibiotics will create selection pressure favoring its growth.* How? By killing off sensitive organisms, the drug will eliminate the toxins they produce, and will thereby facilitate survival of the microbe that is drug resistant. Also, elimination of sensitive organisms will remove competition for available nutrients, thereby making conditions even more favorable for the resistant microbe to flourish. Hence, although drug resistance is of no benefit to an organism when there are no antibiotics present, when antibiotics are introduced, they create selection pressure favoring overgrowth of microbes that are resistant.

Which Antibiotics Promote Resistance? All antimicrobial drugs promote the emergence of drug-resistant organisms. However, some agents are more likely to promote resistance than others. Because broad-spectrum antibiotics kill more competing organisms than do narrow-spectrum drugs, broad-spectrum agents do the most to facilitate emergence of resistance.

Does the Amount of Antibiotic Use Influence the Emergence of Resistance? You bet! The more that antibiotics are used, the faster drug-resistant organisms will emerge. Not only do antibiotics promote emergence of resistant pathogens, they also promote overgrowth of normal flora that possess mechanisms for resistance. Because drug use can increase resistance in normal flora, and because normal flora can transfer resistance to pathogens, every effort should be made to avoid use of antibiotics by individuals who don't actually need them (ie, individuals who don't have a treatable infection). Because all antibiotic use will further the emergence of resistance, there can be no excuse for casual or indiscriminate dispensing of these drugs.

Nosocomial Infections. Because hospitals are sites of intensive antibiotic use, resident organisms can be extremely drug resistant. As a result, *nosocomial infections* (defined as infections acquired in hospitals) are among the most difficult to treat. According to the Centers for Disease Control and Prevention (CDC), about 1.7 million patients acquire an infection while hospitalized each year, and 99,000 die—making nosocomial infections the sixth leading cause of death in the United States. Measures to delay emergence of resistant organisms in hospitals are discussed below.

Suprainfection (Superinfection)

Suprainfection is simply a special example of the emergence of drug resistance. A suprainfection is defined as a *new* infection that appears during the course of treatment for a primary infection. New infections develop when antibiotics eliminate the inhibitory influence of normal flora, thereby allowing a second infectious agent to flourish. Because broad-spectrum antibiotics kill off more normal flora than do narrow-spectrum drugs, suprainfections are more likely in patients receiving broad-spectrum agents. Because suprainfections are caused by drug-resistant microbes, these infections are often difficult to treat. It should be noted that, in most texts,

suprainfections are referred to as *superinfections*; this term may have been chosen to reflect the difficulties of treatment.

Delaying the Emergence of Resistance in Hospitals

In the spring of 2002, the CDC launched its *Campaign to Prevent Antimicrobial Resistance*. The campaign is directed primarily at hospitals, which are major breeding grounds for resistant pathogens. As shown in Figure 83-1, the campaign consists of 12 action steps that fall under four major headings:

- Prevent infection
- Diagnose and treat infection effectively
- Use antimicrobials wisely
- Prevent transmission

The 12 steps are discussed briefly below. You can get more information online at www.cdc.gov/drugresistance.

Because the CDC campaign is limited to antibiotic use by humans, there is a major cause of resistance that it doesn't address: feeding thousands of tons of antibiotics to livestock to promote growth. This important and contentious topic is discussed in Box 83-1.

Step 1. Vaccinate. By preventing infection, vaccination reduces the need to use antimicrobial drugs, and thereby helps prevent emergence of resistance. Accordingly, the CDC recommends predischARGE vaccination of all at-risk patients, especially against two respiratory infections: influenza and pneumococcal pneumonia. In addition, all healthcare personnel who have patient care duties should receive a flu shot annually.

Step 2. Get the catheters out. Catheters and other invasive devices are the leading exogenous cause of nosocomial infections. Infections can occur in association with IV catheters, arterial catheters, urinary tract catheters, endotracheal tubes, and other devices. Every year, an estimated 250,000 Americans develop bacteremia related to use of central venous catheters alone; the cost of treatment ranges from \$35,000 to \$56,000 *per patient*. To help prevent these infections, catheters should be used only when essential, and should be removed as soon as they are no longer needed. Furthermore, best-practice guidelines should be followed during catheter insertion.

Step 3. Target the pathogen. Proper antimicrobial therapy requires that we choose drugs that are active against the causative organism. To do so, we must determine both the identity and drug sensitivity of the pathogen. This important issue is discussed in depth later under *Selection of Antibiotics*.

Step 4. Access the experts. Not surprisingly, input from an infectious disease expert can improve patient outcomes, decrease treatment costs, and shorten the time to discharge. Expert assistance can be especially helpful for (1) patients with serious infections, (2) patients receiving complex antimicrobial regimens, (3) patients who fail to respond as expected, and (4) patients with a complicated underlying illness.

Step 5. Practice antimicrobial control. To facilitate antimicrobial control, institutions are encouraged to implement procedures and programs that can help clinicians use antimicrobial drugs more wisely. Perhaps the most effective option is to implement a computerized support system designed to help clinicians select antimicrobial regimens. Other effective measures include use of standardized antimicrobial

12 STEPS TO PREVENT ANTIMICROBIAL RESISTANCE AMONG HOSPITALIZED ADULTS

PREVENT INFECTION

- 1 Vaccinate
- 2 Get the catheters out

DIAGNOSE AND TREAT INFECTION EFFECTIVELY

- 3 Target the pathogen
- 4 Access the experts

USE ANTIMICROBIALS WISELY

- 5 Practice antimicrobial control
- 6 Use local data
- 7 Treat infection, not contamination
- 8 Treat infection, not colonization
- 9 Know when to say "no" to vanco
- 10 Stop treatment when infection is cured or unlikely

PREVENT TRANSMISSION

- 11 Isolate the pathogen
- 12 Break the chain of contagion

Figure 83-1 ■ Pocket card from the CDC's Campaign to Prevent Antimicrobial Resistance.

order forms, providing interactive education for prescribers, giving individual prescribers critical feedback on their choices, and establishing a multidisciplinary system to evaluate drug utilization.

Step 6. Use local data. Drug susceptibility of microbes varies over time and according to locale, patient population, and hospital unit. To facilitate drug selection, institutions often compile data on drug susceptibility into an "antibiogram," which provides an overview of common local pathogens and their current pattern of drug sensitivity. Clinicians use the antibiogram to guide initial drug selection while awaiting patient-specific data on drug susceptibility from the microbiology lab.

Step 7. Treat infection, not contamination. Contamination of culture samples can lead to false-positive results on bacteriologic tests, and hence can lead to unneeded treatment with antimicrobial drugs. Studies indicate, in fact, that contamination is a major cause of unnecessary antimicrobial use. To decrease contamination, clinicians should simply use approved procedures to obtain and process all culture samples. For example, to prevent contamination when drawing blood, clinicians can decontaminate the skin with tincture of iodine.

Step 8. Treat infection, not colonization. A small, localized colony of bacteria does not constitute an infection. However, for two reasons, colonization is a concern. First, in patients who do *not* have an active infection, treatment

ANTIBIOTICS IN ANIMAL FEED: DYING FOR A BIG MAC AND CHICKEN McNUGGETS

Drug-resistant infection resulting from use of antibiotics in agriculture is a global public health concern. Antibiotics are employed extensively in the livestock and poultry industries. Not surprisingly, this practice has created a large reservoir of drug-resistant bacteria, some of which now infect humans. In addition to being a direct detriment to health, these infections pose an even larger threat: passage of resistance genes to normal intestinal flora, and then from normal flora to human pathogens.

The amount of antibiotics given to food animals is staggering. According to estimates made by the Union for Concerned Scientists, of the 14,800 tons of antibiotics produced in the United States each year, nearly 90% (13,300 tons) goes to animals. Even more surprisingly, of the antibiotics that animals receive, only 7.5% (1000 tons) is given to treat infection. The vast majority—12,300 tons—is mixed with feed to promote growth. Both uses encourage the emergence of resistance.

Of the two agricultural uses—growth promotion and treatment of infection—growth promotion is by far the more controversial. Few authorities would argue that we shouldn't give antibiotics to treat animal infections. In contrast, there are strong arguments against giving antibiotics to promote growth. The doses employed for growth promotion are much lower than those used for infection, and hence are *more* likely to encourage emergence of resistance. Moreover, since growth can be promoted by other means, giving antibiotics for this purpose is unnecessary.

Which antibiotics are employed in agriculture? Essentially all of the antibiotics used in humans are used in animals—including fluoroquinolones and third-generation cephalosporins, agents that are among the most effective we have. Because all antibiotics are being used, we are hastening the day when all will be useless.

The story of virginiamycin and Synercid illustrates the potentially serious consequences of giving antibiotics to farm animals. Virginiamycin is a mixture of two streptogramins. For 30 years, the drug has been used to promote animal growth. In 1999, a mixture of two similar streptogramins—quinupristin and dalfopristin, sold as Synercid—was approved for medical use in the United States. Synercid is an extremely important drug because it can kill vancomycin-resistant *Enterococcus faecium*, a dangerous pathogenic strain that is resistant to all other antibiotics. Unfortunately, agricultural use of virginiamycin is likely to shorten Synercid's useful life: A study of chickens that were fed virginiamycin indicates that 50% of the birds carried Synercid-resistant *E. faecium*. Sooner or later, these birds will pass these resistant pathogens on to humans—if they haven't already.

How can we reduce agriculture-related resistance? Clearly, if we want to delay emergence of resistance, and thereby extend the useful life of our antibiotics, we must limit agricultural use of these drugs. To this end, the World Health Organization has recommended that all antibiotics used by humans be banned from use to promote growth in animals. In 2006, fifteen countries in the European Union complied, banning the use of *all* antibiotics for growth promotion in livestock. What was the impact? Entirely positive, assuming the experience in Denmark applies to the rest of Europe. In the late 1990s, Denmark banned the use of antibiotics for growth promotion in pigs and chickens, with no apparent detriment to either animal health or the incomes of producers. Furthermore, within a few years after these drugs were discontinued, rates of antibiotic resistance among farm animals dropped dramatically. For example, resistance to avoparcin dropped from 73% to 5% in less than 5 years.

In the United States, public health and agriculture officials have discussed and debated the issue for more than 30 years, but no legislation has been enacted. A major stumbling block has been the inability to quantify the problem. That is, although there is universal agreement that giving antibiotics to animals represents a threat to public health, we lack sufficient data to determine just how big that threat is. Hopefully, Congress and the Food and Drug Administration (FDA) will take appropriate action before the threat has grown too large to overcome.

And there *is* some hope. In 2005, the FDA took an important step: For the first time, they banned the agricultural use of a specific drug. The FDA ruling, which took effect September 12, 2005, banned the use of enrofloxacin [Baytril] in chickens and turkeys. (Enrofloxacin is a fluoroquinolone similar to ciprofloxacin [Cipro].) The ban was based on concerns that widespread use of enrofloxacin in poultry was promoting resistance to ciprofloxacin and other fluoroquinolones in humans. This case is significant in that it sets a precedent for FDA action against other animal antibiotics.

Although wide-reaching restrictive rules are not yet in place, they may, at long last, be forthcoming: On June 28, 2010, the FDA posted a draft "guidance" indicating that it no longer considers giving stock antibiotics to promote growth a "judicious use" of these drugs, implying that it plans to ban the practice. The FDA would, however, continue to allow use of antibiotics to treat or prevent the spread of disease—provided such use is overseen by a veterinarian. Let's hope this guidance becomes policy soon.

Note: Use of antibiotics by vegetable and fruit growers is just as widespread as in animal husbandry, and probably just as detrimental to public health—but that's another story.

because of colonization would be an unnecessary use of antibiotics. Second, in patients who *do* have an active infection, wrongly attributing the infection to colonizing bacteria could lead to treatment with drugs that are inactive against the real cause. To avoid both problems, it is essential that we differen-

tiate between bacteria that are simply colonizing a region and those that are causing an actual infection.

Step 9. Know when to say "no" to vanco. "Vanco" (ie, vancomycin) is a drug of last resort against several important pathogens, including methicillin-resistant *Staph. aureus*

(MRSA) and multidrug-resistant *Streptococcus pneumoniae*. To delay emergence of vancomycin-resistant organisms, we must use this drug only when clearly necessary. Guidelines from the CDC spell out situations in which using vancomycin is deemed appropriate and situations in which using the drug should be discouraged.

Step 10. Stop treatment when infection is cured or unlikely. Common sense dictates that we administer antibiotics only when they are actually needed: If the patient doesn't have an infection, we shouldn't use these drugs. When an infection has been cured, antibiotics should be discontinued. Similarly, if antibiotics were started before culture results were available, and if the culture results are negative, then the antibiotics should be stopped.

Step 11. Isolate the pathogen. By using standard infection control procedures, such as proper containment and disposal of contagious body fluids, we can isolate the pathogen, and can thereby reduce the risk of transferring resistant organisms from one patient to another.

Step 12. Break the chain of contagion. This step could also be titled *Wash your hands!* All too often, bacteria are transferred from patient to patient on the hands of physicians, nurses, and other hospital workers. Fortunately, this transfer can be stopped by following a simple rule: Wash your hands before and after touching any patient. Unfortunately, at least 50% of the time, clinicians fail to do so. The issue of hand hygiene is discussed at length in Chapter 96 (Antiseptics and Disinfectants).

SELECTION OF ANTIBIOTICS

When treating infection, the therapeutic objective is to produce maximal antimicrobial effects while causing minimal harm to the host. To achieve this goal, we must select the most appropriate antibiotic for the individual patient. When choosing an antibiotic, three principal factors must be considered: (1) the identity of the infecting organism, (2) drug sensitivity of the infecting organism, and (3) host factors, such as the site of infection and the status of host defenses.

For any given infection, several drugs may be effective. However, for most infections, there is usually one drug that is superior to the alternatives (Table 83-4). This drug of first choice may be preferred for several reasons, such as greater efficacy, lower toxicity, or more narrow spectrum. Whenever possible, the drug of first choice should be employed. Alternative agents should be used only when the first-choice drug is inappropriate. Conditions that might rule out a first-choice agent include (1) allergy to the drug of choice, (2) inability of the drug of choice to penetrate to the site of infection, and (3) heightened susceptibility of the patient to toxicity of the first-choice drug.

Empiric Therapy Prior to Completion of Laboratory Tests

Optimal antimicrobial therapy requires identification of the infecting organism and determination of its drug sensitivity. However, when the patient has a severe infection, we may have to initiate treatment before test results are available. Under these conditions, drug selection must be based on clinical evaluation and knowledge of which microbes are most likely

to cause infection at a particular site. If necessary, a broad-spectrum agent can be used for initial treatment. Once the identity and drug sensitivity of the infecting organism have been determined, we can switch to a more selective antibiotic. When conditions demand that we start therapy in the absence of laboratory data, it is essential that samples of exudates and body fluids be obtained for culture *prior to initiation of treatment*; if antibiotics are present at the time of sampling, they can suppress microbial growth in culture, and can thereby confound identification.

Identifying the Infecting Organism

The first rule of antimicrobial therapy is to *match the drug with the bug*. Hence, whenever possible, the infecting organism should be identified prior to starting treatment. If treatment is begun in the absence of a definitive diagnosis, positive identification should be established as soon as possible, so as to permit adjustment of the regimen to better conform with the drug sensitivity of the infecting organism.

The quickest, simplest, and most versatile technique for identifying microorganisms is microscopic examination of a *Gram-stained preparation*. Samples for examination can be obtained from pus, sputum, urine, blood, and other body fluids. The most useful samples are direct aspirates from the site of infection.

In some cases, only a small number of infecting organisms will be present. Under these conditions, positive identification may require that the microbes be grown out in culture. As stressed above, material for culture should be obtained prior to initiating treatment. Furthermore, the samples should be taken in a fashion that minimizes contamination with normal body flora. Also, the samples should not be exposed to low temperature, antiseptics, or oxygen.

A relatively new method, known as the *polymerase chain reaction (PCR) test* or *nucleic acid amplification test*, can detect very low titers of bacteria and viruses. Testing is done by using an enzyme—either DNA polymerase or RNA polymerase—to generate thousands of copies of DNA or RNA unique to the infecting microbe. As a result of this nucleic acid amplification, there is enough material for detection. Microbes that we can identify with a PCR test include important bacterial pathogens (eg, *Clostridium difficile*, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Helicobacter pylori*) and important viral pathogens (eg, human immunodeficiency virus, influenza virus). Compared with Gram staining, PCR tests are both more specific and more sensitive.

Determining Drug Susceptibility

Owing to the emergence of drug-resistant microbes, testing for drug sensitivity is common. However, sensitivity testing is not always needed. Rather, testing is indicated only when the infecting organism is one in which resistance is likely. Hence, for microbes such as the group A streptococci, which have remained highly susceptible to penicillin G, sensitivity testing is unnecessary. In contrast, when resistance *is* common, as it is with *Staph. aureus* and the gram-negative bacilli, tests for drug sensitivity should be performed. Most tests used today are based on one of three methods: disk diffusion, serial dilution, or gradient diffusion.

TABLE 83-4 ■ Antibacterial Drugs of Choice

Organism

Drug of First Choice

Some Alternative Drugs

Gram-Positive Cocci

Enterococcus

Endocarditis and other severe infections

Uncomplicated urinary tract infection

Staphylococcus aureus or *epidermidis*
Penicillinase producing

Methicillin resistant

Streptococcus pyogenes (group A) and groups C and G*Streptococcus*, group B*Streptococcus viridans* group*Streptococcus bovis**Streptococcus*, anaerobic*Streptococcus pneumoniae*
(pneumococcus)

Gram-Negative Cocci

Neisseria gonorrhoeae (gonococcus)*Neisseria meningitidis*
(meningococcus)

Gram-Positive Bacilli

Bacillus anthracis (anthrax)*Clostridium difficile**Clostridium perfringens**Clostridium tetani**Corynebacterium diphtheriae**Listeria monocytogenes*

Enteric Gram-Negative Bacilli

*Campylobacter jejuni**Escherichia coli**Enterobacter**Klebsiella pneumoniae**Proteus*, indole positive (including*Providencia rettgeri* and*Morganella morganii*)*Proteus mirabilis**Salmonella typhi*Other *Salmonella**Serratia*Penicillin G or ampicillin with either
gentamicin or streptomycin
Ampicillin, amoxicillin

A penicillinase-resistant penicillin

Vancomycin with or without gentamicin
with or without rifampin

Penicillin G, penicillin V

Penicillin G or ampicillin

Penicillin G with or without gentamicin

Penicillin G

Penicillin G

Penicillin G, penicillin V, amoxicillin

See Chapter 95, Table 95-1

Penicillin G

See Chapter 110

See Chapter 85, Box 85-1

Penicillin G, clindamycin

Metronidazole

Erythromycin

Ampicillin with or without gentamicin

Erythromycin, azithromycin

Cefotaxime, ceftazidime, cefepime,
ceftriaxone

Imipenem, meropenem, cefepime

Cefotaxime, ceftriaxone, cefepime,
ceftazidimeCefotaxime, ceftriaxone, cefepime,
ceftazidime

Ampicillin

Ceftriaxone, a fluoroquinolone

Ceftriaxone, cefotaxime, a
fluoroquinolone

Imipenem, meropenem

Vancomycin with either gentamicin or streptomycin,
quinupristin/dalfopristin, linezolid, daptomycin
Nitrofurantoin, a fluoroquinolone; fosfomycinA cephalosporin, vancomycin, imipenem, linezolid,
clindamycin, daptomycin, a fluoroquinolone
Linezolid, quinupristin/dalfopristin, daptomycin,
tigecycline, doxycycline, ceftobiprole, ceftaroline,
trimethoprim/sulfamethoxazole, a fluoroquinoloneClindamycin, vancomycin, erythromycin,
clarithromycin, azithromycin, daptomycin,
linezolid, a cephalosporinA cephalosporin, vancomycin, erythromycin,
daptomycin

A cephalosporin, vancomycin

A cephalosporin, vancomycin

Clindamycin, a cephalosporin, vancomycin

A cephalosporin, erythromycin, azithromycin,
clarithromycin, levofloxacin, gemifloxacin,
moxifloxacin, meropenem, imipenem, ertapenem,
trimethoprim/sulfamethoxazole, clindamycin, a
tetracycline, vancomycinCefotaxime, ceftriaxone, ceftizoxime,
chloramphenicol, a sulfonamide, a fluoroquinoloneMetronidazole, chloramphenicol, imipenem,
meropenem, ertapenem

Penicillin G, doxycycline

Penicillin G

Trimethoprim/sulfamethoxazole

A fluoroquinolone, gentamicin, a tetracycline

Ampicillin with or without gentamicin, ticarcillin/
clavulanic acid, trimethoprim/sulfamethoxazole,
imipenem, meropenem, othersTrimethoprim/sulfamethoxazole, gentamicin,
tobramycin, amikacin, ciprofloxacin, cefotaxime,
ticarcillin/clavulanic acid, piperacillin/tazobactam,
aztreonam, ceftizoxime, ceftazidime, tigecyclineImipenem, meropenem, ertapenem, gentamicin,
tobramycin, amikacin, othersImipenem, meropenem, ertapenem, gentamicin, a
fluoroquinolone, trimethoprim/sulfamethoxazole,
othersA cephalosporin, ticarcillin, trimethoprim/
sulfamethoxazole, imipenem, meropenem,
ertapenem, gentamicin, othersTrimethoprim/sulfamethoxazole, ampicillin,
amoxicillin, chloramphenicol, azithromycinTrimethoprim/sulfamethoxazole, chloramphenicol,
ampicillin, amoxicillinGentamicin, amikacin, cefotaxime, a fluoroquinolone,
trimethoprim/sulfamethoxazole, aztreonam, others

TABLE 83-4 ■ Antibacterial Drugs of Choice—cont'd

Organism	Drug of First Choice	Some Alternative Drugs
Enteric Gram-Negative Bacilli—cont'd		
<i>Shigella</i>	A fluoroquinolone	Trimethoprim/sulfamethoxazole, ampicillin, ceftriaxone, azithromycin
<i>Yersinia enterocolitica</i>	Trimethoprim/sulfamethoxazole	A fluoroquinolone, gentamicin, tobramycin, amikacin, cefotaxime
Other Gram-Negative Bacilli		
<i>Acinetobacter</i>	Imipenem, meropenem	An aminoglycoside, trimethoprim/sulfamethoxazole, doxycycline, ciprofloxacin, ceftazidime, ticarcillin/clavulanic acid, piperacillin/tazobactam
<i>Bacteroides</i>	Metronidazole	Imipenem, ertapenem, meropenem, amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, piperacillin/tazobactam, ampicillin/sulbactam, chloramphenicol
<i>Bordetella pertussis</i> (whooping cough)	Azithromycin, clarithromycin, erythromycin	Trimethoprim/sulfamethoxazole
<i>Brucella</i> (brucellosis)	A tetracycline <i>plus</i> rifampin	A tetracycline <i>plus either</i> gentamicin or streptomycin, trimethoprim/sulfamethoxazole <i>with or without</i> gentamicin, chloramphenicol <i>with or without</i> streptomycin, ciprofloxacin <i>plus</i> rifampin
<i>Calymmatobacterium granulomatis</i>	Trimethoprim/sulfamethoxazole	Doxycycline or ciprofloxacin
<i>Francisella tularensis</i> (tularemia)	See Chapter 110	
<i>Gardnerella vaginalis</i>	Metronidazole (PO)	Topical clindamycin or metronidazole, clindamycin (PO)
<i>Haemophilus ducreyi</i> (chancroid)	Azithromycin, ceftriaxone	Ciprofloxacin, erythromycin
<i>Haemophilus influenzae</i>		
Meningitis, epiglottitis, arthritis, and other serious infections	Cefotaxime, ceftriaxone	Cefuroxime, chloramphenicol, meropenem
Upper respiratory infection and bronchitis	Trimethoprim/sulfamethoxazole	Cefuroxime, amoxicillin/clavulanic acid, a fluoroquinolone, others
<i>Helicobacter pylori</i>	Clarithromycin <i>plus</i> amoxicillin <i>plus</i> esomeprazole (a proton pump inhibitor)	Tetracycline <i>plus</i> metronidazole <i>plus</i> bismuth subsalicylate <i>plus</i> esomeprazole (a proton pump inhibitor)
<i>Legionella</i> species	Azithromycin, a fluoroquinolone <i>with or without</i> rifampin	Doxycycline <i>with or without</i> rifampin, trimethoprim/sulfamethoxazole, erythromycin
<i>Pasteurella multocida</i>	Penicillin G	Doxycycline, a second- or third-generation cephalosporin, amoxicillin/clavulanic acid, ampicillin/sulbactam
<i>Pseudomonas aeruginosa</i>		
Urinary tract infection	Ciprofloxacin	Levofloxacin, piperacillin/tazobactam, ceftazidime, cefepime, imipenem, meropenem, gentamicin, tobramycin, amikacin, aztreonam
Other infections	Piperacillin/tazobactam (or ticarcillin/clavulanic acid) <i>with or without</i> tobramycin, gentamicin, or amikacin	Ceftazidime, ciprofloxacin, imipenem, meropenem, aztreonam, or cefepime, <i>any one with or without</i> tobramycin, gentamicin, or amikacin
<i>Spirillum minus</i> (rat bite fever)	Penicillin G	Doxycycline, streptomycin
<i>Streptobacillus moniliformis</i> (rat bite fever)	Penicillin G	Doxycycline, streptomycin
<i>Vibrio cholerae</i> (cholera)	A tetracycline	
<i>Yersinia pestis</i> (plague)	See Chapter 110	Trimethoprim/sulfamethoxazole, a fluoroquinolone
Mycobacteria		
<i>Mycobacterium tuberculosis</i>	See Chapter 90	
<i>Mycobacterium leprae</i> (leprosy)	See Chapter 90	
<i>Mycobacterium avium</i> complex	See Chapter 90	
Actinomycetes		
<i>Actinomycetes israelii</i>	Penicillin G	Doxycycline, erythromycin, clindamycin
<i>Nocardia</i>	Trimethoprim/sulfamethoxazole	Sulfisoxazole, imipenem, meropenem, amikacin, a tetracycline, linezolid, ceftriaxone, cycloserine
Chlamydiae		
<i>Chlamydia psittaci</i>	Doxycycline	Chloramphenicol
<i>Chlamydia trachomatis</i>	See Chapter 95, Table 95-1	

Continued

TABLE 83-4 ■ Antibacterial Drugs of Choice—cont'd

Organism	Drug of First Choice	Some Alternative Drugs
Mycoplasma		A fluoroquinolone
<i>Mycoplasma pneumoniae</i>	Erythromycin, clarithromycin, azithromycin, a tetracycline	A tetracycline, clarithromycin, erythromycin, ofloxacin
<i>Ureaplasma urealyticum</i>	Azithromycin	
Rickettsia		Chloramphenicol, a fluoroquinolone
Rocky Mountain spotted fever, endemic typhus (murine), trench fever, typhus, scrub typhus, Q fever	Doxycycline	
Spirochetes		Ceftriaxone, cefotaxime, penicillin G, azithromycin, clarithromycin
<i>Borrelia burgdorferi</i> (Lyme disease)	Doxycycline, amoxicillin, cefuroxime	Penicillin G, erythromycin
<i>Borrelia recurrentis</i> (relapsing fever)	A tetracycline	Doxycycline, ceftriaxone
<i>Leptospira</i>	Penicillin G	Doxycycline, ceftriaxone
<i>Treponema pallidum</i> (syphilis)	Penicillin G	Doxycycline
<i>Treponema pertenue</i> (yaws)	Penicillin G	

Before sensitivity testing can be done, we must first identify the microbe. Why? So we can test for sensitivity to the appropriate drugs. For example, if the infection is caused by *Clostridium difficile*, we might test for sensitivity to metronidazole or vancomycin. We would not test for sensitivity to aminoglycosides or cephalosporins—because we already know these drugs won't work.

Disk Diffusion. The disk-diffusion test, also known as the Kirby-Bauer test, is performed by seeding an agar plate with a solution of the infecting organism, and then placing on the plate several paper disks that have been impregnated with different antibiotics. Because of diffusion, an antibiotic-containing zone becomes established around each disk. As the bacteria proliferate, growth will be inhibited around the disks that contain an antibiotic to which the bacteria are sensitive. The degree of drug sensitivity is proportional to the size of the bacteria-free zone. Hence, by measuring the diameter of these zones, we can determine the drugs to which the organism is more susceptible, and the drugs to which it is highly resistant.

Serial Dilution. In this procedure, bacteria are grown in a series of tubes containing different concentrations of an antibiotic. The advantage of this method over the disk-diffusion test is that it provides a more precise measure of drug sensitivity. By using serial dilution, we can establish close estimates of two clinically useful values: (1) the *minimum inhibitory concentration* (MIC), defined as the lowest concentration of antibiotic that produces complete inhibition of bacterial growth (but does not kill bacteria); and (2) the *minimum bactericidal concentration* (MBC), defined as the lowest concentration of drug that produces a 99.9% decline in the number of bacterial colonies (indicating bacterial kill). Because of the quantitative information provided, serial dilution procedures are especially useful for guiding therapy of infections that are unusually difficult to treat.

Gradient Diffusion. The gradient-diffusion procedure is similar to the disk-diffusion procedure, but provides a more precise indication of MIC. Like the disk-diffusion test, the gradient-diffusion test begins with seeding an agar plate with the infecting organism. Then, a narrow test *strip*, rather than a disk, is placed on the plate. Unlike the disk, which is im-

pregnated with just one concentration of an antibiotic, the strip is impregnated with 15 or so different concentrations of the same antibiotic, such that there is a concentration gradient that runs from low to high along the length of the strip. Hence, as antibiotic diffuses from the strip into the agar, the concentration of drug in the agar establishes a gradient as well. Bacteria on the plate will continue to grow until they reach a zone of the plate where the antibiotic concentration is high enough to inhibit further growth. The point where the zone of inhibition intersects the strip, which is calibrated at short intervals along its length, indicates the MIC.

HOST FACTORS THAT MODIFY DRUG CHOICE, ROUTE OF ADMINISTRATION, OR DOSAGE

In addition to matching the drug with the bug and determining the drug sensitivity of an infecting organism, we must consider host factors when prescribing an antimicrobial drug. Two host factors—host defenses and infection site—are unique to the selection of antibiotics. Other host factors, such as age, pregnancy, and previous drug reactions, are the same factors that must be considered when choosing any other drug.

Host Defenses

Host defenses consist primarily of the immune system and phagocytic cells (macrophages, neutrophils). Without the contribution of these defenses, successful antimicrobial therapy would be rare. In most cases, the drugs we use don't cure infection on their own. Rather, they work in concert with host defense systems to subdue infection. Accordingly, the usual objective of antibiotic treatment is not outright kill of infecting organisms. Rather, the goal is to suppress microbial growth to the point at which the balance is tipped in favor of the host. Underscoring the critical role of host defenses is the grim fact that people whose defenses are impaired, such as those with AIDS and those undergoing cancer chemotherapy, frequently die from infections that drugs alone are unable to

control. When treating the immunocompromised host, our only hope lies with drugs that are rapidly bactericidal, and even these may prove inadequate.

Site of Infection

To be effective, an antibiotic must be present at the site of infection in a concentration greater than the MIC. At some sites, drug penetration may be hampered, making it difficult to achieve the MIC. For example, drug access can be impeded in meningitis (because of the blood-brain barrier), endocarditis (because bacterial vegetations in the heart are difficult to penetrate), and infected abscesses (because of poor vascularity and the presence of pus and other material). When treating meningitis, two approaches may be used: (1) we can select a drug that readily crosses the blood-brain barrier, and (2) we can inject an antibiotic directly into the subarachnoid space. When pus and other fluids hinder drug access, surgical drainage is indicated.

Foreign materials (eg, cardiac pacemakers, prosthetic joints and heart valves, synthetic vascular shunts) present a special local problem. Phagocytes react to these objects and attempt to destroy them. Because of this behavior, the phagocytes are less able to attack bacteria, thereby allowing microbes to flourish. Treatment of these infections often results in failure or relapse. In many cases, the infection can be eliminated only by removing the foreign material.

Other Host Factors

Age. Infants and the elderly are highly vulnerable to drug toxicity. In the elderly, heightened drug sensitivity is due in large part to reduced rates of drug metabolism and drug excretion, which can result in accumulation of antibiotics to toxic levels.

Multiple factors contribute to antibiotic sensitivity in infants. Because of poorly developed kidney and liver function, neonates eliminate drugs slowly. To avoid drug accumulation, many antibiotics must be used in low dosage. The very young are also subject to special toxicities. For example, use of sulfonamides in newborns can produce kernicterus, a severe neurologic disorder caused by displacement of bilirubin from plasma proteins (see Chapter 88). The tetracyclines provide another example of toxicity unique to the young: These antibiotics bind to developing teeth, causing discoloration.

Pregnancy and Lactation. Antimicrobial drugs can cross the placenta, posing a risk to the developing fetus. For example, when gentamicin is used during pregnancy, irreversible hearing loss in the infant may result. Also, tetracyclines can stain immature teeth.

Antibiotic use during pregnancy may pose a risk to the expectant mother. It has been shown, for example, that during pregnancy there is an increased incidence of toxicity from tetracycline, characterized by hepatic necrosis, pancreatitis, renal damage, and, in extreme cases, death.

Antibiotics can enter breast milk, possibly affecting the nursing infant. Sulfonamides, for example, can reach levels in milk that are sufficient to cause kernicterus in nursing newborns. As a general guideline, antibiotics and all other drugs should be avoided by women who are breast-feeding.

Previous Allergic Reaction. Severe allergic reactions are more common with the penicillins than with any other family

of drugs. As a rule, patients with a history of allergy to the penicillins should not receive them again. The exception is treatment of a life-threatening infection for which no suitable alternative is available. In addition to the penicillins, other antibiotics (sulfonamides, trimethoprim, erythromycin) are associated with a high incidence of allergic responses. However, severe reactions to these agents are rare.

Genetic Factors. As with other drugs, responses to antibiotics can be influenced by the patient's genetic heritage. For example, some antibiotics (eg, sulfonamides, nalidixic acid) can cause hemolysis in patients who, because of their genetic makeup, have red blood cells that are deficient in glucose-6-phosphate dehydrogenase. Clearly, people with this deficiency should not be given antibiotics that are likely to induce red cell lysis.

Genetic factors can also affect rates of metabolism. For example, hepatic inactivation of isoniazid is rapid in some people and slow in others. If the dosage is not adjusted accordingly, isoniazid may accumulate to toxic levels in the slow metabolizers, and may fail to achieve therapeutic levels in the rapid metabolizers.

DOSAGE SIZE AND DURATION OF TREATMENT

Success requires that the antibiotic be present at the site of infection in an effective concentration for a sufficient time. Dosages should be adjusted to produce drug concentrations that are equal to or greater than the MIC for the infection being treated. Drug levels 4 to 8 times the MIC are often desirable.

Duration of therapy depends on a number of variables, including the status of host defenses, the site of the infection, and the identity of the infecting organism. *It is imperative that antibiotics not be discontinued prematurely.* Accordingly, *patients should be instructed to take their medication for the entire prescribed course, even though symptoms may subside before the full course has been completed.* Early withdrawal is a common cause of recurrent infection, and the organisms responsible for relapse are likely to be more drug resistant than those present when treatment began.

THERAPY WITH ANTIBIOTIC COMBINATIONS

Therapy with a combination of antimicrobial agents is indicated only in specific situations. Under these well-defined conditions, use of multiple drugs may be lifesaving. However, it should be stressed that, although antibiotic combinations do have a valuable therapeutic role, routine use of two or more antibiotics should be discouraged. When an infection is caused by a single, identified microbe, treatment with just one drug is usually most appropriate.

Antimicrobial Effects of Antibiotic Combinations

When two antibiotics are used together, the result may be *additive*, *potentiative*, or, in certain cases, *antagonistic*. An *additive* response is one in which the antimicrobial effect of the combination is equal to the sum of the effects of the two

drugs alone. A *potentiative* interaction (also called a *synergistic* interaction) is one in which the effect of the combination is greater than the sum of the effects of the individual agents. A classic example of potentiation is produced by trimethoprim plus sulfamethoxazole, drugs that inhibit sequential steps in the synthesis of tetrahydrofolic acid (see Chapter 88).

In certain cases, a combination of two antibiotics may be *less* effective than one of the agents by itself, indicating *antagonism* between the drugs. Antagonism is most likely when a *bacteriostatic* agent (eg, tetracycline) is combined with a *bactericidal* drug (eg, penicillin). Antagonism occurs because bactericidal drugs are usually effective only against organisms that are actively growing. Hence, when bacterial growth has been suppressed by a bacteriostatic drug, the effects of a bactericidal agent can be reduced. If host defenses are intact, antagonism between two antibiotics may have little significance. However, if host defenses are compromised, the consequences can be dire.

Indications for Antibiotic Combinations

Initial Therapy of Severe Infection. The most common indication for using multiple antibiotics is initial therapy of severe infection of unknown etiology, especially in the neutropenic host. Until the infecting organism has been identified, wide antimicrobial coverage is appropriate. Just how broad the coverage should be depends on the clinician's skill in narrowing the field of potential pathogens. Once the identity of the infecting microbe is known, drug selection can be adjusted accordingly. As discussed above, samples for culture should be obtained before drug therapy starts.

Mixed Infections. An infection may be caused by more than one microbe. Multiple infecting organisms are common in brain abscesses, pelvic infections, and infections resulting from perforation of abdominal organs. When the infecting microbes differ from one another in drug susceptibility, treatment with more than one antibiotic is required.

Preventing Resistance. Although use of multiple antibiotics is usually associated with *promoting* drug resistance, there is one infectious disease—tuberculosis—in which drug combinations are employed for the specific purpose of *suppressing* the emergence of resistant bacteria. Just why tuberculosis differs from other infections in this regard is discussed in Chapter 90.

Decreased Toxicity. In some situations, an antibiotic combination can reduce toxicity to the host. For example, by combining flucytosine with amphotericin B in the treatment of fungal meningitis, the dosage of amphotericin B can be reduced, thereby decreasing the risk of amphotericin-induced damage to the kidneys.

Enhanced Antibacterial Action. In specific infections, a combination of antibiotics can have greater antibacterial action than a single agent. This is true of the combined use of penicillin plus an aminoglycoside in the treatment of enterococcal endocarditis. Penicillin acts to weaken the bacterial cell wall; the aminoglycoside acts to suppress protein synthesis. The combination has enhanced antibacterial action because, by weakening the cell wall, penicillin facilitates penetration of the aminoglycoside to its intracellular site of action.

Disadvantages of Antibiotic Combinations

Use of multiple antibiotics has several drawbacks, including (1) increased risk of toxic and allergic reactions, (2) possible antagonism of antimicrobial effects, (3) increased risk of superinfection, (4) selection of drug-resistant bacteria, and (5) increased cost. Accordingly, antimicrobial combinations should be employed only when clearly indicated.

PROPHYLACTIC USE OF ANTIMICROBIAL DRUGS

Estimates indicate that between 30% and 50% of the antibiotics used in the United States are administered for prophylaxis. That is, these agents are given to prevent an infection rather than to treat an established infection. Much of this prophylactic use is uncalled for. However, in certain situations, antimicrobial prophylaxis is both appropriate and effective. Whenever prophylaxis is attempted, the benefits must be weighed against the risks of toxicity, allergic reactions, superinfection, and selection of drug-resistant organisms. Generally approved indications for prophylaxis are discussed below.

Surgery. Prophylactic use of antibiotics can decrease the incidence of infection in certain kinds of surgery. Procedures in which prophylactic efficacy has been documented include cardiac surgery, peripheral vascular surgery, orthopedic surgery, and surgery on the GI tract (stomach, duodenum, colon, rectum, and appendix). Prophylaxis is also beneficial for women undergoing a hysterectomy or an emergency cesarean section. In “dirty” surgery (operations performed on perforated abdominal organs, compound fractures, or lacerations from animal bites), the risk of infection is nearly 100%. Hence, for these operations, use of antibiotics is considered *treatment*, not prophylaxis. When antibiotics are given for prophylaxis, they should be given before the surgery. If the procedure is unusually long, dosing again during surgery may be indicated. As a rule, postoperative antibiotics are unnecessary. For most operations, a first-generation cephalosporin (eg, cefazolin) will suffice.

Bacterial Endocarditis. Individuals with congenital or valvular heart disease and those with prosthetic heart valves are unusually susceptible to bacterial endocarditis. For these people, endocarditis can develop following certain dental and medical procedures that dislodge bacteria into the bloodstream. Hence, prior to undergoing such procedures, these patients may need prophylactic antimicrobial medication. However, according to guidelines released by the American Heart Association in 2007, antibiotic prophylaxis is less necessary than previously believed, and hence should be done much less often than in the past.

Neutropenia. Severe neutropenia puts individuals at high risk of infection. There is some evidence that the incidence of bacterial infection may be reduced through antibiotic prophylaxis. However, prophylaxis may increase the risk of infection with fungi: By killing normal flora, whose presence helps suppress fungal growth, antibiotics can encourage fungal invasion.

Other Indications for Antimicrobial Prophylaxis. For young women with recurrent urinary tract infection, prophylaxis with trimethoprim-sulfamethoxazole may be helpful. Oseltamivir (an antiviral agent) may be employed for prophylaxis.

laxis against influenza. For individuals who have had severe rheumatic endocarditis, lifelong prophylaxis with penicillin may be needed. Antimicrobial prophylaxis is indicated following exposure to organisms responsible for sexually transmitted diseases (eg, syphilis, gonorrhea).

MISUSES OF ANTIMICROBIAL DRUGS

Misuse of antibiotics is common. How common? According to the Centers for Disease Control and Prevention, about 50% of antibiotic prescriptions are either inappropriate or entirely unnecessary. This fact is underscored by the data in Table 83-5. Ways that we misuse antibiotics are discussed below.

Attempted Treatment of Untreatable Infection. The majority of viral infections—including mumps, chickenpox, and the common cold—do not respond to currently available drugs. Hence, when drug therapy of these disorders is attempted, patients are exposed to all the risks of drugs but have no chance of receiving benefits.

Acute upper respiratory tract infections, including the common cold, are a particular concern. When these infections are treated with antibiotics, only 1 patient out of 4000 is likely to benefit. However, the risks remain high: 1 in 4 patients will get diarrhea, 1 in 50 will get a rash, and 1 in 1000 will need to visit an emergency department, usually because of a severe allergic reaction.

Treatment of Fever of Unknown Origin. Although fever can be a sign of infection, it can also signify other diseases, including hepatitis, arthritis, and cancer. Unless the cause of a fever is a proven infection, antibiotics should not be employed. Why? Because (1) if the fever is *not* due to an infection, antibiotics would not only be inappropriate, they would expose the patient to unnecessary toxicity and delay correct diagnosis of the fever's cause; and (2) if the fever is caused by infection, antibiotics could hamper later attempts to identify the infecting organism.

The only situation in which fever, by itself, constitutes a legitimate indication for antibiotic use is when fever occurs in the severely immunocompromised host. Since fever may indicate infection, and since infection can be lethal to the immu-

nocompromised patient, these patients should be given antibiotics when fever occurs—even if fever is the only indication that an infection may be present.

Improper Dosage. Like all other medications, antibiotics must be used in the right dosage. If the dosage is too low, the patient will be exposed to a risk of adverse effects without benefit of antibacterial effects. If the dosage is too high, the risks of suprainfection and adverse effects become unnecessarily high.

Treatment in the Absence of Adequate Bacteriologic Information. As stressed earlier, proper antimicrobial therapy requires information on the identity and drug sensitivity of the infecting organism. Except in life-threatening situations, therapy should not be undertaken in the absence of bacteriologic information. This important guideline is often ignored.

Omission of Surgical Drainage. Antibiotics may have limited efficacy in the presence of foreign material, necrotic tissue, or pus. Hence, when appropriate, surgical drainage and cleansing should be performed to promote antimicrobial effects.

MONITORING ANTIMICROBIAL THERAPY

Antimicrobial therapy is assessed by monitoring clinical responses and laboratory results. The frequency of monitoring is directly proportional to the severity of infection. Important clinical indicators of success are reduction of fever and resolution of signs and symptoms related to the affected organ system (eg, improvement of breath sounds in patients with pneumonia).

Various laboratory tests are used to monitor treatment. Serum drug levels may be monitored for two reasons: to ensure that levels are sufficient for antimicrobial effects and to avoid toxicity from excessive levels. Success of therapy is indicated by the disappearance of infectious organisms from post-treatment cultures. Cultures may become sterile within hours of the onset of treatment (as may happen with urinary tract infections), or they may not become sterile for weeks (as may happen with tuberculosis).

TABLE 83-5 ■ Examples of Inappropriate Antibiotic Prescriptions

Type of Infection	Prescriptions per Year	Percent Inappropriate	Comment
Common cold	18 million	100	Antibiotics are ineffective against the common cold.
Bronchitis	16 million	80	Antibiotics are ineffective against bronchitis, except in a few infections or in patients with chronic severe lung disease.
Sore throat	13 million	50	Antibiotics should be used only in patients with confirmed strep infection.
Sinusitis	13 million	50	Most cases are viral, not bacterial. In the absence of facial pain or swelling, antibiotics should be withheld for about 10 days to see if symptoms improve without drugs.

KEY POINTS

- In antimicrobial therapy, the term *selective toxicity* refers to the ability of a drug to injure invading microbes without injuring cells of the host.
- Narrow-spectrum antibiotics are active against only a few microorganisms, whereas broad-spectrum antibiotics are active against a wide array of microbes.
- Bactericidal drugs kill bacteria, whereas bacteriostatic drugs only suppress growth.
- Emergence of resistance to antibiotics is a major concern in antimicrobial therapy.
- Mechanisms of resistance include increased drug efflux, altered drug targets, and enzymatic inactivation of drugs.
- Bacteria with the NDM-1 gene are resistant to nearly all available antibiotics.
- An important method by which bacteria acquire resistance is conjugation, a process in which DNA coding for drug resistance is transferred from one bacterium to another.
- Antibiotics do not cause the genetic changes that underlie resistance. Rather, antibiotics promote emergence of drug-resistant organisms by creating selection pressures that favor them.
- Broad-spectrum antibiotics promote the emergence of resistance more than do narrow-spectrum antibiotics.
- In the hospital, we can delay the emergence of antibiotic resistance in four basic ways: (1) preventing infection, (2) diagnosing and treating infection effectively, (3) using antimicrobial drugs wisely, and (4) preventing patient-to-patient transmission.
- Use of antibiotics to promote growth in livestock is a major force for promoting emergence of resistance.
- Effective antimicrobial therapy requires that we determine both the identity and drug sensitivity of the infecting organism.
- The minimum inhibitory concentration (MIC) of an antibiotic is defined as the lowest concentration needed to completely suppress bacterial growth.
- The minimum bactericidal concentration (MBC) is defined as the concentration that decreases the number of bacterial colonies by 99.9%.
- Host defenses—the immune system and phagocytic cells—are essential to the success of antimicrobial therapy.
- Patients should complete the prescribed course of antibiotic treatment, even though symptoms may abate before the full course is over.
- Although combinations of antibiotics should generally be avoided, they are appropriate in some situations, including (1) initial treatment of severe infections, (2) infection with more than one organism, (3) treatment of tuberculosis, and (4) treatment of an infection in which combination therapy can greatly enhance antibacterial effects.
- Appropriate indications for prophylactic antimicrobial treatment include (1) certain surgeries, (2) neutropenia, (3) recurrent urinary tract infections, and (4) patients at risk of bacterial endocarditis (eg, those with prosthetic heart valves or congenital heart disease).
- Important misuses of antibiotics include (1) treatment of untreatable infections (eg, the common cold and most other acute infections of the upper respiratory tract), (2) treatment of fever of unknown origin (except in the immunocompromised host), (3) treatment in the absence of adequate bacteriologic information, and (4) treatment in the absence of appropriate surgical drainage.

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Drugs That Weaken the Bacterial Cell Wall I: Penicillins

Introduction to the Penicillins

Mechanism of Action

Mechanisms of Bacterial Resistance

Chemistry

Classification

Properties of Individual Penicillins

Penicillin G

Penicillin V

Penicillinase-Resistant Penicillins (Antistaphylococcal Penicillins)

Broad-Spectrum Penicillins (Aminopenicillins)

Extended-Spectrum Penicillins (Antipseudomonal Penicillins)

Penicillins Combined with a Beta-Lactamase Inhibitor

Box 84-1. Methicillin-Resistant *Staphylococcus aureus*

INTRODUCTION TO THE PENICILLINS

The penicillins are practically ideal antibiotics. Why? Because they are active against a variety of bacteria and their direct toxicity is low. Allergic reactions are the principal adverse effects. Owing to their safety and efficacy, the penicillins are widely prescribed.

Because they have a beta-lactam ring in their structure (Fig. 84-1), the penicillins are known as *beta-lactam antibiotics*. The beta-lactam family also includes the cephalosporins, carbapenems, and aztreonam (see Chapter 85). All of the beta-lactam antibiotics share the same mechanism of action: disruption of the bacterial cell wall.

Mechanism of Action

To understand the actions of the penicillins, we must first understand the structure and function of the bacterial cell wall—a rigid, permeable, mesh-like structure that lies outside the cytoplasmic membrane. Inside the cytoplasmic membrane, osmotic pressure is very high. Hence, were it not for the rigid cell wall, which prevents expansion, bacteria would take up water, swell, and then burst.

Penicillins weaken the cell wall, causing bacteria to take up excessive amounts of water and rupture. As a result, penicillins are generally *bactericidal*. However, it is important to

note that penicillins are active only against bacteria that are undergoing growth and division (see below).

Penicillins weaken the cell wall by two actions: (1) *inhibition of transpeptidases* and (2) *disinhibition (activation) of autolysins*. Transpeptidases are enzymes critical to cell wall synthesis. Specifically, they catalyze the formation of cross-bridges between the peptidoglycan polymer strands that form the cell wall, and thereby give the cell wall its strength (Fig. 84-2). Autolysins are bacterial enzymes that cleave bonds in the cell wall. Bacteria employ these enzymes to break down segments of the cell wall to permit growth and division. By simultaneously inhibiting transpeptidases and activating autolysins, the penicillins (1) disrupt synthesis of the cell wall and (2) promote its active destruction. These combined actions result in cell lysis and death.

The molecular targets of the penicillins (transpeptidases, autolysins, other bacterial enzymes) are known collectively as *penicillin-binding proteins* (PBPs). These molecules are so named because penicillins must bind to them to produce antibacterial effects. As indicated in Figure 84-3, PBPs are located on the outer surface of the cytoplasmic membrane. More than eight different PBPs have been identified. Of these, PBP1 and PBP3 are most critical to penicillin's antibacterial effects. Bacteria express PBPs only during growth and division. Accordingly, since PBPs must be present for penicillins to work, these drugs work only when bacteria are growing.

Since mammalian cells lack a cell wall, and since penicillins act specifically on enzymes that affect cell wall integrity, the penicillins have virtually no *direct* effects on cells of the host. As a result, the penicillins are among our safest antibiotics.

Mechanisms of Bacterial Resistance

Bacterial resistance to penicillins is determined primarily by three factors: (1) inability of penicillins to reach their targets (PBPs), (2) inactivation of penicillins by bacterial enzymes, and (3) production of PBPs that have a low affinity for penicillins.

The Gram-Negative Cell Envelope

All bacteria are surrounded by a cell envelope. However, the cell envelope of gram-negative organisms differs from that of gram-positive organisms. Because of this difference, some penicillins are ineffective against gram-negative bacteria.

As indicated in Figure 84-3, the cell envelope of *gram-positive* bacteria has only two layers: the cytoplasmic membrane plus a relatively thick cell wall. Despite its thickness, the cell wall can be readily penetrated by penicillins, giving them easy access to PBPs on the cytoplasmic membrane. As

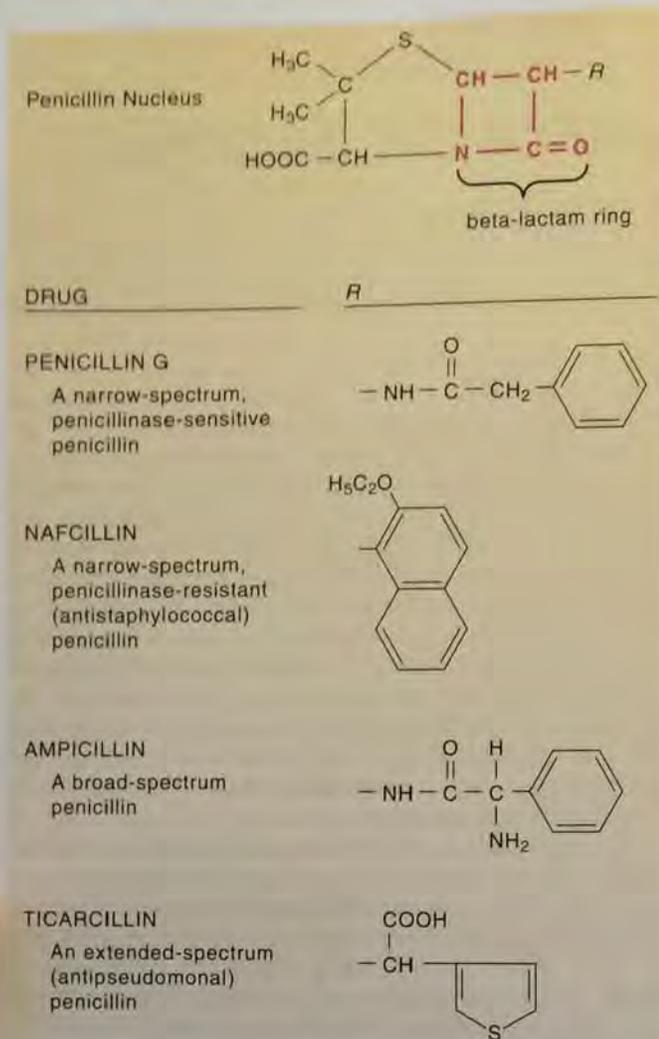


Figure 84-1 = Structural formulas of representative penicillins.

The unique structure of individual penicillins is determined by the side chain coupled to the penicillin nucleus at the position labeled R. This side chain influences acid stability, pharmacokinetic properties, penicillinase resistance, and ability to bind specific penicillin-binding proteins.

a result, penicillins are generally very active against gram-positive organisms.

The gram-negative cell envelope has three layers: the cytoplasmic membrane, a relatively thin cell wall, and an additional outer membrane (see Fig. 84-3). Like the gram-positive cell wall, the gram-negative cell wall can be easily penetrated by penicillins. The outer membrane, however, is difficult to penetrate. As a result, only certain penicillins (eg, ampicillin) are able to cross it and thereby reach PBPs on the cytoplasmic membrane.

Penicillinases (Beta-Lactamases)

Beta-lactamases are enzymes that cleave the beta-lactam ring, and thereby render penicillins and other beta-lactam antibiotics inactive (Fig. 84-4). Bacteria produce a large variety of beta-lactamases; some are specific for penicillins, some are

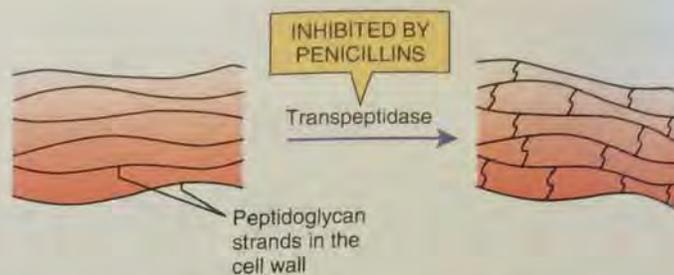


Figure 84-2 = Inhibition of transpeptidase by penicillins. The bacterial cell wall is composed of long strands of a peptidoglycan polymer. As depicted, transpeptidase enzymes create cross-bridges between the peptidoglycan strands, giving the cell wall added strength. By inhibiting transpeptidases, penicillins prevent cross-bridge synthesis and thereby weaken the cell wall.

specific for other beta-lactam antibiotics (eg, cephalosporins), and some act on several kinds of beta-lactam antibiotics. Beta-lactamases that act selectively on penicillins are known as penicillinases.

Penicillinases are synthesized by gram-positive and gram-negative bacteria. Gram-positive organisms produce large amounts of these enzymes, and then export them into the surrounding medium. In contrast, gram-negative bacteria produce penicillinases in relatively small amounts, and, rather than exporting them to the environment, secrete them into the periplasmic space (see Fig. 84-3).

The genes that code for beta-lactamases are located on chromosomes and on plasmids (extrachromosomal DNA). The genes on plasmids may be transferred from one bacterium to another, thereby promoting the spread of penicillin resistance.

Transfer of resistance is of special importance with *Staphylococcus aureus*. When penicillin was first introduced in the early 1940s, all strains of *Staph. aureus* were sensitive. However, by 1960, as many as 80% of *Staph. aureus* isolates in hospitals displayed penicillin resistance. Fortunately, a penicillin derivative (methicillin) that has resistance to the actions of beta-lactamases was introduced at this time. To date, no known strains of *Staph. aureus* produce beta-lactamases capable of inactivating methicillin or related penicillinase-resistant penicillins (although some strains are resistant to these drugs for other reasons).

Altered Penicillin-Binding Proteins

Certain bacterial strains, known collectively as methicillin-resistant *Staphylococcus aureus* (MRSA), have a unique mechanism of resistance: production of PBPs with a low affinity for penicillins and all other beta-lactam antibiotics. How did MRSA develop this ability? By acquiring genes that code for low-affinity PBPs from other bacteria. Infection with MRSA and its management are discussed in Box 84-1.

Chemistry

All of the penicillins are derived from a common nucleus: 6-aminopenicillanic acid. As shown in Figure 84-1, this nucleus contains a beta-lactam ring joined to a second ring. The beta-lactam ring is essential for antibacterial actions. Proper-

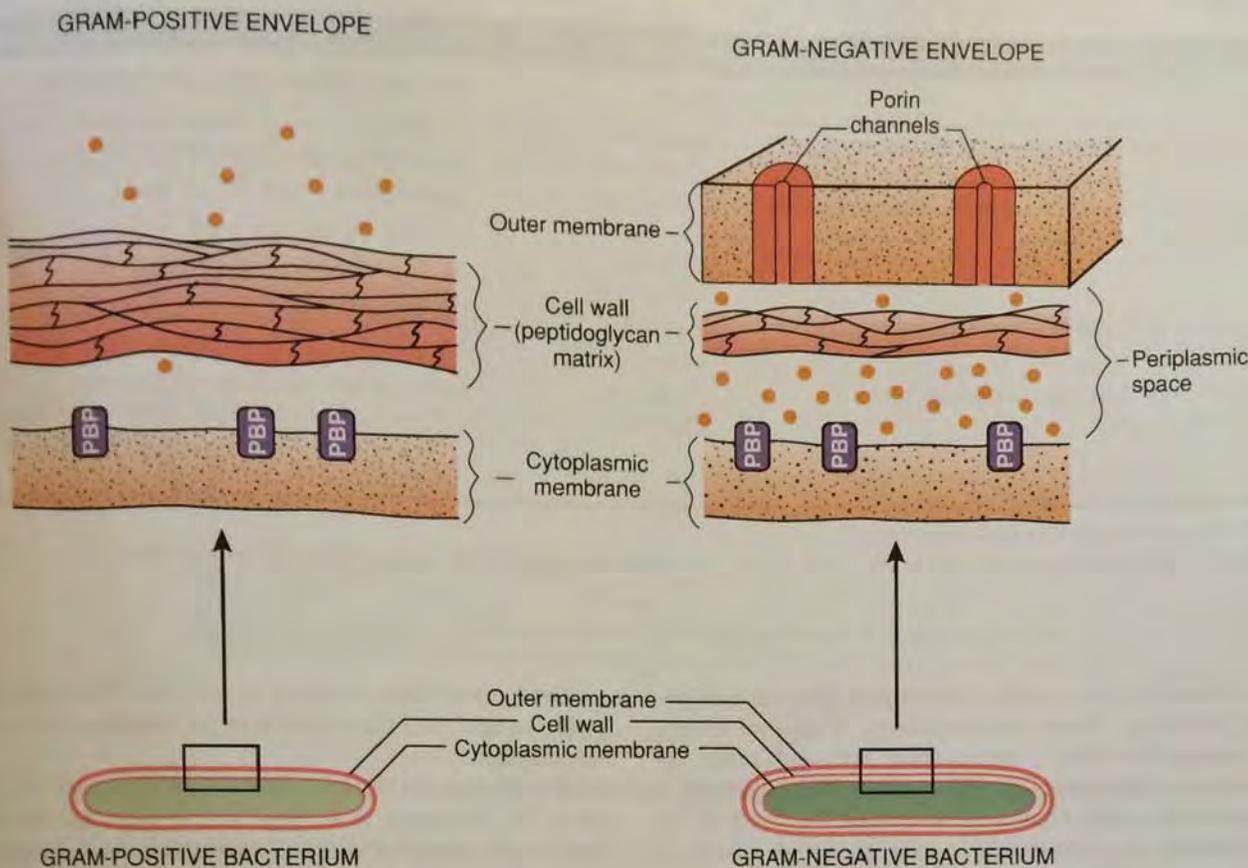


Figure 84-3 • The bacterial cell envelope.

Note that the gram-negative cell envelope has an outer membrane, whereas the gram-positive envelope does not. The outer membrane of the gram-negative cell envelope prevents certain penicillins from reaching their target molecules. (PBP = penicillin-binding protein [transpeptidases and other penicillin target molecules], • = beta-lactamases.)

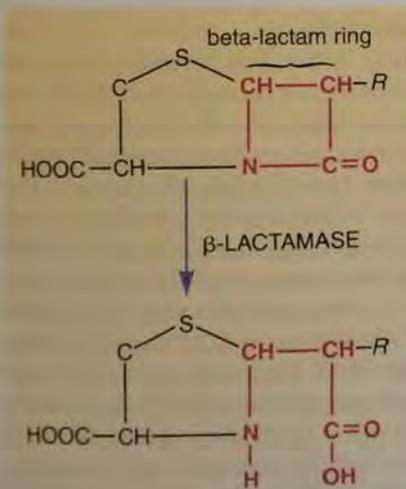


Figure 84-4 • The effect of beta-lactamase on the penicillin nucleus.

Properties of individual penicillins are determined by additions made to the basic nucleus, primarily at the site labeled R. These modifications determine (1) affinity for PBPs, (2) resistance to penicillinases, (3) ability to penetrate the gram-negative cell envelope, (4) resistance to stomach acid, and (5) pharmacokinetic properties.

Classification

The most useful classification of penicillins is based on antimicrobial spectrum. When classified this way, the penicillins fall into four major groups: (1) narrow-spectrum penicillins that are penicillinase sensitive, (2) narrow-spectrum penicillins that are penicillinase resistant (antistaphylococcal penicillins), (3) broad-spectrum penicillins (aminopenicillins), and (4) extended-spectrum penicillins (antipseudomonal penicillins). Table 84-1 lists the members of each group and their principal target organisms.

PROPERTIES OF INDIVIDUAL PENICILLINS

Penicillin G

Penicillin G (benzylpenicillin) was the first penicillin available and will serve as our prototype for the penicillin family. This drug is often referred to simply as *penicillin*. Penicillin G is bactericidal to a number of gram-positive bacteria as well as to some gram-negative bacteria. Despite the introduction of newer antibiotics, penicillin G remains a drug of choice for many infections. Its structure is shown in Figure 84-1.

Antimicrobial Spectrum

Penicillin G is active against most *gram-positive bacteria* (except penicillinase-producing staphylococci), *gram-negative cocci* (*Neisseria meningitidis* and non-penicillinase-producing

TABLE 84-1 • Classification of the Penicillins

Penicillin Class	Drug	Clinically Useful Antimicrobial Spectrum
Narrow-spectrum penicillins: penicillinase sensitive	Penicillin G Penicillin V	<i>Streptococcus</i> species, <i>Neisseria</i> species, many anaerobes, spirochetes, others
Narrow-spectrum penicillins: penicillinase resistant (antistaphylococcal penicillins)	Methicillin* Nafcillin Oxacillin Dicloxacillin	<i>Staphylococcus aureus</i>
Broad-spectrum penicillins (aminopenicillins)	Ampicillin Amoxicillin	<i>Haemophilus influenzae</i> , <i>Escherichia coli</i> , <i>Proteus mirabilis</i> , enterococci, <i>Neisseria gonorrhoeae</i>
Extended-spectrum penicillins (antipseudomonal penicillins)	Ticarcillin† Piperacillin	Same as broad-spectrum penicillins plus <i>Pseudomonas aeruginosa</i> , <i>Enterobacter</i> species, <i>Proteus</i> (indole positive), <i>Bacteroides fragilis</i> , many <i>Klebsiella</i>

*Methicillin is no longer used in the United States.

†Ticarcillin, by itself, is no longer available in the United States, but ticarcillin combined with clavulanic acid is still available.

strains of *Neisseria gonorrhoeae*), anaerobic bacteria, and spirochetes (including *Treponema pallidum*). With few exceptions, gram-negative bacilli are resistant. Although many organisms respond to penicillin G, the drug is considered a narrow-spectrum agent, compared with other members of the penicillin family.

Therapeutic Uses

Penicillin G is a drug of first choice for infections caused by sensitive gram-positive cocci. Important among these are pneumonia and meningitis caused by *Streptococcus pneumoniae* (pneumococcus), pharyngitis caused by *Streptococcus pyogenes*, and infectious endocarditis caused by *Streptococcus viridans*. Penicillin is also the preferred drug for those few strains of *Staph. aureus* that do not produce penicillinase.

Penicillin is a preferred agent for infections caused by several gram-positive bacilli, specifically, gas gangrene (caused by *Clostridium perfringens*), tetanus (caused by *Clostridium tetani*), and anthrax (caused by *Bacillus anthracis*).

Penicillin is the drug of first choice for meningitis caused by *N. meningitidis* (meningococcus).

Although once the drug of choice for gonorrhea (caused by *N. gonorrhoeae*), penicillin has been replaced by ceftriaxone as the primary treatment. Penicillin is now limited to infections caused by non-penicillinase-producing strains of *N. gonorrhoeae*.

Penicillin is the drug of choice for syphilis, an infection caused by the spirochete *T. pallidum*.

In addition to treating active infections, penicillin G has important prophylactic applications. The drug is used to prevent syphilis in sexual partners of individuals who have this infection. Benzathine penicillin G (administered monthly for life) is employed for prophylaxis against recurrent attacks of rheumatic fever; treatment is recommended for patients with a history of recurrent rheumatic fever and for those with clear evidence of rheumatic heart disease. Penicillin is also employed for prophylaxis of bacterial endocarditis; candidates include individuals with (1) prosthetic heart valves, (2) most congenital heart diseases, (3) acquired valvular heart disease, (4) mitral valve prolapse, and (5) previous history of bacterial endocarditis. For prevention of endocarditis, penicillin is administered prior to dental procedures and other procedures that are likely to produce temporary bacteremia.

Pharmacokinetics

Absorption. Penicillin G is available as three salts: (1) potassium penicillin G, (2) procaine penicillin G, and (3) benzathine penicillin G. These salts differ with respect to route of administration and time course of action. With all three forms, the salt dissociates to release penicillin G, the active component.

Oral. Oral administration is obsolete. Penicillin G is unstable in acid, and the majority of an oral dose is destroyed in the stomach.

Intramuscular. All forms of penicillin may be administered IM. However, it is important to note that the different salts are absorbed at very different rates. As indicated in Figure 84-5, absorption of potassium penicillin G is rapid; blood levels peak about 15 minutes after injection. In contrast, the procaine and benzathine salts are absorbed slowly, and hence are considered repository preparations. When benzathine penicillin is injected IM, penicillin G is absorbed for weeks, producing blood levels that are persistent but very low (see Fig. 84-5). Consequently, this preparation is useful only against highly sensitive organisms (eg, *T. pallidum*, the bacterium that causes syphilis).

Intravenous. When high blood levels are needed rapidly, penicillin can be administered IV. Only the potassium salt should be used by this route. Owing to poor water solubility, procaine and benzathine salts must never be administered IV.

Distribution. Penicillin distributes well to most tissues and body fluids. In the absence of inflammation, penetration of the meninges and into fluids of joints and the eye is poor. By contrast, in the presence of inflammation, entry into cerebrospinal fluid, joints, and the eye is enhanced, permitting treatment of infections caused by susceptible organisms.

Metabolism and Excretion. Penicillin undergoes minimal metabolism, and is eliminated by the kidneys, primarily as the unchanged drug. Renal excretion is accomplished mainly (90%) by active tubular secretion; the remaining 10% results from glomerular filtration. In older children and adults, the half-life is very short (about 30 minutes). Renal impairment causes the half-life to increase dramatically, and may necessitate a reduction in dosage. In patients at high risk of toxicity (those with renal impairment, the acutely ill, the elderly, the very young), kidney function should be monitored.

Renal excretion of penicillin can be delayed with probenecid, a compound that competes with penicillin for active tubular transport. In the past, when penicillin was both scarce and expensive, probenecid was employed routinely to prolong antibacterial effects. However, since penicillin is now available in abundance at low cost, concurrent use of probenecid is seldom indicated.

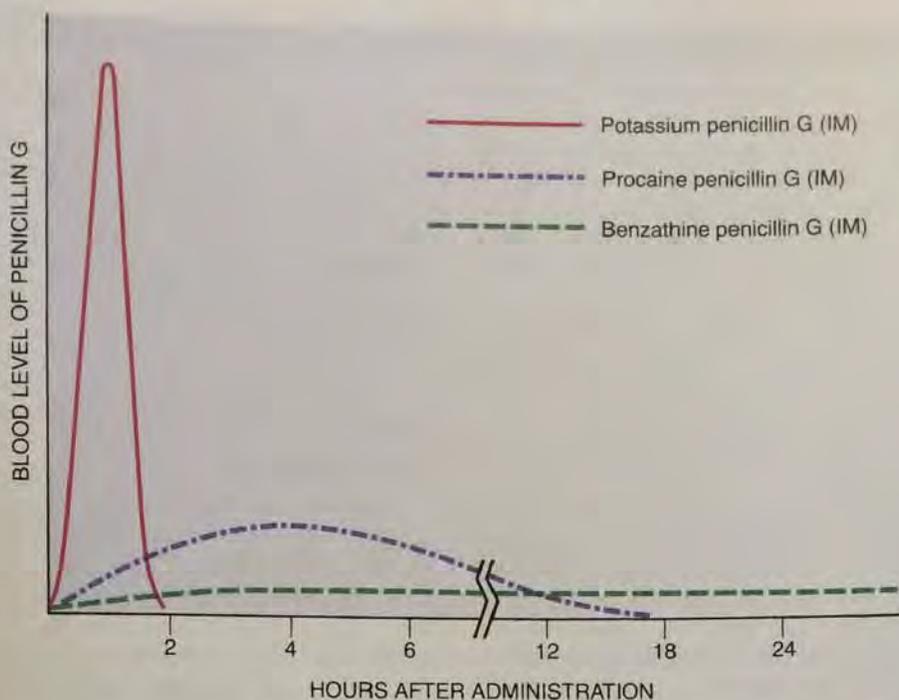


Figure 84-5 ■ Blood levels of penicillin G following IM injection of three different penicillin G salts.

(Adapted from Pratt WB, Fekety R: *The Antimicrobial Drugs*. New York: Oxford University Press, 1986.)

Side Effects and Toxicities

Penicillin G is the least toxic of all antibiotics, and among the safest of all medications. Allergic reactions, the principal concern with penicillin, are discussed separately below. Other reactions include *pain at sites of IM injection*, prolonged (but reversible) *sensory and motor dysfunction* following accidental injection into a peripheral nerve, and *neurotoxicity* (seizures, confusion, hallucinations) if blood levels are too high. Inadvertent *intra-arterial* injection can produce severe reactions—gangrene, necrosis, sloughing of tissue—and must be avoided.

Certain adverse effects may be caused by compounds co-administered with penicillin. For example, the procaine component of procaine penicillin G may cause bizarre behavioral effects when procaine penicillin is given in large doses. When large IV doses of potassium penicillin G are administered rapidly, hyperkalemia can result, possibly causing dysrhythmias and even cardiac arrest.

Penicillin Allergy

General Considerations. *Penicillins are the most common cause of drug allergy.* Between 0.4% and 7% of patients who receive penicillins experience an allergic reaction. Severity can range from a minor rash to life-threatening anaphylaxis. As with most allergic reactions, there is no direct relationship between the size of the dose and the intensity of the response. Although prior exposure to penicillins is required for an allergic reaction, responses may occur in the absence of prior penicillin use. How can this be? Because patients may have been exposed to penicillins produced by fungi or to penicillins present in foods of animal origin.

Because of cross sensitivity, patients allergic to one penicillin should be considered allergic to all other penicillins. In addition, a few patients (about 1%) display cross sensitivity to *cephalosporins*. If at all possible, patients with penicillin allergy should not be treated with any member of the penicillin family. Use of cephalosporins depends on the intensity of allergic response: If the penicillin allergy is mild, use of cephalosporins is probably safe; however, if the allergy is severe, cephalosporins should be avoided.

Individuals allergic to penicillin should be encouraged to wear a Medic Alert bracelet to alert healthcare personnel to their condition.

Types of Allergic Reactions. Penicillin reactions are classified as *immediate*, *accelerated*, and *late*. Immediate reactions occur 2 to 30 minutes after drug administration; accelerated reactions occur within 1 to 72 hours; and late reactions occur within days to weeks. Immediate and accelerated reactions are mediated by immunoglobulin E (IgE) antibodies.

Anaphylaxis (laryngeal edema, bronchoconstriction, severe hypotension) is an immediate hypersensitivity reaction, mediated by IgE. Anaphylactic reactions occur more frequently with penicillins than with any other drugs. However, even with penicillins, the incidence of anaphylaxis is extremely low (the estimated incidence is between 0.004% and 0.04%). Nonetheless, when these reactions do occur, the risk of mortality is high (about 10%). The primary treatment is *epinephrine* (subQ, IM, or IV) plus respiratory support. To ensure prompt treatment if anaphylaxis should develop, patients should remain in the prescriber's office for at least 30 minutes after drug injection (ie, until the risk of an anaphylactic reaction has passed).

Development of Penicillin Allergy. Before discussing penicillin allergy further, we need to review development of allergy to small molecules as a class. Small molecules, such as penicillin and most other drugs, are unable to induce antibody formation directly. Therefore, in order to promote antibody formation, the small molecule must first bond covalently to a larger molecule, usually a protein. In these combinations, the small molecule is referred to as a *hapten*. The hapten-protein combination constitutes the complete *antigen* that stimulates antibody formation.

The hapten that stimulates production of penicillin antibodies is rarely intact penicillin itself. Rather, compounds formed from the degradation of penicillin are the actual cause. As a result, most "penicillin antibodies" are not directed at penicillin itself. Rather, they are directed at various penicillin degradation products.

Skin Tests for Penicillin Allergy. Allergy to penicillin can decrease over time. Hence, an intense allergic reaction in the past does not necessarily mean that an intense reaction will occur again. In patients with a history of penicillin allergy, skin tests can be employed to assess current risk. These tests are performed by injecting a tiny amount of allergen intradermally and observing for a local allergic response. A positive test indicates the presence of IgE antibodies, which can mediate severe penicillin allergy. Accordingly, if skin testing is negative, a severe allergic reaction (anaphylaxis) is unlikely.

It is important to note that skin testing can be dangerous: In patients with severe penicillin allergy, the skin test itself can precipitate an anaphylactic reaction. Accordingly, the test should be performed only if epinephrine and facilities for respiratory support are immediately available.

Current guidelines recommend skin testing with two reagents, which test for the major (more common) and minor (less common) determinants of penicillin allergy. The minor determinants, although less common, mediate the majority of severe penicillin reactions.

The major determinant reagent, available commercially as Pre-Pen, contains a single component: *benzylpenicilloyl-polylysine*. Benzylpenicilloyl-polylysine is a large polymeric molecule that is poorly absorbed. Hence, even in patients with severe penicillin allergy, this skin test carries a low risk of a systemic reaction.

The recommended minor determinant reagent, which is not available commercially, is a mixture of three compounds: benzylpenicillin G, benzylpenicilloate, and penicilloyl propylamine. As noted, the term *minor* indicates that the antibodies being tested for are relatively uncommon and not that the allergic response mediated by these antibodies is of minor significance. In fact, the minor determinants are responsible for the majority of severe penicillin reactions.

Management of Patients with a History of Penicillin Allergy. All patients who are candidates for penicillin therapy should be asked if they have penicillin allergy. For patients who answer "yes," the general rule is to avoid penicillins. If the allergy is mild, a *cephalosporin* is often an appropriate alternative. However, if there is a history of anaphylaxis or some other severe allergic reaction, it is prudent to avoid cephalosporins as well (because there is about a 1% risk of cross sensitivity to cephalosporins). When a cephalosporin is indicated, an oral cephalosporin is preferred (because the risk of a severe reaction is lower than with parenteral therapy). For many infections, *vancomycin*, *erythromycin*,

and *clindamycin* are effective and safe alternatives for patients with penicillin allergy.

Rarely, a patient with a history of anaphylaxis may have a life-threatening infection (eg, enterococcal endocarditis) for which alternatives to penicillins are ineffective. In these cases, the potential benefits of penicillin therapy outweigh the risks, and treatment should be instituted. To minimize the chances of an anaphylactic reaction, penicillin should be administered according to a desensitization schedule. In this procedure, an initial small dose is followed at 60-minute intervals by progressively larger doses until the full therapeutic dose has been achieved. It should be noted that the desensitization procedure is not without risk. Accordingly, epinephrine and facilities for respiratory support should be immediately available.

Drug Interactions

Aminoglycosides. For some infections, penicillins are used in combination with an aminoglycoside (eg, gentamicin). By weakening the cell wall, the penicillin facilitates access of the aminoglycoside to its intracellular site of action, thereby increasing bactericidal effects. Unfortunately, when penicillins are present in high concentrations, they interact chemically with aminoglycosides and thereby inactivate the aminoglycoside. Accordingly, *penicillins and aminoglycosides should never be mixed in the same IV solution*. Rather, they should be administered separately. Once a penicillin has been diluted in body fluids, the potential for inactivating the aminoglycoside is minimal.

Probenecid. As noted, probenecid can delay renal excretion of penicillin, thereby prolonging antibacterial effects.

Bacteriostatic Antibiotics. Since penicillins are most effective against actively growing bacteria, concurrent use of a bacteriostatic antibiotic (eg, tetracycline) could, in theory, reduce the bactericidal effects of the penicillin. However, the clinical significance of such interactions is not known. Nonetheless, combined use of penicillin and bacteriostatic agents is generally avoided.

Preparations, Dosage, and Administration

Preparations and Routes of Administration. Penicillin G is available as three different salts (potassium, procaine, and benzathine). These salts differ with respect to routes of administration: *potassium penicillin G* [Pfizerpen] is administered IM, IV, and by local infusion (eg, intrapleural); all others salts—*benzathine penicillin G* [Permapen], *procaine penicillin G*, and a combination product [Bicillin C-R], composed of benzathine penicillin G plus procaine penicillin G—are administered IM. Check to ensure that the penicillin salt to be administered is appropriate for the intended route.

Dosage. Dosage of penicillin G is prescribed in units (1 unit equals 0.6 mg). Dosage ranges are summarized in Table 84-2. For any particular patient, the specific dosage will depend on the type and severity of infection. Dosage should be reduced in patients with severe renal impairment.

Administration. Solutions for parenteral administration should be prepared according to the manufacturer's instructions. During IM administration, take care to avoid inadvertent injection into an artery or peripheral nerve.

Penicillin V

Penicillin V, also known as penicillin VK, is similar to penicillin G in most respects. The principal difference is acid stability: penicillin V is stable in stomach acid, whereas penicillin G is not. Because of its acid stability, penicillin V has replaced penicillin G for oral therapy. Penicillin V may be taken with meals. Dosages are summarized in Table 84-2.

Penicillinase-Resistant Penicillins (Antistaphylococcal Penicillins)

By altering the penicillin side chain, pharmaceutical chemists have created a group of penicillins that are highly resistant to inactivation by beta-lactamases. In the United States, three such drugs are available: *nafcillin*, *oxacillin*, and *dicloxacillin*. These

TABLE 84-2 • Dosages for Penicillins

Generic Name	Trade Name	Usual Routes	Dosing Interval (hr)	Total Daily Dosage ^a	
				Adults	Children
Narrow-Spectrum Penicillins: Penicillinase-Sensitive					
Penicillin G	Bicillin C-R, Permapen, Pfizerpen	IM, IV	4	1.2–2.4 million units ^b	100,000–250,000 units/kg ^b
Penicillin V	generic only	PO	4–6	0.5–2 gm	25–50 mg/kg
Narrow-Spectrum Penicillins: Penicillinase-Resistant (Antistaphylococcal Penicillins)					
Nafcillin		IV	4–6	2–12 gm	100–200 mg/kg
Oxacillin		IV	4–6	2–12 gm	100–200 mg/kg
Dicloxacillin		PO	6	1–4 gm	12.5–25 mg/kg
Broad-Spectrum Penicillins (Aminopenicillins)					
Ampicillin	generic only	PO	6–8	2–4 gm	50–100 mg/kg
		IV	6–8	2–12 gm	10–200 mg/kg
Ampicillin/sulbactam	Unasyn	IV	6	4–8 gm ^c	300 mg/kg ^c
Amoxicillin	generic only	PO	8	750–1500 mg	20–40 mg/kg
Amoxicillin, ER	Moxatag	PO	24	775 mg	775 mg
Amoxicillin/clavulanate	Augmentin, Clavulin ⁺	PO	8	250–500 mg ^d	20–40 mg/kg ^d
	Augmentin ES-600	PO	12	—	90 mg/kg
	Augmentin XR	PO	12	4000 mg	—
Extended-Spectrum Penicillins (Antipseudomonal Penicillins)					
Ticarcillin/clavulanate	Timentin	IV	4–6	200–300 mg/kg ^e	200 mg/kg ^e
Piperacillin		IV	4–6	12–24 gm	200–300 mg/kg
Piperacillin/tazobactam	Zosyn, Tazocin ⁺	IV	4–6	12 gm ^f	80–100 mg/kg ^f

ER = extended release.

^aDoses vary widely, depending upon the type and severity of infection; doses and dosing intervals presented here may not be appropriate for all patients.

^b10,000 units = 6 mg.

^cDose based on ampicillin content.

^dDose based on amoxicillin content.

^eDose based on ticarcillin content.

^fDose based on piperacillin content.

agents have a very narrow antimicrobial spectrum and are used only against penicillinase-producing strains of staphylococci (*Staph. aureus* and *Staph. epidermidis*). Since most strains of staphylococci produce penicillinase, the penicillinase-resistant penicillins are drugs of choice for the majority of staphylococcal infections. It should be noted that these agents should not be used against infections caused by non-penicillinase-producing staphylococci, since they are less active than penicillin G against these bacteria.

An increasing clinical problem is the emergence of staphylococcal strains referred to as *methicillin-resistant Staphylococcus aureus (MRSA)*, a term used to indicate lack of susceptibility to methicillin (an obsolete penicillinase-resistant penicillin) and all other penicillinase-resistant penicillins. Resistance appears to result from production of PBPs to which the penicillinase-resistant penicillins cannot bind. Currently, vancomycin (alone or combined with rifampin) is the treatment of choice. Infection with MRSA is discussed further in Box 84-1.

Nafcillin

Nafcillin is usually administered IV. Intramuscular use is rare. Absorption from the GI tract is erratic and incomplete, and hence oral formulations have been discontinued. Dosage is summarized in Table 84-2.

Oxacillin and Dicloxacillin

These drugs are similar in structure and pharmacokinetic properties. Both are acid stable, but only dicloxacillin is formulated for oral dosing. Oxacillin is administered IV. Dosages are summarized in Table 84-2.

Methicillin

Methicillin, the oldest penicillinase-resistant penicillin, is no longer available. In addition to causing allergic reactions typical of all penicillins, methicillin may produce interstitial nephritis, an adverse effect that is usually reversible but sometimes progresses to complete renal failure.

Broad-Spectrum Penicillins (Aminopenicillins)

Only two broad-spectrum penicillins are available: *ampicillin* and *amoxicillin*. Both have the same antimicrobial spectrum as penicillin G, plus increased activity against certain gram-negative bacilli, including *Haemophilus influenzae*, *Escherichia coli*, *Salmonella*, and *Shigella*. This broadened spectrum is due in large part to an increased ability to penetrate the gram-negative cell envelope. Both drugs are readily inactivated by beta-lactamases, and hence are ineffective against most infections caused by *Staph. aureus*.

Ampicillin

Ampicillin, formerly available as Principen, was the first broad-spectrum penicillin in clinical use. The drug is useful against infections caused by *Enterococcus faecalis*, *Proteus mirabilis*, *E. coli*, *Salmonella*, *Shigella*, and *H. influenzae*. The most common side effects are rash and diarrhea, both of which occur more frequently with ampicillin than with any

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

Staphylococcus aureus is a gram-positive bacterium that often colonizes the skin and nostrils of healthy people. Infection usually involves the skin and soft tissues, causing abscesses, boils, cellulitis, and impetigo. However, more serious infections can also develop, including infections of the lungs and bloodstream, which can be fatal.

Like other pathogens, *Staph. aureus* has developed resistance over the years. When penicillins were introduced in the 1940s, all strains of *Staph. aureus* were susceptible. However, penicillin-resistant strains quickly emerged, owing to bacterial production of penicillinases. In 1959, this resistance was overcome with methicillin, the first penicillinase-resistant penicillin. Unfortunately, by 1968, strains resistant to methicillin had emerged. These highly resistant bacteria, known as *methicillin-resistant Staph. aureus (MRSA)*, are resistant not only to methicillin (now obsolete), but to all penicillins and all cephalosporins as well. The basis of MRSA resistance is acquisition of genes that code for penicillin-binding proteins that have very low affinity for penicillins and cephalosporins. Resistant strains were initially limited to healthcare facilities, but are now found in the community as well.

In the United States, MRSA is a serious public health problem. Between 2000 and 2005, hospital stays for MRSA infection tripled, rising from 128,500 to 368,800. In 2005, MRSA caused an estimated 94,360 *severe* (ie, invasive) infections, resulting in 18,650 deaths—6150 *more* than were caused by HIV/AIDS. Not only does MRSA increase mortality, it increases costs: Treating hospitalized MRSA patients runs about \$35,000, compared with \$14,000 for patients with methicillin-sensitive infections. Fortunately, the MRSA news isn't all bad. For one thing, although MRSA infections are now common, most patients can be cured. Also, rates of MRSA infection among hospitalized patients are now falling, after rising steadily for many years.

There are two distinct types of MRSA, referred to as *hospital-associated MRSA (HA-MRSA)* and *community-associated MRSA (CA-MRSA)*. Of the two, HA-MRSA is more prevalent (85% vs. 15%) and emerged earlier (1968 vs. 1981). Also, HA-MRSA infection is generally more serious and harder to treat. Molecular typing indicates that HA-MRSA and CA-MRSA are genetically distinct strains, known as USA100 and USA300, respectively.

Hospital-Associated MRSA

Methicillin resistance in *Staph. aureus* was first reported in isolates from hospitalized patients. The year was 1968. For most of the next four decades, the prevalence of HA-MRSA among hospitalized patients climbed steadily, reaching 85% of all invasive *Staph. aureus* infections by 2004. However, rates of HA-MRSA are now falling: Between 2005 and 2008, the prevalence of hospital-onset invasive MRSA infections fell by an average of 9.4% a year.

Although many infections with HA-MRSA *surface* in the community, nearly all occur in people who had been exposed to a healthcare facility within the prior year, indicating that acquisition of the infection probably occurred in a healthcare

setting—not out in the community. Transmission of HA-MRSA is usually through person-to-person contact, very often between healthcare workers and patients. Risk factors for acquiring HA-MRSA include old age, recent surgery or hospitalization, dialysis, treatment in an ICU, prolonged antibiotic therapy, an indwelling catheter, and residence in a long-term care facility.

How do we treat HA-MRSA infection? The issue is addressed at length in a new guideline—Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children—issued January 5, 2011. The guideline stresses the importance of selecting drugs based on the site of the infection, age of the patient, and drug sensitivity of the pathogen. For complicated skin and soft tissue infections in adults, the preferred drugs are IV vancomycin, linezolid [Zyvox], daptomycin [Cubicin], telavancin [Vibativ], clindamycin, and ceftaroline [Teflaro]. Intravenous vancomycin is the preferred drug for children. For bacteremia or endocarditis in adults or children, IV vancomycin and daptomycin are drugs of choice. Preferred drugs for pneumonia in adults and children are IV vancomycin, linezolid, and clindamycin. Because most strains of MRSA are multidrug resistant, many other antibiotics are ineffective, including tetracyclines, clindamycin, trimethoprim/sulfamethoxazole, and beta-lactam agents (except ceftaroline).

Community-Associated MRSA

Infection with CA-MRSA, first reported in 1981, is caused by staphylococcal strains that are genetically distinct from HA-MRSA. For example, most strains of CA-MRSA carry a gene for Panton-Valentine leukocidin (a cytotoxin that causes necrosis), whereas HA-MRSA strains do not. Many people are now asymptomatic carriers of CA-MRSA. In fact, between 20% and 30% of the population is colonized, typically on the skin and in the nostrils.

Infection with CA-MRSA is generally less dangerous than with HA-MRSA, but more dangerous than with methicillin-sensitive *Staph. aureus*. In most cases, CA-MRSA causes mild infections of the skin and soft tissues, manifesting as boils, impetigo, and so forth. However, CA-MRSA can also cause more serious infections, including necrotizing fasciitis, severe necrotizing pneumonia, and severe sepsis. Fortunately, these invasive infections are relatively rare. On the other hand, infections of the skin and soft tissues are now common, with CA-MRSA accounting for more than 50% of the *Staph. aureus* isolates from these sites.

How is CA-MRSA transmitted? And who is vulnerable? Transmission is by skin-to-skin contact, and by contact with contaminated objects, including frequently touched surfaces, sports equipment, and personal items (eg, razors). In contrast to HA-MRSA infection, CA-MRSA infection is seen primarily in young, healthy people with no recent exposure to healthcare facilities. Individuals at risk include athletes in contact sports (eg, wrestling), men who have sex with men, and people who live in close quarters, such as family members, day care clients, prison inmates, military personnel, and college students.

BOX 84-1 ■ SPECIAL INTEREST TOPIC—cont'd

Several measures can reduce the risk of CA-MRSA transmission. Topping the list is good hand hygiene—washing with soap and water or applying an alcohol-based sanitizer. Other measures include showering after contact sports, cleaning frequently touched surfaces, keeping infected sites covered, and not sharing towels and personal items.

Treatment depends on infection severity. For boils, small abscesses, and other superficial infections, surgical drainage may

be all that is needed. For more serious infections, drugs may be indicated. Preferred agents are trimethoprim/sulfamethoxazole, minocycline, doxycycline, and clindamycin. Alternative drugs—vancomycin, daptomycin, and linezolid—should be reserved for severe infections and treatment failures. To eradicate the carrier state, intranasal application of a topical antibiotic—mupirocin or retapamulin—can be effective. Like HA-MRSA, CA-MRSA does not respond to beta-lactam antibiotics, except ceftaroline.

other penicillin. Administration may be oral or IV. It should be noted, however, that for oral therapy, amoxicillin is preferred (see below). Dosages for patients with normal kidney function are summarized in Table 84-2. For patients with renal impairment, dosage should be reduced.

As discussed below, ampicillin is also available in a fixed-dose combination with sulbactam, an inhibitor of bacterial beta-lactamase. The combination is sold as *Unasyn*.

Amoxicillin

Amoxicillin [Moxatag] is similar to ampicillin in structure and actions. The drugs differ primarily in acid stability, amoxicillin being the more acid stable. Hence, when the two are administered orally in equivalent doses, blood levels of amoxicillin are greater. Accordingly, when oral therapy is indicated, amoxicillin is preferred. Amoxicillin produces less diarrhea than ampicillin, perhaps because less amoxicillin remains unabsorbed in the intestine.

As discussed below, amoxicillin is also available in a fixed-dose combination with clavulanic acid, an inhibitor of bacterial beta-lactamases. The combination is marketed as *Augmentin*. Amoxicillin, by itself, is one of our most frequently prescribed antibiotics.

Extended-Spectrum Penicillins (Antipseudomonal Penicillins)

Only two extended-spectrum penicillins are available: *ticarcillin* and *piperacillin*. The antimicrobial spectrum of these drugs includes organisms that are susceptible to the aminopenicillins plus *Pseudomonas aeruginosa*, *Enterobacter* species, *Proteus* (indole positive), *Bacteroides fragilis*, and many *Klebsiella*. Both extended-spectrum penicillins are susceptible to beta-lactamases, and hence are ineffective against most strains of *Staph. aureus*.

The extended-spectrum penicillins are used primarily for infections with *P. aeruginosa*. These infections often occur in the immunocompromised host and can be very difficult to eradicate. To increase killing of *Pseudomonas*, an antipseudomonal aminoglycoside (gentamicin, tobramycin, amikacin, netilmicin) is almost always added to the regimen. When these combinations are employed, the penicillin and the aminoglycoside should not be mixed in the same IV solution. Why? Because high concentrations of penicillins can inactivate aminoglycosides.

Ticarcillin

Ticarcillin has one of the broadest antimicrobial spectra of all penicillins—but is susceptible to destruction by penicillinase. Like all other penicillins, ticarcillin can trigger allergic reactions. Also, since ticarcillin is administered as the *disodium salt*, and since large IV doses are often required, symptoms of *sodium overload* (eg, congestive heart failure) may develop. In addition, ticarcillin interferes with platelet function and can thereby promote *bleeding*. At this time, ticarcillin is available only in a fixed-dose combination with clavulanic acid, a beta-lactamase inhibitor (see below). The combination [Timentin] is administered IV.

Piperacillin

Piperacillin has a broad antimicrobial spectrum; however, like ticarcillin, the drug is penicillinase sensitive. Piperacillin is highly active against *P. aeruginosa*, its principal target. Like ticarcillin, piperacillin can cause bleeding secondary to disrupting platelet function. The drug is acid labile and hence must be administered parenterally, usually IV. The risk of sodium overload is much less than with IV ticarcillin. When piperacillin is used in combination with an aminoglycoside, it should not be mixed in the same IV solution. Dosages for patients with normal kidney function are shown in Table 84-2. Dosage should be reduced in patients with renal impairment. As discussed below, piperacillin is also available in a fixed-dose combination with tazobactam, a beta-lactamase inhibitor. The combination is marketed as *Zosyn*.

Penicillins Combined with a Beta-Lactamase Inhibitor

As their name indicates, beta-lactamase inhibitors are drugs that inhibit bacterial beta-lactamases. By combining a beta-lactamase inhibitor with a penicillinase-sensitive penicillin, we can extend the antimicrobial spectrum of the penicillin. In the United States, three beta-lactamase inhibitors are used: *sulbactam*, *tazobactam*, and *clavulanic acid* (clavulanate). These drugs are not available alone. Rather, they are available only in fixed-dose combinations with a penicillin. Four such combination products are available:

- Ampicillin/sulbactam [Unasyn]
- Amoxicillin/clavulanate [Augmentin, Clavulin ♦]
- Ticarcillin/clavulanate [Timentin]
- Piperacillin/tazobactam [Zosyn, Tazocin ♦]

Because beta-lactamase inhibitors have minimal toxicity, any adverse effects that occur with the combination products are due to the penicillin. Routes and dosages are summarized in Table 84-2.

KEY POINTS

- Penicillins weaken the bacterial cell wall, causing lysis and death.
- Some bacteria resist penicillins by producing penicillinases (beta-lactamases), enzymes that inactivate penicillins.
- Gram-negative bacteria are resistant to penicillins that cannot penetrate the gram-negative cell envelope.
- Penicillins are the safest antibiotics available.
- The principal adverse effect of penicillins is allergic reaction, which can range from rash to life-threatening anaphylaxis.
- Patients allergic to one penicillin should be considered cross-allergic to all other penicillins. In addition, they have about a 1% chance of cross-allergy to cephalosporins.
- Vancomycin, erythromycin, and clindamycin are safe and effective alternatives to penicillins for patients with penicillin allergy.
- Penicillins are normally eliminated rapidly by the kidney, but can accumulate to harmful levels if renal function is severely impaired.
- The principal differences among the penicillins relate to antibacterial spectrum, stability in stomach acid, and duration of action.
- Penicillin G has a narrow antibacterial spectrum and is unstable in stomach acid.
- Benzathine penicillin G is released very slowly following IM injection, and thereby produces prolonged antibacterial effects.
- The penicillinase-resistant penicillins (eg, nafcillin) are used primarily against penicillinase-producing strains of *Staph. aureus*.
- In contrast to penicillin G, the broad-spectrum penicillins, such as ampicillin and amoxicillin, have useful activity against gram-negative bacilli.
- Extended-spectrum penicillins—piperacillin and ticarcillin—are useful against *P. aeruginosa*.
- Beta-lactamase inhibitors, such as clavulanic acid, are combined with certain penicillins to increase their activity against beta-lactamase-producing bacteria.
- Penicillins should not be combined with aminoglycosides (eg, gentamicin) in the same IV solution.

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Summary of Major Nursing Implications*

PENICILLINS

Amoxicillin
Amoxicillin/clavulanate
Ampicillin
Ampicillin/sulbactam
Dicloxacillin
Nafcillin
Oxacillin
Penicillin G
Penicillin V
Piperacillin
Piperacillin/tazobactam
Ticarcillin/clavulanate

Except where indicated otherwise, the implications summarized below apply to all members of the penicillin family.

Preadministration Assessment

Therapeutic Goal

Treatment of infections caused by sensitive bacteria.

Baseline Data

The prescriber may order tests to identify the infecting organism and its drug sensitivity. Take samples for microbiologic culture prior to starting treatment.

In patients with a history of penicillin allergy, a skin test may be performed to determine current allergic status.

Identifying High-Risk Patients

Penicillins should be used with *extreme caution*, if at all, in patients with a history of *severe* allergic reactions to penicillins, cephalosporins, or carbapenems.

Implementation: Administration

Routes

Penicillins are administered orally, IM, and IV. Routes for individual agents are summarized in Table 84-2. Before giving a penicillin, make sure the preparation is appropriate for the intended route.

Dosage

Doses for penicillin G are prescribed in units (1 unit equals 0.6 mg). Doses for all other penicillins are prescribed in milligrams or grams. Dosages for individual penicillins are summarized in Table 84-2.

Administration

During IM injection, aspirate to avoid injection into an artery. Take care to avoid injection into a nerve.

Instruct the patient to take oral penicillins with a full glass of water 1 hour before meals or 2 hours after. *Penicillin V*, *amoxicillin*, and *amoxicillin/clavulanate* may be taken with meals.

Instruct the patient to complete the prescribed course of treatment, even though symptoms may abate before the full course is over.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor the patient for indications of antimicrobial effects (eg, reduction in fever, pain, or inflammation; improved appetite or sense of well-being).

Monitoring Kidney Function

Renal impairment can cause penicillins to accumulate to toxic levels, and hence monitoring kidney function can help avoid injury. Measuring intake and output is especially helpful in patients with kidney disease, acutely ill patients, and the very old and very young. Notify the prescriber if a significant change in intake/output ratio develops.

Minimizing Adverse Effects

Allergic Reactions. Penicillin allergy is common. Very rarely, life-threatening anaphylaxis occurs. Interview the patient for a history of penicillin allergy.

For patients with prior allergic responses, a skin test may be ordered to assess current allergy status. Exercise caution: The skin test itself can cause a severe reaction. When skin tests are performed, epinephrine and facilities for respiratory support should be immediately available.

Advise patients with penicillin allergy to wear some form of identification (eg, Medic Alert bracelet) to alert emergency healthcare personnel.

Instruct outpatients to report any signs of an allergic response (eg, skin rash, itching, hives).

Whenever a parenteral penicillin is used, keep the patient under observation for at least 30 minutes. If anaphylaxis oc-

curs, treatment consists of *epinephrine* (subQ, IM, or IV) plus respiratory support.

As a rule, patients with a history of penicillin allergy should not receive penicillins again. If previous reactions have been mild, a cephalosporin (preferably oral) may be an appropriate alternative. However, if severe immediate reactions have occurred, cephalosporins should be avoided too.

Rarely, a patient with a history of anaphylaxis nonetheless requires penicillin. To minimize the risk of a severe reaction, administer penicillin according to a desensitization schedule. Be aware, however, that the procedure does not guarantee that anaphylaxis will not occur. Accordingly, have epinephrine and facilities for respiratory support immediately available.

Sodium Loading. High IV doses of *ticarcillin/clavulanate* can produce sodium overload. Exercise caution in patients under sodium restriction (eg, cardiac patients, those with hypertension). Monitor electrolytes and cardiac status.

Hyperkalemia. High doses of IV *potassium penicillin G* may cause hyperkalemia, possibly resulting in dysrhythmias or cardiac arrest. Monitor electrolyte and cardiac status.

Effects Resulting from Incorrect Injection. Take care to avoid intra-arterial injection or injection into peripheral nerves, because serious injury can result.

Minimizing Adverse Interactions

Aminoglycosides. When present in high concentration, penicillins can inactivate aminoglycosides (eg, gentamicin). Do not mix penicillins and aminoglycosides in the same IV solution.

*Patient education information is highlighted as blue text.

Drugs That Weaken the Bacterial Cell Wall II: Cephalosporins, Carbapenems, Vancomycin, Telavancin, Aztreonam, Teicoplanin, and Fosfomycin

Cephalosporins

Carbapenems

Imipenem

Other Carbapenems

Other Inhibitors of Cell Wall Synthesis

Vancomycin

Telavancin

Aztreonam

Teicoplanin

Fosfomycin

Box 85-1. *Clostridium difficile* Infection

Like the penicillins, the drugs discussed in this chapter are inhibitors of cell wall synthesis. By disrupting the cell wall, these drugs produce bacterial lysis and death. Much of the chapter focuses on the cephalosporins, our most widely used antibacterial drugs. With only four exceptions—vancomycin, telavancin, teicoplanin, and fosfomycin—the agents addressed here are beta-lactam drugs.

CEPHALOSPORINS

The cephalosporins are beta-lactam antibiotics similar in structure and actions to the penicillins. These drugs are bactericidal, often resistant to beta-lactamases, and active against a broad spectrum of pathogens. Their toxicity is low. Because of these attributes, the cephalosporins are popular therapeutic agents and constitute our most widely used group of antibiotics.

Chemistry

All cephalosporins are derived from the same nucleus. As shown in Figure 85-1, this nucleus contains a *beta-lactam ring* fused to a second ring. The beta-lactam ring is required for antibacterial activity. Unique properties of individual

cephalosporins are determined by additions made to the nucleus at the sites labeled R_1 and R_2 .

Mechanism of Action

The cephalosporins are bactericidal drugs with a mechanism like that of the penicillins. These agents bind to penicillin-binding proteins (PBPs) and thereby (1) disrupt cell wall synthesis and (2) activate autolysins (enzymes that cleave bonds in the cell wall). The resultant damage to the cell wall causes death by lysis. Like the penicillins, cephalosporins are most effective against cells undergoing active growth and division.

Resistance

The principal cause of cephalosporin resistance is production of beta-lactamases, enzymes that cleave the beta-lactam ring, and thereby render these drugs inactive. Beta-lactamases that act on cephalosporins are sometimes referred to as *cephalosporinases*. Some of the beta-lactamases that act on cephalosporins can also cleave the beta-lactam ring of penicillins.

Not all cephalosporins are equally susceptible to beta-lactamases. Most *first-generation* cephalosporins are destroyed by beta-lactamases; *second-generation* cephalosporins are less sensitive to destruction; and *third-* and *fourth-generation* cephalosporins are highly resistant.

In some cases, bacterial resistance results from producing altered PBPs that have a low affinity for cephalosporins. Methicillin-resistant staphylococci produce these unusual PBPs and are resistant to cephalosporins as a result.

Classification and Antimicrobial Spectra

The cephalosporins can be grouped into four “generations” based on the order of their introduction to clinical use. The generations differ significantly with respect to antimicrobial spectrum and susceptibility to beta-lactamases. In general, *as we progress from first-generation agents to fourth-generation agents, there is (1) increasing activity against gram-negative bacteria and anaerobes, (2) increasing resistance to destruction by beta-lactamases, and (3) increasing ability to reach the cerebrospinal fluid (CSF)*. These differences are summarized in Table 85-1.

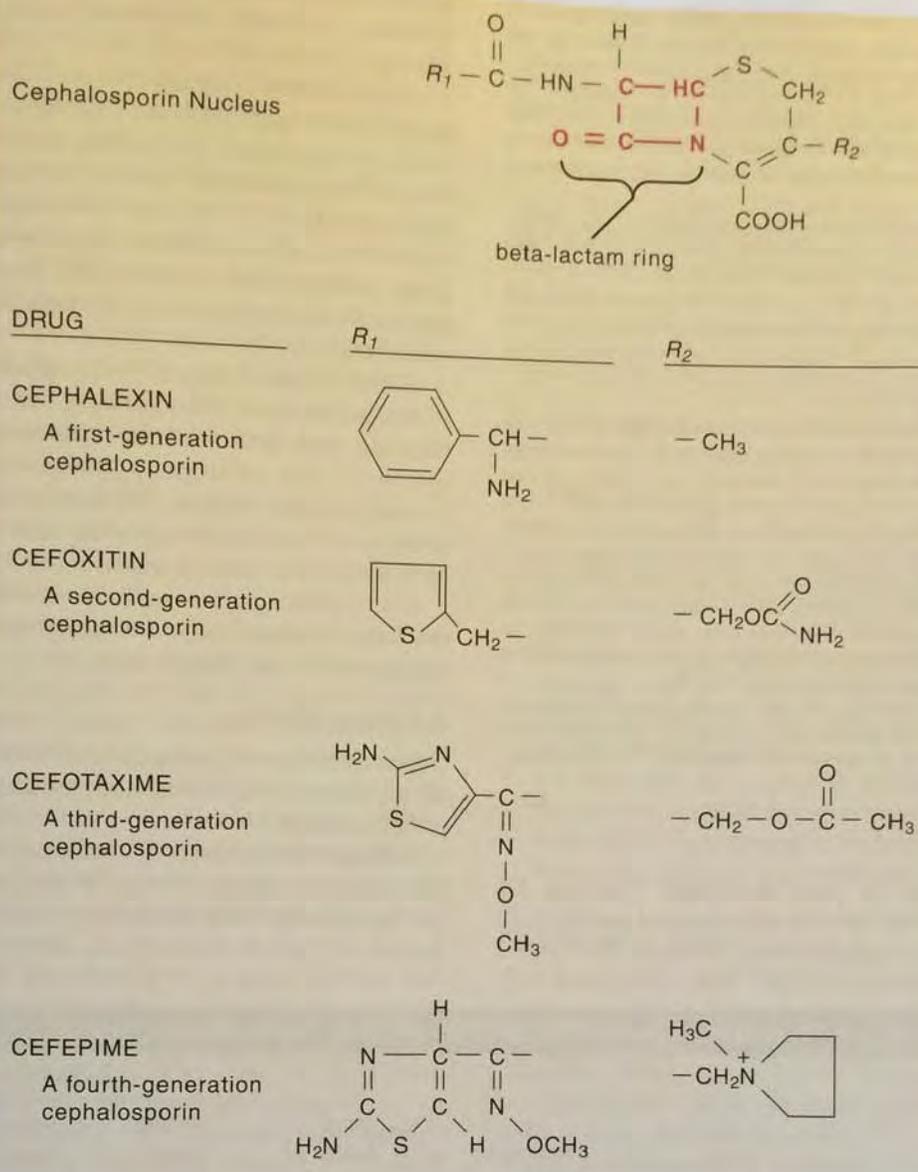


Figure 85-1 ■ Structural formulas of representative cephalosporins.

The unique structure and pharmacologic properties of individual cephalosporins are determined by additions made to the cephalosporin nucleus at the positions labeled R_1 and R_2 .

TABLE 85-1 ■ Major Differences Between Cephalosporin Generations

Class	Activity Against Gram-Negative Bacteria	Resistance to Beta-Lactamases	Distribution to Cerebrospinal Fluid
First generation (eg, cephalalexin)	Low	Low	Poor
Second generation (eg, cefoxitin)	Higher	Higher	Poor
Third generation (eg, cefotaxime)	Higher	Higher	Good
Fourth generation (cefepime)	Highest	Highest	Good

First Generation. First-generation cephalosporins, represented by *cephalexin*, are highly active against gram-positive bacteria. These drugs are the most active of all cephalosporins against staphylococci and nonenterococcal streptococci. However, staphylococci that are resistant to methicillin-like drugs are also resistant to first-generation cephalosporins (and to most other cephalosporins as well). The first-generation agents have only modest activity against gram-negative bacteria and do not reach effective concentrations in the CSF.

Second Generation. Second-generation cephalosporins (eg, cefoxitin) have enhanced activity against gram-negative bacteria. The increase is due to a combination of factors: (1) increased affinity for PBPs of gram-negative bacteria, (2) increased ability to penetrate the gram-negative cell envelope, and (3) increased resistance to beta-lactamases produced by gram-negative organisms. However, none of the second-generation agents is active against *Pseudomonas aeruginosa*. These drugs do not reach effective concentrations in the CSF.

Third Generation. Third-generation cephalosporins (eg, cefotaxime) have a broad spectrum of antimicrobial activity. Because of increased resistance to beta-lactamases, these drugs are considerably more active against gram-negative aerobes than are the first- and second-generation agents. Some third-generation cephalosporins (eg, ceftazidime) have important activity against *P. aeruginosa*. Others (eg, cefixime) lack such activity. A new drug—*ceftaroline* [Teflaro]—has a spectrum like that of the third-generation agents, but with one important exception: ceftaroline is the only cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA). In contrast to first- and second-generation cephalosporins, the third-generation agents reach clinically effective concentrations in the CSF.

Fourth Generation. Cefepime, the only fourth-generation cephalosporin, is highly resistant to beta-lactamases and has a very broad antibacterial spectrum. Activity against *P. aeruginosa* equals that of ceftazidime. Penetration to the CSF is good.

Pharmacokinetics

Absorption. Because of poor absorption from the GI tract, many cephalosporins must be administered parenterally (IM or IV). Of the 20 cephalosporins used in the United

States, only 10 can be administered by mouth (Table 85-2). Of these, only one—*cefuroxime*—can be administered orally and by injection.

Distribution. Cephalosporins distribute well to most body fluids and tissues. Therapeutic concentrations are achieved in pleural, pericardial, and peritoneal fluids. However, concentrations in ocular fluids are generally low. Penetration to the CSF by first- and second-generation drugs is unreliable, and hence these drugs should not be used for bacterial meningitis. In contrast, CSF levels achieved with third- and fourth-generation drugs are generally sufficient for bactericidal effects.

Elimination. Practically all cephalosporins are eliminated by the kidneys; excretion is by a combination of glomerular filtration and active tubular secretion. Probenecid can decrease tubular secretion of some cephalosporins, thereby prolonging their effects. In patients with renal insufficiency, dosages of most cephalosporins must be reduced (to prevent accumulation to toxic levels).

One cephalosporin—*ceftriaxone*—is eliminated largely by the liver. Consequently, dosage reduction is unnecessary in patients with renal impairment.

Adverse Effects

Cephalosporins are generally well tolerated and constitute one of our safest groups of antimicrobial drugs. Serious adverse effects are rare.

Allergic Reactions. Hypersensitivity reactions are the most frequent adverse events. Maculopapular rash that develops several days after the onset of treatment is most common. Severe, immediate reactions (eg, bronchospasm, anaphylaxis)

TABLE 85-2 ■ Pharmacokinetic Properties of the Cephalosporins

Class	Drug	Routes of Administration	Major Route of Elimination	Half-Life (hr)	
				Normal Renal Function	Severe Renal Impairment
First Generation	Cefadroxil	PO	Renal	1.2–1.3	20–25
	Cefazolin	IM, IV	Renal	1.5–2.2	24–50
	Cephalexin	PO	Renal	0.4–1	10–20
Second Generation	Cefaclor	PO	Renal	0.6–0.9	2–3
	Cefotetan	IM, IV	Renal	3–4.5	13–35
	Cefoxitin	IM, IV	Renal	0.7–1	13–22
	Cefprozil	PO	Renal	1.3	5–6
	Cefuroxime	PO, IM, IV	Renal	1–1.9	15–22
Third Generation	Cefdinir	PO	Renal	1.7	16
	Cefditoren	PO	Renal	1.6	—
	Cefixime	PO	Renal	3–4	11.5
	Cefoperazone	IM, IV	Biliary	1.7–2.6	2.2
	Cefotaxime	IM, IV	Renal	0.9–1.4	3–11
	Cefpodoxime	PO	Renal	2–3	9.8
	Ceftaroline*	IV	Renal	2.6	Increased
	Ceftazidime	IM, IV	Renal	1.9–2	—
	Ceftibuten	PO	Renal	2	Increased
	Ceftizoxime	IM, IV	Renal	1.1–2.3	30
Ceftriaxone	IM, IV	Hepatic	5.8–8.7	15.7	
Fourth Generation	Cefepime	IM, IV	Renal	2	Increased

*Ceftaroline is classified here as a third-generation cephalosporin, because it has an antimicrobial spectrum much like that of ceftriaxone. However, ceftaroline is sometimes classified as a fifth-generation agent, because it is the only cephalosporin with activity against MRSA.

are rare. If, during the course of treatment, signs of allergy appear (eg, urticaria, rash, hypotension, difficulty in breathing), the cephalosporin should be discontinued immediately. Anaphylaxis is treated with respiratory support and parenteral epinephrine. Patients with a history of cephalosporin allergy should not be given these drugs.

Because of structural similarities between penicillins and cephalosporins, a few patients allergic to one type of drug may experience cross-reactivity with the other. In clinical practice, the incidence of cross-reactivity has been low: Only 1% of penicillin-allergic patients experience an allergic reaction if given a cephalosporin. For patients with mild penicillin allergy, cephalosporins can be used with minimal concern. However, because of the potential for fatal anaphylaxis, *cephalosporins should not be given to patients with a history of severe reactions to penicillins.*

Bleeding. Three cephalosporins—*cefoperazone*, *cefotetan*, and *ceftriaxone*—can cause bleeding tendencies. The mechanism is reduction of prothrombin levels through interference with vitamin K metabolism.

Several measures can reduce the risk of hemorrhage. During prolonged treatment, patients should be monitored for prothrombin time, bleeding time, or both. Parenteral vitamin K can correct an abnormal prothrombin time. Patients should be observed for signs of bleeding, and, if bleeding develops, the cephalosporin should be withdrawn. Caution should be exercised during concurrent use of anticoagulants or thrombolytic agents. Because of their antiplatelet effects, aspirin and other nonsteroidal anti-inflammatory drugs should be used with care. Caution is needed in patients with a history of bleeding disorders.

Thrombophlebitis. Thrombophlebitis may develop during IV infusion. This reaction can be minimized by rotating the infusion site and by administering cephalosporins slowly and in dilute solution. Patients should be observed for phlebitis. If it develops, the infusion site should be changed.

Hemolytic Anemia. Rarely, cephalosporins have induced immune-mediated hemolytic anemia, a condition in which antibodies mediate destruction of red blood cells. If hemolytic anemia develops, the cephalosporin should be discontinued. Blood transfusions may be given as needed.

Other Adverse Effects. Cephalosporins may cause pain at sites of IM injection; patients should be forewarned. Rarely, cephalosporins may be the cause of *pseudomembranous colitis* due to colonic overgrowth with *Clostridium difficile*. If this suprainfection develops, the cephalosporin should be discontinued and, if necessary, oral vancomycin should be given.

With one cephalosporin—*cefditoren*—there are two unique concerns. First, the drug contains a milk protein (sodium caseinate), and hence should be avoided by patients with *milk-protein hypersensitivity* (as opposed to lactose intolerance). Second, *cefditoren* is excreted in combination with carnitine, and hence can cause *carnitine loss*. Accordingly, the drug is contraindicated for patients with existing carnitine deficiency or with conditions that predispose to carnitine deficiency.

Drug Interactions

Probenecid. Probenecid delays renal excretion of some cephalosporins and can thereby prolong their effects. This is the same interaction that occurs between probenecid and penicillins.

Alcohol. Four cephalosporins—*cefazolin*, *cefmetazole*, *cefoperazone*, and *cefotetan*—can induce a state of alcohol intolerance. If a patient taking these drugs were to ingest alcohol, a disulfiram-like reaction could occur. (As discussed in Chapter 38,

the disulfiram effect, which can be very dangerous, is brought on by accumulation of acetaldehyde secondary to inhibition of aldehyde dehydrogenase.) Patients using these cephalosporins must not consume alcohol in any form.

Drugs That Promote Bleeding. As noted, *cefmetazole*, *cefoperazone*, *cefotetan*, and *ceftriaxone* can promote bleeding. Caution is needed if these drugs are combined with other agents that promote bleeding (anticoagulants, thrombolytics, nonsteroidal anti-inflammatory drugs and other antiplatelet agents).

Calcium and Ceftriaxone. Combining calcium with ceftriaxone can form potentially fatal precipitates. In neonates, but not in older patients, the combination of IV calcium and IV ceftriaxone has caused death from depositing precipitates in the lungs and kidneys. To minimize risk, the following rules apply:

- Don't reconstitute powdered ceftriaxone with calcium-containing diluents (eg, Ringer's solution).
- Don't mix reconstituted ceftriaxone with calcium-containing solutions.
- For patients other than neonates, IV ceftriaxone and IV calcium may be administered sequentially (not concurrently) through the same line, provided the line is flushed between the infusions.
- For neonates, don't give IV ceftriaxone and IV calcium through the same line or different lines within 48 hours of each other. If the patient must receive ceftriaxone and calcium, use *oral* calcium or *IM* ceftriaxone.

Therapeutic Uses

The therapeutic role of the cephalosporins is continually evolving as new agents are introduced and more experience is gained with older ones. Only general recommendations are considered here.

The cephalosporins are broad-spectrum, bactericidal drugs with a high therapeutic index. They have been employed widely and successfully against a variety of infections. Cephalosporins can be useful alternatives for patients with mild penicillin allergy.

The four generations of cephalosporins differ significantly in their applications. With one important exception—the use of first-generation agents for infections caused by sensitive staphylococci—the *first- and second-generation cephalosporins are rarely drugs of choice for active infections*. In most cases, equally effective and less expensive alternatives are available. In contrast, *the third-generation agents have qualities that make them the preferred therapy for several infections*. The role of *fourth-generation agents* is yet to be established.

First-Generation Cephalosporins. When a cephalosporin is indicated for a *gram-positive infection*, a first-generation drug should be used; these agents are the most active of the cephalosporins against gram-positive organisms and are less expensive than other cephalosporins. First-generation agents are frequently employed as alternatives to penicillins to treat infections caused by staphylococci or streptococci (except enterococci) in patients with penicillin allergy. However, it is important to note that cephalosporins should be given only to patients with a history of *mild* penicillin allergy—not those who have experienced a severe, immediate hypersensitivity reaction.

The first-generation agents have been employed widely for *prophylaxis against infection in surgical patients*. First-generation agents are preferred to second- or third-generation cephalosporins for surgical prophylaxis. Why? Because they are as effective as the newer drugs, are less expensive, and have a more narrow antimicrobial spectrum.

Second-Generation Cephalosporins. Specific indications for second-generation cephalosporins are limited. *Cefuroxime*, a prototype for the group, has been used with success against pneumonia caused by *Haemophilus influenzae*, *Klebsiella*, pneumococci, and staphylococci. Oral *cefuroxime* is useful for otitis, sinusitis, and respiratory tract infections. *Cefoxitin* is useful for abdominal and pelvic infections.

Third-Generation Cephalosporins. Because they are highly active against gram-negative organisms, and because they penetrate to the CSF, third-generation cephalosporins are drugs of choice for meningitis caused by enteric, gram-negative bacilli. *Ceftazidime* is of special utility for treating meningitis caused by *P. aeruginosa*. Nosocomial infections caused by gram-negative bacilli, which are often resistant to first- and second-generation cephalosporins (and most other commonly used antibiotics), are appropriate indications for the third-generation drugs. Two third-generation agents—*ceftriaxone* and *cefotaxime*—are drugs of choice for infections caused by *Neisseria gonorrhoeae* (gonorrhea), *H. influenzae*, *Proteus*, *Salmonella*, *Klebsiella*, and *Serratia*; these drugs are also effective against meningitis caused by *Streptococcus pneumoniae*, a gram-positive bacterium. One agent—*ceftaroline*—is the only cephalosporin approved for MRSA infections.

The third-generation cephalosporins should not be used routinely. Rather, they should be given only when conditions demand, so as to delay emergence of resistance.

Drug Selection

Twenty cephalosporins are currently employed in the United States, and selection among them can be a challenge. Within each generation, the similarities among cephalosporins are more pronounced than the differences. Hence, aside from cost,

there is frequently no rational basis for choosing one drug over another. However, there are some differences between cephalosporins, and these differences may render one agent preferable to another for treating a specific infection in a specific host. The differences that do exist can be grouped into three main categories: (1) antimicrobial spectrum, (2) adverse effects, and (3) pharmacokinetics (eg, route of administration, penetration to the CSF, time course, mode of elimination). Drug selection based on these differences is discussed below.

Antimicrobial Spectrum. A prime rule of antimicrobial therapy is to match the drug with the bug: The drug should be active against known or suspected pathogens, but its spectrum should be no broader than required. When a cephalosporin is appropriate, we should select from among those drugs known to have good activity against the causative pathogen. The third- and fourth-generation agents, with their very broad antimicrobial spectra, should be avoided in situations where a narrower spectrum, first- or second-generation drug would suffice.

For some infections, one cephalosporin may be decidedly more effective than all others, and should be selected on this basis. For example, *cefazidime* (a third-generation drug) is the most effective of all cephalosporins against *P. aeruginosa* and is clearly the preferred cephalosporin for treating infections caused by this microbe. Similarly, *ceftaroline* is the only cephalosporin with activity against MRSA, and hence is preferred to all other cephalosporins for treating these infections.

Adverse Effects. Although most cephalosporins produce the same spectrum of adverse effects, a few can cause unique reactions. For example, *cefmetazole*, *cefoperazone*, *cefotetan*, and *ceftriaxone* can cause bleeding

TABLE 85-3 • Cephalosporin Dosages

Drug	Trade Name	Route	Dosing Interval (hr)	Total Daily Dosage*	
				Adults (gm)	Children (mg/kg)
First Generation					
Cefadroxil	generic only	PO	12, 24	1–2	30
Cefazolin	generic only	IM, IV	6, 8	2–12	80–160
Cephalexin	Keflex	PO	6	1–4	25–50
Second Generation					
Cefaclor	Ceclor, Raniclor	PO	8	0.75–1.5	20–40
Cefotetan	generic only	IM, IV	12	2–6	—
Cefoxitin	generic only	IM, IV	4, 8	3–12	80–160
Cefprozil	generic only	PO	12, 24	0.5–1	30
Cefuroxime	Ceftin	PO	12	0.5–1	250–500
	Zinacef	IM, IV	8	2.25–9	50–100
Third Generation					
Cefdinir	Omnicef	PO	12, 24	0.6	14
Cefditoren	Spectracef	PO	12	0.4–0.8	—
Cefixime	Suprax	PO	24	0.4	8
Cefoperazone	Cefobid	IM, IV	6, 8	2–12	100–150
Cefotaxime	Claforan	IM, IV	4, 8	2–12	100–200
Cefpodoxime	Vantin	PO	12	0.2–0.4	10
Ceftaroline [†]	Teflaro	IV	12	1.2	—
Ceftazidime	Ceptaz, Fortaz, Tazidime, Tazicef	IM, IV	8, 12	0.5–6	90–150
Ceftibuten	Cedax	PO	24	0.4	9
Ceftizoxime	Cefizox	IM, IV	6, 12	2–12	150–200
Ceftriaxone	Rocephin	IM, IV	12, 24	1–4	50–100
Fourth Generation					
Cefepime	Maxipime	IM, IV	12	1–2	100

*With the exception of ceftriaxone, cephalosporins require a dosage reduction in patients with severe renal impairment.

[†]Ceftaroline is classified here as a third-generation cephalosporin, because it has an antimicrobial spectrum much like that of ceftriaxone. However, ceftaroline is sometimes classified as a fifth-generation agent, because it is the only cephalosporin with activity against MRSA.

tendencies. When an equally effective alternative is available, it would be prudent to avoid these drugs.

Pharmacokinetics. Four pharmacokinetic properties are of interest: (1) route of administration, (2) duration of action, (3) distribution to the CSF, and (4) route of elimination. The relationship of these properties to drug selection is discussed below.

Route of Administration. Ten cephalosporins can be administered orally. These drugs may be preferred for mild to moderate infections in patients who can't tolerate parenteral agents.

Duration of Action. In patients with normal renal function, the half-lives of the cephalosporins range from about 30 minutes to 9 hours (see Table 85-2). Because they require fewer doses per day, drugs with a long half-life are frequently preferred. Cephalosporins with the longest half-lives in each generation are as follows: first generation, *cefazolin* (1.5 to 2 hours); second generation, *cefotetan* (3 to 4.5 hours); and third generation, *ceftriaxone* (6 to 9 hours).

Distribution to CSF. Only the third- and fourth-generation agents achieve CSF concentrations sufficient for bactericidal effects. Hence, for meningitis caused by susceptible organisms, these drugs are preferred over first- and second-generation agents.

Route of Elimination. Most cephalosporins are eliminated by the kidneys and, if dosage is not carefully adjusted, may accumulate to toxic levels in patients with renal impairment. Only one agent—*ceftriaxone*—is eliminated primarily by nonrenal routes, and hence can be used with relative safety in patients with kidney dysfunction.

Dosage and Administration

Routes. Many cephalosporins cannot be absorbed from the GI tract and must therefore be administered parenterally (IM or IV). As shown in Table 85-2, only 10 cephalosporins can be given orally. One drug—*cefuroxime*—can be administered both orally and by injection.

Dosage. Dosages are summarized in Table 85-3. For most cephalosporins (*ceftriaxone* excepted), dosage should be reduced in patients with significant renal impairment.

Administration. Oral. If oral cephalosporins produce nausea, administration with food can reduce the response. Oral suspensions should be stored cold.

Intramuscular. Intramuscular injections should be made deep into a large muscle. Intramuscular injection of cephalosporins is frequently painful; the patient should be forewarned. The injection site should be checked for induration, tenderness, and redness, and the prescriber informed if these occur.

Intravenous. For IV therapy, cephalosporins may be administered by three techniques: (1) bolus injection, (2) slow injection (over 3 to 5 minutes), and (3) continuous infusion. The prescriber's order should state which method to use. If there is uncertainty as to method, request clarification. Prepare solutions for parenteral administration according to the manufacturer's recommendations.

CARBAPENEMS

Carbapenems are beta-lactam antibiotics that have very broad antimicrobial spectra—although none is active against MRSA. Four carbapenems are available: imipenem, meropenem, ertapenem, and doripenem. With all four, administration is parenteral. To delay emergence of resistance, these drugs should be reserved for patients who cannot be treated with a more narrow-spectrum agent.

Imipenem

Imipenem [Primaxin], a beta-lactam antibiotic (Fig. 85-2), has an extremely broad antimicrobial spectrum—broader, in fact, than nearly all other antimicrobial drugs. As a result, imipenem may be of special use for treating mixed infections in which anaerobes, *Staph. aureus*, and gram-negative bacilli may all be involved. Imipenem is supplied in fixed-dose combinations with cilastatin, a compound that inhibits destruction of imipenem by renal enzymes.

Mechanism of Action. Imipenem binds to two PBPs (PBP1 and PBP2), causing weakening of the bacterial cell

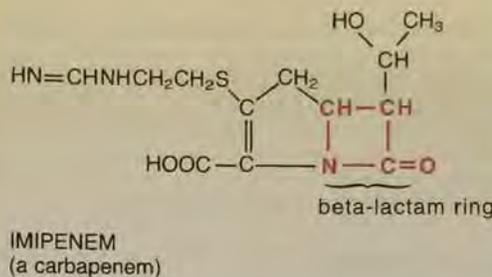
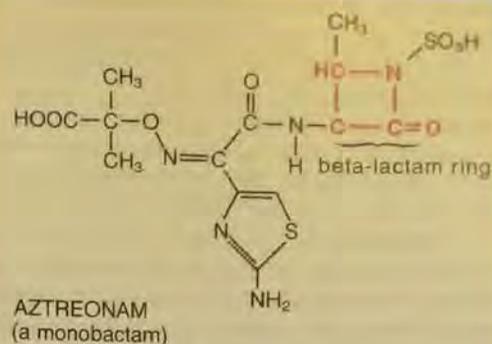


Figure 85-2 • Miscellaneous beta-lactam antibiotics.

wall with subsequent cell lysis and death. Antimicrobial effects are enhanced by the drug's resistance to practically all beta-lactamases, and by its ability to penetrate the gram-negative cell envelope.

Antimicrobial Spectrum. Imipenem is active against most bacterial pathogens, including organisms resistant to other antibiotics. The drug is highly active against gram-positive cocci and most gram-negative cocci and bacilli. In addition, imipenem is the most effective beta-lactam antibiotic for use against anaerobic bacteria.

Pharmacokinetics. Imipenem is not absorbed from the GI tract and hence must be given parenterally (IV or IM). The drug is well distributed to body fluids and tissues. Imipenem penetrates the meninges to produce therapeutic concentrations in the CSF.

Elimination is primarily renal. When employed alone, imipenem is inactivated by dipeptidase, an enzyme present in the kidney. As a result, drug levels in urine are low. To increase urinary concentrations, imipenem is administered in combination with *cilastatin*, a dipeptidase inhibitor. When the combination is used, about 70% of imipenem is excreted unchanged in the urine. The elimination half-life is about 1 hour.

Adverse Effects. Imipenem is generally well tolerated. Gastrointestinal effects (nausea, vomiting, diarrhea) are most common. Suprainfections with bacteria or fungi develop in about 4% of patients. Rarely, seizures have occurred.

Hypersensitivity reactions (rashes, pruritus, drug fever) have occurred, and patients allergic to other beta-lactam antibiotics may be cross-allergic with imipenem. Fortunately, the incidence of cross sensitivity with penicillins is low—only about 1%.

Interaction with Valproate. Imipenem can reduce blood levels of valproate, a drug used to control seizures (see

Chapter 24). Breakthrough seizures have occurred. If possible, combined use of imipenem and valproate should be avoided. If no other antibiotic will suffice, supplemental anti-seizure therapy should be considered.

Therapeutic Use. Because of its broad spectrum and low toxicity, imipenem is used widely. The drug is effective for serious infections caused by gram-positive cocci, gram-negative cocci, gram-negative bacilli, and anaerobic bacteria. This broad antimicrobial spectrum gives imipenem special utility for chemotherapy of mixed infections (eg, simultaneous infection with aerobic and anaerobic bacteria). When imipenem has been given alone to treat infection with *P. aeruginosa*, resistant organisms have emerged. Consequently, imipenem should be combined with another antipseudomonal drug when used against this microbe.

Preparations, Dosage, and Administration. Imipenem is formulated in 1:1 fixed-dose combinations with cilastatin. The combination products are marketed under the trade name *Primaxin*. Two formulations are available: *Primaxin I.V.* and *Primaxin I.M.*, for intravenous and intramuscular use, respectively. These products are supplied in powdered form and must be reconstituted in accord with the manufacturer's instructions. The usual adult dosage (based on imipenem content) is 250 to 500 mg every 6 hours. Dosage should be reduced in patients with renal impairment.

Other Carbapenems

Meropenem

Actions and Uses. Meropenem [Merrem IV] is a beta-lactam antibiotic similar in structure and actions to imipenem. Meropenem is active against most clinically important gram-positive and gram-negative aerobes and anaerobes. Approved indications are (1) bacterial meningitis in children age 3 months or older, (2) intra-abdominal infections in children and adults, and (3) complicated skin and skin structure infections in children and adults. Meropenem may prove especially useful for nosocomial infections caused by organisms resistant to other antibiotics.

Pharmacokinetics. Meropenem is given IV and distributes to all body fluids and tissues. The drug has a plasma half-life of 1 hour and is eliminated primarily unchanged in the urine. In contrast to imipenem, meropenem is not degraded by renal dipeptidases, and hence is not combined with cilastatin.

Adverse Effect and Interactions. Like other beta-lactam antibiotics, meropenem is generally well tolerated. Principal adverse effects are rashes, diarrhea, nausea, and vomiting. The risk of cross sensitivity in patients allergic to penicillins is about 1%. As with imipenem, seizures occur rarely. The risk of seizures is highest in patients with central nervous system (CNS) disorders (eg, brain lesions, history of seizures) and bacterial meningitis. Like imipenem, meropenem can reduce levels of valproate, and may thereby permit breakthrough seizures in patients taking the drug.

Preparations, Dosage, and Administration. Meropenem [Merrem IV] is supplied in powdered form to be reconstituted for IV administration. Depending on the volume employed, the drug may be (1) infused over 15 to 30 minutes or (2) injected as a bolus over 3 to 5 minutes. The dosage for adults is 1 gm every 8 hours. The dosage for pediatric patients is 20 mg/kg every 8 hours (for intra-abdominal infections) and 40 mg/kg every 8 hours (for bacterial meningitis). Adult and pediatric dosages must be reduced for patients with significant renal impairment (creatinine clearance less than 50 mL/min).

Ertapenem

Actions and Uses. Like other carbapenems, ertapenem [Invanz] weakens the bacterial cell wall, and thereby causes cell lysis and death. Also like other carbapenems, ertapenem is highly resistant to beta-lactamases, and hence has a very broad antimicrobial spectrum—but less broad than that of imipenem or meropenem. Ertapenem is active against most gram-positive bacteria and most anaerobes. However, in contrast to imipenem and meropenem, the drug has little or no activity against *P. aeruginosa* or *Acinetobacter* species. In addition, ertapenem has minimal activity against pneumococci that are highly resistant to penicillin, and has no activity against methicillin-resistant staphylococci, *Enterococcus faecium*, *Enterococcus faecalis*, or atypical respiratory tract pathogens, including *Chlamydia* species, *Legionella* species, and *Mycoplasma pneumoniae*. Ertapenem is indicated for parenteral therapy of acute pelvic infections, community-acquired pneumo-

nia, prophylaxis following elective colorectal surgery, and complicated infections of the urinary tract, abdomen, and skin and skin structures.

Pharmacokinetics. Ertapenem may be administered by IM injection or IV infusion. Absorption following IM injection is complete. In the blood, ertapenem is highly bound to plasma proteins. The drug undergoes some hydrolysis of the beta-lactam ring prior to excretion in the urine (80%) and feces (10%). Its half-life is approximately 4 hours (compared with only 1 hour for imipenem or meropenem).

Adverse Effects and Interactions. Like other carbapenems, ertapenem is generally well tolerated. In clinical trials, the most common adverse effects were diarrhea (10.3%), nausea (8%), infused-vein complications (7.1%), headache (5.6%), vomiting (3.7%), and edema (3.4%). In addition, CNS effects (agitation, confusion, disorientation, decreased mental acuity, somnolence, stupor) were reported in 5.1% of patients. Like most other antibiotics, ertapenem can promote *C. difficile* infection. Like imipenem and meropenem, ertapenem can cause seizures, but the incidence is relatively low (0.5%). Like other carbapenems, ertapenem can reduce levels of valproate, and may thereby cause loss of seizure control.

Preparations, Dosage, and Administration. Ertapenem [Invanz] is available as a powder to be reconstituted for IM or IV administration. For IV therapy, the drug is infused over 30 minutes, and should not be mixed with other drugs or with diluents that contain dextrose. The dosage (IM or IV) for adults and children 13 years and older is 1 gm once daily (for patients with good kidney function) or 500 mg once daily (for patients with significant renal impairment). The dosage for children ages 3 months to 12 years is 15 mg/kg twice daily (for children with good renal function); dosages for children with impaired renal function have not been established. For adults and children, the duration of treatment is 3 to 14 days, depending on the infection.

Doripenem

Actions and Uses. Doripenem [Doribax], approved in 2007, is active against a broad spectrum of gram-positive, gram-negative, and anaerobic bacteria. Activity against *P. aeruginosa* is greater than with other carbapenems. Cell kill results from disrupting cell wall synthesis. Doripenem has two approved indications: complicated intra-abdominal infections and complicated urinary tract infections. To delay emergence of resistance, the drug should be reserved for seriously ill patients with mixed infections or infection with multidrug-resistant, gram-negative bacteria or *Pseudomonas*.

Pharmacokinetics. Doripenem is administered by IV infusion. Binding to plasma proteins is low, and hepatic metabolism is minimal. Elimination is renal, primarily as unchanged drug. In patients with normal kidney function, the half-life is about 1 hour. In patients with renal impairment, the half-life is longer, and hence these people require a reduced dosage to prevent doripenem from accumulating to dangerous levels.

Adverse Effects and Interactions. Like other carbapenems, doripenem is generally well tolerated. The most common side effects are headache (4% to 16%), nausea (4% to 12%), diarrhea (6% to 11%), rash (up to 3%), and injection-site phlebitis (4% to 8%). In contrast to other carbapenems, doripenem does not cause seizures. However, like other carbapenems, doripenem can reduce levels of valproic acid, and may thereby cause loss of seizure control.

Preparations, Dosage, and Administration. Doripenem [Doribax] is supplied as a powder (500 mg) to be reconstituted in 110 mL of normal saline or sterile water (to make 250 mg/55 mL). All doses are administered by IV infusion over a 1-hour span. Dosage depends on renal function as follows: normal renal function, 500 mg every 8 hours; creatinine clearance 30 to 50 mL/min, 250 mg every 8 hours; and creatinine clearance 11 to 29 mL/min, 250 mg every 12 hours.

OTHER INHIBITORS OF CELL WALL SYNTHESIS

Vancomycin

Vancomycin [Vancocin] is the most widely used antibiotic in U.S. hospitals. Principal indications are *C. difficile* infection (CDI), MRSA infection, and treatment of serious infections with susceptible organisms in patients allergic to penicillins. The major toxicity is renal failure. Unlike most other drugs discussed in this chapter, vancomycin does not contain a beta-lactam ring.

Mechanism of Action. Like the beta-lactam antibiotics, vancomycin inhibits cell wall synthesis and thereby promotes

bacterial lysis and death. However, in contrast to the beta-lactams, vancomycin does not interact with PBPs. Instead, it disrupts the cell wall by binding to molecules that serve as precursors for cell wall biosynthesis.

Antimicrobial Spectrum. Vancomycin is active only against gram-positive bacteria. The drug is especially active against *Staph. aureus* and *Staphylococcus epidermidis*, including strains of both species that are methicillin resistant. Other susceptible organisms include streptococci, penicillin-resistant pneumococci, and *C. difficile*.

Pharmacokinetics. Absorption from the GI tract is poor. Hence, for most infections, vancomycin is given parenterally (by slow IV infusion). Oral administration is employed only for infections of the intestine, mainly CDI.

Vancomycin is well distributed to most body fluids and tissues. Although it enters the CSF, levels may be insufficient to treat meningitis. Hence, if meningeal infection fails to respond to IV therapy, concurrent intrathecal dosing may be required.

Vancomycin is eliminated unchanged by the kidneys. In patients with renal impairment, dosage must be reduced.

Therapeutic Use. Vancomycin should be reserved for serious infections. This agent is the drug of choice for infections caused by MRSA or *Staph. epidermidis*; most strains of these bacteria are still sensitive to vancomycin. Vancomycin is also the drug of choice for severe CDI, but not for mild CDI (Box 85-1). The drug is also employed as an alternative to penicillins and cephalosporins to treat severe infections (eg, staphylococcal and streptococcal endocarditis) in patients allergic to beta-lactam antibiotics.

Adverse Effects. The major toxicity is renal failure. Risk is dose related and increased by concurrent use of other nephrotoxic drugs (eg, aminoglycosides, cyclosporine, nonsteroidal anti-inflammatory drugs). To minimize risk, trough serum levels of vancomycin should be no greater than needed (see below). If significant kidney damage develops, as indicated by

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BOX 85-1 ■ SPECIAL INTEREST TOPIC

***Clostridium difficile* INFECTION**

Clostridium difficile, aka *C. difficile* or simply *C. diff*, is a gram-positive, spore-forming, anaerobic bacillus that infects the bowel. Injury results from release of two toxins, called toxin A and toxin B. Symptoms range from relatively mild (abdominal discomfort, nausea, fever, diarrhea) to very severe (toxic megacolon, pseudomembranous colitis, colon perforation, sepsis, and death). Over the past decade, *C. difficile* infection (CDI) has become more common and more severe. The reason is the spread of a new, more virulent strain—known as NAP1/BI/027—that releases more toxin than the older strains. In many hospitals, rates of infection caused by *C. diff* now exceed those caused by MRSA (methicillin-resistant *Staphylococcus aureus*). Fortunately, most cases of CDI can be managed well with antibiotics, usually metronidazole [Flagyl] or vancomycin [Vancocin].

Infection with *C. diff* is almost always preceded by use of antibiotics, which kill off normal gut flora and thereby allow *C. diff* to flourish. Today, *C. diff* is responsible for 15% to 25% of cases of antibiotic-associated diarrhea and nearly all cases of antibiotic-associated colitis. Antibiotics that are most likely to promote CDI are clindamycin, second- and third-generation cephalosporins, and fluoroquinolones. In fact, intensive use of fluoroquinolones, such as ciprofloxacin [Cipro] and levofloxacin [Levaquin], is believed responsible for the rapid spread of the NAP1/BI/027 strain.

CDI is acquired by ingesting *C. difficile* spores, which are shed in the feces. Any object that feces contact—including commodes, bath tubs, and rectal thermometers—can be a source of infection. Within hospitals, spores are transferred to patients primarily on the hands of healthcare workers who have touched a contaminated person or object. Of note, spores of *C. diff* are extremely hardy, being resistant to drying, temperature changes, and alcohol. Because of their hardiness, viable spores can remain in the environment for weeks.

CDI is defined by (1) the passage of three or more unformed stools in 24 hours or less plus (2) a positive stool test for *C. difficile* or its toxins. Intestinal damage is caused by toxins A and B, which attack the lining of the colon. As noted, symptoms range from watery diarrhea to life-threatening

pseudomembranous colitis, characterized by patches of severe inflammation and pus. Complications of severe *C. difficile* colitis include dehydration, electrolyte disturbances, toxic megacolon, bowel perforation, renal failure, sepsis, and death. Among patients successfully treated for CDI, the recurrence rate is 15% to 30%.

The principal risk factor for CDI is treatment with antibiotics: In almost all cases, individuals who develop CDI had received antibiotics in the recent past. Risk is especially high among the elderly who take antibiotics. Other risk factors include GI surgery, serious illness, prolonged hospitalization, and immunosuppression, which may result from cancer chemotherapy, immunosuppressive therapy, or infection with HIV.

Treatment of CDI consists of stopping one antibiotic and starting another, as recommended in a 2010 clinical guideline issued by the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA). As soon as possible after CDI has been diagnosed, we should stop the antibiotic that facilitated *C. diff* overgrowth, since doing so (1) will reduce the risk of reinfection once CDI has cleared, and (2) in 25% of patients with mild CDI, will cause the infection to resolve. At the same time, we should start an antibiotic to eradicate *C. diff*. Drug selection is based on infection severity, as judged by two laboratory values: white blood cell (WBC) counts and serum creatinine (SCr). Higher WBC counts indicate more severe colonic inflammation. Higher SCr values indicate more severe dehydration (from diarrhea) and worsening renal perfusion (from dehydration). As shown in the table, oral metronidazole is recommended for a mild/moderate initial episode, and oral vancomycin is recommended for a severe initial episode. For a complicated severe initial episode, the guidelines recommend IV metronidazole plus vancomycin given either PO or through a nasogastric (NG) tube. If the patient has complete ileus (absence of intestinal motility), rectal instillation of vancomycin may be added. If CDI recurs after being cleared, the regimen used for initial therapy should be tried again. If there is a second recurrence, the guidelines recommend a prolonged course of oral vancomycin in which the number of daily doses is gradually decreased.

Continued



Alternatives and supplements to metronidazole and vancomycin are being studied. Promising options include:

- *Fidaxomicin* [Dificid]—a narrow-spectrum macrolide antibiotic with high selectivity for *C. difficile*—was approved for treating *C. difficile*-associated diarrhea in 2011. In a Phase III trial, the cure rate with fidaxomicin was higher than with vancomycin, and the recurrence rate was lower.
- *Nitazoxanide*, approved for diarrhea caused by *Giardia* species and *Cryptosporidium* species, appears equal to metronidazole or vancomycin for treating CDI.
- *Rifaximin*, approved for diarrhea caused by *Escherichia coli*, can reduce CDI recurrence following treatment with vancomycin.
- *Monoclonal antibodies* directed against *C. difficile* toxins A and B can reduce CDI recurrence when given concurrently with metronidazole or vancomycin.
- Inoculating the bowel with a *benign strain* of *C. difficile* can protect against developing CDI. How? Presumably, when the benign strain colonizes the bowel, it occupies the same niche that a virulent strain would occupy, and thereby prevents the virulent strain from becoming established.

How can we control the spread of CDI? The IDSA/SHEA guidelines offer the following recommendations:

- Use antibiotics judiciously, especially those associated with a high risk of CDI (clindamycin, cephalosporins, and fluoroquinolones).
- If possible, isolate patients with CDI in a private room, or have them share a room with another patient with CDI.
- Wear gloves and a gown when entering the room of a patient with CDI.
- After contacting a patient with CDI, wash hands with soap and running water. Soap and water won't kill *C. diff* spores, but it will flush them off the hands. Alcohol-based hand rubs will not kill spores, and will not remove them from the hands.
- Use disposable rectal thermometers rather than electronic thermometers.
- In areas associated with increased rates of CDI, decontaminate surfaces with a chlorine-containing cleaning agent (or any other agent that can kill *C. diff* spores).

Recommended Treatments for Clostridium difficile Infection

Clinical Definition	Supportive Clinical Data	Drug Therapy
Initial episode: mild or moderate	Leukocytosis with a WBC count of 15,000 cells/mcL or lower and SCr less than 1.5 times baseline	Metronidazole, 500 mg PO tid for 10–14 days
Initial episode: severe	Leukocytosis with a WBC count of 15,000 cells/mcL or higher or SCr 1.5 times baseline or higher	Vancomycin, 125 mg PO qid for 10–14 days
Initial episode: severe, complicated	Leukocytosis with a WBC count of 15,000 cells/mcL or higher or SCr 1.5 times baseline or higher, either one, plus hypotension/shock, ileus, megacolon	Metronidazole 500 mg IV every 8 hr plus vancomycin, 500 mg PO/NG qid for 10–14 days. If complete ileus is present, consider adding rectal instillation of vancomycin
First recurrence		Same as initial episode
Second recurrence		Vancomycin PO in a tapered regimen, for example: 125 mg qid for 10–14 days, then 125 mg twice daily for 7 days, then 125 mg once daily for 7 days, then 125 mg every 2 or 3 days for 2–8 wk

mcL = microliter, NG = by nasogastric tube, PO = by mouth, qid = 4 times a day, SCr = serum creatinine, tid = three times a day, WBC = white blood cell.

Recommendations are from Cohen SH, et al.: Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA), 2010.

a 50% increase in serum creatinine level, vancomycin dosage should be reduced.

Ototoxicity develops rarely, and is usually reversible. Risk is increased by prolonged treatment, renal impairment, and concurrent use of other ototoxic drugs (eg, aminoglycosides, ethacrynic acid).

Rapid infusion of vancomycin can cause a constellation of disturbing effects—flushing, rash, pruritus, urticaria, tachycardia, and hypotension—known collectively as *red man syndrome*, *red person syndrome*, or simply *red neck*. These effects, which may result from release of histamine, can usually be avoided by infusing vancomycin slowly (over 60 minutes or more).

Thrombophlebitis is common. The reaction can be minimized by administering vancomycin in dilute solution and by changing the infusion site frequently.

Rarely, vancomycin causes *immune-mediated thrombocytopenia*, a condition in which platelets are lost and spontaneous bleeding results. The underlying mechanism is development of unusual antibodies that bind to platelets—but only if the platelets first bind with vancomycin (forming a vancomycin-platelet complex). The resulting antibody-vancomycin-platelet complexes are then removed from the circulation by macrophages.

Patients allergic to penicillins do not show cross-reactivity with vancomycin. Accordingly, vancomycin is an alternative to penicillins in patients with penicillin allergy.

Preparations, Dosage, and Administration. *Intravenous Dosing.* For systemic infection, vancomycin is administered by intermittent infusion over 60 minutes or longer. The traditional dosage is 15 mg/kg every 12 hours. However, a higher dosage (15 to 20 mg/kg every 8 to 12 hours) is now recommended. For patients with severe infection, a loading dose (25 to 30 mg/kg) may be used. In patients with renal impairment, dosages must be reduced.

Dosage should be adjusted to achieve effective trough serum levels of vancomycin. For serious infections (eg, bacteremia, osteomyelitis, meningitis, hospital-acquired pneumonia), trough levels should be 15 to 20 mcg/mL. For less serious infections, trough levels should be at least 10 mcg/mL.

Oral Dosing. Vancomycin is given orally for CDI and other intestinal infections. Dosages for CDI are shown in Box 85-1. Because vancomycin is not absorbed from the GI tract, there is no need to decrease oral doses in patients with renal impairment.

Rectal Dosing. Rectal dosing may be used for patients with complicated CDI. One recommended regimen consists of giving 500 mg in 100 mL of normal saline every 6 hours, using a Foley catheter inserted in the rectum.

Telavancin

Actions and Uses. Telavancin [Vibativ], approved in 2009, is the first representative of a new class of agents, the *lipoglycoproteins*, synthetic derivatives of vancomycin. Like vancomycin, telavancin is active only against gram-positive bacteria. Cell kill results from two mechanisms. First, like vancomycin, telavancin inhibits bacterial cell wall synthesis. Second, telavancin binds to the bacterial cell membrane and thereby disrupts membrane function. Telavancin is approved only for IV therapy of *complicated skin and skin structure infections* caused by susceptible strains of the following gram-positive organisms: *Staph. aureus* (including methicillin-sensitive and methicillin-resistant strains), *Strep. pyogenes*, *Strep. agalactiae*, *Strep. anginosus* group, and *Enterococcus faecalis* (but only vancomycin-sensitive strains). To delay development of resistance, telavancin should be reserved for treating vancomycin-resistant infections, or for use as an alternative to linezolid [Zyvox], daptomycin [Cubicin], or tigecycline [Tygacil] in patients who cannot take these drugs.

Pharmacokinetics. Following IV infusion, telavancin undergoes 90% binding to plasma proteins. Elimination is primarily renal. In healthy volunteers, the plasma half-life was approximately 8 hours. In patients with renal impairment, the half-life is prolonged and blood levels increase. In patients with moderate hepatic impairment, the kinetics of telavancin remain unchanged.

Adverse Effects. Telavancin can cause multiple adverse effects. The most common are taste disturbance (33%), nausea (27%), vomiting (14%), and foamy urine (13%). As with vancomycin, rapid infusion can cause "red man syndrome," characterized by flushing, rash, pruritus, urticaria, tachycardia, and hypotension.

Kidney damage develops in 3% of patients, as indicated by increased serum creatinine, renal insufficiency, or even renal failure. To reduce risk, kidney function should be measured at baseline, every 72 hours during treatment, and at the end of treatment. If these tests indicate nephrotoxicity, switching to a different antibiotic should be considered. In most cases, kidney function normalizes after telavancin is withdrawn. The risk of kidney damage is increased by using other nephrotoxic drugs.

Telavancin can *prolong the QT interval*. However, serious dysrhythmias have not been reported. Nonetheless, telavancin should not be given to patients at high risk, including those with congenital long QT syndrome, untreated compensated heart failure, or severe left ventricular hypertrophy, and those using other QT drugs.

Avoid telavancin during pregnancy. When given to pregnant animals, telavancin reduced fetal weight and increased the risk of digit and limb deformities. The drug has not been studied in pregnant women. Nonetheless, because telavancin is fetotoxic in animals, it is classified in FDA Pregnancy Risk Category C (risk cannot be ruled out). Accordingly, telavancin should not be used during pregnancy unless the benefits to the patient are deemed to outweigh the risks to the fetus. Before telavancin is used, pregnancy should be ruled out with a serum pregnancy test.

Drug Interactions. Telavancin should be used with caution in patients taking other drugs that can damage the kidneys (eg, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, aminoglycosides), and in patients taking drugs that prolong the QT interval (eg, clarithromycin, ketoconazole). Clinically significant interactions involving cytochrome P450 enzymes have not been observed.

Preparations, Dosage, and Administration. Telavancin [Vibativ] is supplied as a powder (250 or 750 mg) for reconstitution as a concentrated solution (115 mg/mL), followed by dilution to a final concentration of 0.6 to

8 mg/mL. The usual dosage is 10 mg/kg once daily, infused over 60 minutes to reduce the risk of red man syndrome. Treatment duration is 7 to 14 days. Monitoring telavancin blood levels is unnecessary. In patients with renal impairment, as indicated by reduced creatinine clearance (CrCl), dosage should be decreased as follows:

- CrCl above 50 mL/min—No adjustment needed
- CrCl 30 to 50 mL/min—7.5 mg/kg once daily
- CrCl 10 to 29 mL/min—10 mg/kg every 48 hours
- CrCl below 10 mL/min—There are no data to recommend a dosage

In patients with moderate hepatic impairment, no dosage adjustment is needed.

Aztreonam

Chemistry. Aztreonam [Azactam, Cayston] belongs to a class of beta-lactam antibiotics known as *monobactams*. These agents contain a beta-lactam ring, but the ring is not fused with a second ring. The structure of aztreonam is shown in Figure 85-2.

Mechanism of Action. Aztreonam binds to PBP3. Hence, like most beta-lactam antibiotics, the drug inhibits bacterial cell wall synthesis, and thereby promotes cell lysis and death. The drug does not bind to PBPs produced by anaerobes or gram-positive bacteria.

Antimicrobial Spectrum and Therapeutic Use. Aztreonam has a narrow antimicrobial spectrum, being active only against gram-negative aerobic bacteria. Susceptible organisms include *Neisseria* species, *H. influenzae*, *P. aeruginosa*, and Enterobacteriaceae (eg, *Escherichia coli*, *Klebsiella*, *Proteus*, *Serratia*, *Salmonella*, *Shigella*). Aztreonam is highly resistant to beta-lactamases, and therefore is active against many gram-negative aerobes that produce them. The drug is not active against gram-positive bacteria and anaerobes.

Pharmacokinetics. Aztreonam is not absorbed from the GI tract and hence must be administered parenterally (IM or IV) for systemic therapy. Once in the blood, the drug distributes widely to most body fluids and tissues. Therapeutic concentrations can be achieved in the CSF. Aztreonam is eliminated by the kidneys, primarily unchanged.

In addition to being administered IM and IV, aztreonam can be inhaled for delivery directly to the lungs. This route is used to treat *P. aeruginosa* lung infection in patients with cystic fibrosis.

Adverse Effects. Aztreonam is generally well tolerated. Adverse effects are like those of other beta-lactam antibiotics. The most common effects are pain and thrombophlebitis at the site of injection. Because aztreonam differs greatly in structure from penicillins and cephalosporins, there is little cross-allergenicity with them. Hence, aztreonam appears safe for patients with allergies to other beta-lactam antibiotics.

Preparations, Dosage, and Administration. Parenteral. Aztreonam is available in powdered form, sold as *Azactam*, to be reconstituted for IM or IV administration. The usual adult dosage is 1 to 2 gm every 8 to 12 hours. Dosage should be reduced in patients with renal impairment.

Inhalational. Aztreonam is available in powdered form, sold as Cayston, to be reconstituted with the diluent supplied, and then inhaled using the *Altera Nebulizer System*. Dosing is done as a repeating cycle of 75 mg 3 times a day for 28 days, followed by 28 days off.

Teicoplanin

Chemistry and Actions. Teicoplanin [Targocid] is similar in structure and actions to vancomycin. Both drugs disrupt cell wall synthesis to cause lysis and death, and both are active only against gram-positive bacteria. Sensitive organisms include *C. difficile*, MRSA, and enterococci. Like vancomycin—and unlike most other drugs discussed in the chapter—teicoplanin does not have a beta-lactam ring. Teicoplanin is approved in Japan and Europe, but not in the United States or Canada.

Pharmacokinetics. The kinetics of teicoplanin are much like those of vancomycin—except that teicoplanin can be administered IM as well as IV. Neither drug is absorbed from the GI tract, so oral administration is reserved for infection of the intestine. Following parenteral administration, teicoplanin is well distributed to tissues and most body fluids, but not to the CSF. Teicoplanin has a long half-life (up to 100 hours) and is eliminated intact by the kidneys.

Therapeutic Use. The drug has been used with success against an array of infections. Potential applications include osteomyelitis and endocarditis caused by methicillin-resistant staphylococci, streptococci, and enterococci. Combining the drug with gentamicin can increase bactericidal effects.

Teicoplanin represents a safe and effective alternative to vancomycin, and offers several advantages, namely (1) the option of IM administration, (2)

shorter infusion time with IV administration (30 vs. 60 minutes), (3) once-a-day dosing, and (4) the absence of serious adverse effects, including infusion-related reactions.

Adverse Effects. Teicoplanin is largely devoid of adverse effects. In contrast to vancomycin, teicoplanin does not promote histamine release, and hence does not cause infusion-related reactions (eg, flushing, tachycardia, hypotension). Ototoxicity may occur but is rare. Not surprisingly, patients allergic to beta-lactam antibiotics are *not* cross-allergic to teicoplanin.

Dosage and Administration. Teicoplanin may be given parenterally or orally. Parenteral administration is done by IM injection, IV injection, or 30-minute IV infusion. For parenteral therapy, the usual adult dosage is 6 mg/kg initially followed by 3 mg/kg every 24 hours. Dosage should be reduced in patients with renal impairment. As noted, oral therapy is used only for intestinal infections.

Fosfomycin

Fosfomycin [Monurol] is a unique antibiotic approved for single-dose therapy in women with uncomplicated urinary tract infections (ie, acute cystitis) caused by *E. coli* or *Enterococcus faecalis*. The drug kills bacteria by disrupting synthesis of the peptidoglycan polymer strands that compose the cell wall. (As discussed in Chapter 83, penicillins kill bacteria in part by preventing cross-linking of peptidoglycan strands.)

The most common adverse effects are diarrhea (10.4%), headache (10.3%), vaginitis (7.6%), and nausea (5.2%). Fosfomycin may also cause abdominal pain, rhinitis, drowsiness, dizziness, and rash.

Fosfomycin is supplied as a water-soluble powder in single-dose, 3-gm packets. Dosing may be done with or without food. Symptoms of cystitis should improve in 2 to 3 days. If symptoms fail to improve, additional doses will not help—but will increase the risk of side effects.

KEY POINTS

- Cephalosporins are beta-lactam antibiotics that weaken the bacterial cell wall, causing lysis and death.
- The major cause of cephalosporin resistance is production of beta-lactamases.
- Cephalosporins can be grouped into four “generations.” As we progress from first- to fourth-generation drugs, there is (1) increasing activity against gram-negative bacteria, (2) increasing resistance to destruction by beta-lactamases, and (3) increasing ability to reach the CSF.
- Except for ceftriaxone, all cephalosporins are eliminated by the kidney, and therefore must be given in reduced dosage to patients with renal impairment.
- The most common adverse effects of cephalosporins are allergic reactions. Patients allergic to penicillins have about a 1% risk of cross-reactivity with cephalosporins.
- Four cephalosporins—cefmetazole, cefoperazone, cefotetan, and ceftriaxone—can cause bleeding tendencies.
- Four cephalosporins—cefazolin, cefmetazole, cefoperazone, and cefotetan—can cause a disulfiram-like reaction.
- Imipenem, a beta-lactam antibiotic, has an antimicrobial spectrum that is broader than that of practically all other antimicrobial drugs.
- Vancomycin is an important but potentially toxic drug used primarily for (1) *Clostridium difficile* infection, (2) MRSA infection, and (3) serious infections by susceptible organisms in patients allergic to penicillins.
- The principal toxicity of vancomycin is renal failure.

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Summary of Major Nursing Implications

CEPHALOSPORINS

Cefaclor	Cefoxitin
Cefadroxil	Cefpodoxime
Cefazolin	Cefprozil
Cefdinir	Ceftaroline
Cefditoren	Ceftazidime
Cefepime	Cefibuten
Cefixime	Ceftizoxime
Cefoperazone	Ceftriaxone
Cefotaxime	Cefuroxime
Cefotetan	Cephalexin

Except where indicated, the implications summarized below apply to all members of the cephalosporin family.

Preadministration Assessment

Therapeutic Goal

Treatment of infections caused by susceptible organisms.

Baseline Data

The prescriber may order tests to determine the identity and drug sensitivity of the infecting organism. Take samples for culture prior to initiating treatment.

Identifying High-Risk Patients

Cephalosporins are *contraindicated* for patients with a history of allergic reactions to cephalosporins or of severe allergic reactions to penicillins. *Ceftriaxone* is *contraindicated* for neonates who are receiving (or expected to receive) IV calcium.

Implementation: Administration

Routes

Ten cephalosporins are given only parenterally (IM or IV), nine are given only orally, and one—*cefuroxime*—is given orally and parenterally (see Table 85-3).

Summary of Major Nursing Implications*—cont'd

Dosage

Dosages are summarized in Table 85-3. Dosages for all cephalosporins—except *ceftriaxone*—should be reduced in patients with significant renal impairment.

Administration

Oral. Advise patients to take oral cephalosporins with food if gastric upset occurs. Instruct patients to refrigerate oral suspensions.

Instruct patients to complete the prescribed course of therapy even though symptoms may abate before the full course is over.

Intramuscular. Make IM injections deep into a large muscle. Intramuscular injections are frequently painful; forewarn the patient. Check the injection site for induration, tenderness, and redness—and notify the prescriber if these occur.

Intravenous. Techniques for IV administration are bolus injection, slow injection (over 3 to 5 minutes), and continuous infusion. The prescriber's order should specify which method to use; request clarification if the order is unclear.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor for indications of antimicrobial effects (eg, reduction in fever, pain, or inflammation; improved appetite or sense of well-being).

Minimizing Adverse Effects

Allergic Reactions. Hypersensitivity reactions are relatively common. Rarely, life-threatening anaphylaxis occurs. Avoid cephalosporins in patients with a history of cephalosporin allergy or severe penicillin allergy. If penicillin allergy is mild, cephalosporins can be used with relative safety. Instruct the patient to report any signs of allergy (eg, skin rash, itching, hives). If anaphylaxis occurs, administer parenteral epinephrine and provide respiratory support.

Bleeding. Four cephalosporins—*cefmetazole*, *cefoperazone*, *cefotetan*, and *ceftriaxone*—can promote bleeding. Monitor prothrombin time, bleeding time, or both. Parenteral vitamin K can correct abnormal prothrombin time. Observe patients for signs of bleeding and, if bleeding develops, discontinue the drug. Exercise caution in patients with a history of bleeding disorders and in patients receiving drugs that can interfere with hemostasis (anticoagulants; thrombolytics; antiplatelet drugs, including aspirin and other nonsteroidal anti-inflammatory drugs).

Thrombophlebitis. Intravenous cephalosporins may cause thrombophlebitis. To minimize this reaction, rotate the injection site and inject cephalosporins slowly and in dilute solution. Observe the patient for phlebitis and change the infusion site if phlebitis develops.

Hemolytic Anemia. Cephalosporins can promote immune-mediated hemolytic anemia. If hemolytic anemia develops, the cephalosporin should be discontinued. Blood transfusions may be given as needed.

***Clostridium difficile* Infection (CDI).** All cephalosporins, and especially the broad-spectrum agents, can promote CDI, which can cause diarrhea and pseudomembranous colitis. Notify the prescriber if diarrhea occurs. If CDI is diagnosed, discontinue the cephalosporin. Treat with metronidazole or vancomycin, depending on the severity of the infection.

Milk-Protein Hypersensitivity. *Cefditoren* tablets contain sodium caseinate, a milk protein. Do not give *cefditoren* to patients with milk-protein allergy. (The drug is safe in patients with lactose intolerance.)

Carnitine Deficiency. *Cefditoren* is excreted in combination with carnitine, and can thereby lower carnitine levels. Do not give *cefditoren* to patients with pre-existing carnitine deficiency or with conditions that predispose to carnitine deficiency.

Minimizing Adverse Interactions

Alcohol. *Cefazolin*, *cefmetazole*, *cefoperazone*, and *cefotetan* can cause alcohol intolerance. A serious disulfiram-like reaction may occur if alcohol is consumed. Inform patients about alcohol intolerance and warn them not to drink alcoholic beverages.

Drugs That Promote Bleeding. Drugs that interfere with hemostasis—anticoagulants, thrombolytics, and antiplatelet drugs (including aspirin and other nonsteroidal anti-inflammatory drugs)—can intensify bleeding tendencies caused by *cefmetazole*, *cefoperazone*, *cefotetan*, and *ceftriaxone*. Avoid these combinations.

Calcium and Ceftriaxone. Combining calcium with *ceftriaxone* can form potentially fatal precipitates. To avoid harm, don't reconstitute powdered *ceftriaxone* with calcium-containing diluents, and don't mix reconstituted *ceftriaxone* with calcium-containing solutions. In patients other than neonates, *ceftriaxone* and calcium-containing solutions may be administered sequentially, provided the infusion line is flushed between infusions. Do not give IV *ceftriaxone* to neonates who are receiving IV calcium, or if they are expected to receive IV calcium.

VANCOMYCIN

Preadministration Assessment

Therapeutic Goal

Treatment of serious infections, including *C. difficile* infection (CDI), infection with methicillin-resistant *Staph. aureus* (MRSA), and serious infections with susceptible organisms in patients allergic to penicillins.

Baseline Data

The prescriber may order tests to determine the identity and drug sensitivity of the infecting organisms. Take samples for culture prior to initiating treatment.

Identifying High Risk Patients

Exercise caution in patients with renal impairment.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Implementation: Administration

Routes

Intravenous. For systemic infections, and possibly for CDI.

Oral. For CDI and other intestinal infections.

Rectal. An investigational route for complicated CDI.

Dosage

Intravenous. The recommended dosage is 15 to 20 mg/kg every 8 to 12 hours, possibly preceded by a loading dose (25 to 30 mg/kg) in patients with severe infection. Dosage must be reduced in patients with renal impairment. Adjust the dosage to achieve an effective *trough* serum level: 15 to 20 mcg/mL for serious infections and 10 mcg/mL for less serious infections.

Oral. Doses for CDI are shown in Box 85-1. Dosage needn't be reduced in patients with renal impairment.

Rectal. One recommended regimen consists of 500 mg every 6 hours.

Administration

Intravenous. Infuse slowly, over 60 minutes or longer. Use a dilute solution and rotate the infusion site.

Oral. Instruct patients to complete the prescribed course of therapy even though symptoms may abate before the full course is over.

Rectal. Dissolve in 100 mL of normal saline and administer through a Foley catheter inserted in the rectum.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor for indications of antimicrobial effects (eg, reduction in fever, pain, or inflammation; improved appetite or sense of well-being, decreased diarrhea in patients with CDI).

Minimizing Adverse Effects and Interactions

Renal Failure. Vancomycin can cause dose-related nephrotoxicity. To minimize risk, ensure that serum trough levels are no greater than required. If significant kidney damage develops, as indicated by a 50% increase in serum creatinine level, dosage should be reduced.

Nephrotoxic Drugs. Nephrotoxic drugs—including aminoglycosides, cyclosporine, and nonsteroidal anti-inflammatory drugs—can increase the risk of kidney damage. Concurrent use of these agents should be avoided, if possible.

Red Man Syndrome. Rapid infusion can cause red man syndrome (aka red person syndrome, red neck), characterized by flushing, rash, pruritus, urticaria, tachycardia, and hypotension. To minimize risk, infuse vancomycin slowly, over 60 minutes or longer.

Thrombophlebitis. To help avoid this common reaction, use vancomycin in dilute solution and change the infusion site often.

*Patient education information is highlighted as blue text.

Bacteriostatic Inhibitors of Protein Synthesis: Tetracyclines, Macrolides, and Others

Tetracyclines

Macrolides

Erythromycin

Clarithromycin

Azithromycin

Other Bacteriostatic Inhibitors of Protein Synthesis

Clindamycin

Linezolid

Telithromycin

Dalfopristin/Quinupristin

Chloramphenicol

Tigecycline

Retapamulin and Mupirocin

All of the drugs discussed in this chapter inhibit bacterial protein synthesis. However, unlike the aminoglycosides, which are bactericidal, the drugs considered here are largely bacteriostatic. That is, they suppress bacterial growth and replication but do not produce outright kill. In general, the drugs presented here are second-line agents, used primarily for infections resistant to first-line agents.

TETRACYCLINES

The tetracyclines are *broad-spectrum* antibiotics. In the United States, four tetracyclines are available for systemic therapy. All four—tetracycline, demeclocycline, doxycycline, and minocycline—are similar in structure, antimicrobial actions, and adverse effects. Principal differences among them are pharmacokinetic. Because the similarities among these drugs are more pronounced than their differences, we will discuss the tetracyclines as a group, rather than focusing on a prototype. Unique properties of individual tetracyclines are indicated as appropriate.

Mechanism of Action

The tetracyclines suppress bacterial growth by inhibiting protein synthesis. These drugs bind to the 30S ribosomal subunit, and thereby inhibit binding of transfer RNA to the messenger

RNA-ribosome complex.* As a result, addition of amino acids to the growing peptide chain is prevented. At the concentrations achieved clinically, the tetracyclines are bacteriostatic.

Selective toxicity of the tetracyclines results from their poor ability to cross mammalian cell membranes. In order to influence protein synthesis, tetracyclines must first gain access to the cell interior. These drugs enter bacteria by way of an energy-dependent transport system. Mammalian cells lack this transport system, and hence do not actively accumulate the drug. Consequently, although tetracyclines are inherently capable of inhibiting protein synthesis in mammalian cells, their levels within host cells remain too low to be harmful.

Microbial Resistance

Bacterial resistance results from increased drug inactivation, decreased access to ribosomes (owing to the presence of ribosome protection proteins), and reduced intracellular accumulation (owing to decreased uptake and increased export).

Antimicrobial Spectrum

The tetracyclines are broad-spectrum antibiotics, active against a wide variety of gram-positive and gram-negative bacteria. Sensitive organisms include *Rickettsia*, spirochetes, *Brucella*, *Chlamydia*, *Mycoplasma*, *Helicobacter pylori*, *Borrelia burgdorferi*, *Bacillus anthracis*, and *Vibrio cholerae*.

Therapeutic Uses

Treatment of Infectious Diseases. Extensive use of tetracyclines has resulted in increasing bacterial resistance. Because of resistance, and because antibiotics with greater selectivity and less toxicity are now available, use of tetracyclines has declined. Today, tetracyclines are rarely drugs of first choice. Disorders for which they *are* first-line drugs include (1) rickettsial diseases (eg, Rocky Mountain spotted fever, typhus fever, Q fever); (2) infections caused by *Chlamydia trachomatis* (trachoma, lymphogranuloma venereum, urethritis, cervicitis); (3) brucellosis; (4) cholera; (5) pneumonia caused by *Mycoplasma pneumoniae*; (6) Lyme disease; (7) anthrax; and (8) gastric infection with *H. pylori*.

Treatment of Acne. Tetracyclines are used topically and orally for severe acne vulgaris. Beneficial effects derive from suppressing the growth and metabolic activity of *Propionibacterium acnes*, an organism that secretes inflammatory chemicals. Oral doses for acne are relatively low. As a result, adverse effects are minimal. Acne is discussed at length in Chapter 105 (Drugs for the Skin).

*Figure 87-2 in Chapter 87 depicts the role of the 30S ribosomal subunit in bacterial protein synthesis.

TABLE 86-1 • Pharmacokinetic Properties of the Tetracyclines

Class	Drug	Lipid Solubility	Percent of Oral Dose Absorbed*	Effect of Food on Absorption	Route of Elimination	Half-Life	
						Normal (hr)	Anuric (hr)
Short Acting	Tetracycline	Low	60-80	Large decrease	Renal	8	57-108†
Intermediate Acting	Demeclocycline	Moderate	60-80	Large decrease	Renal	12	40-60†
Long Acting	Doxycycline	High	90-100	Small decrease	Hepatic	18	17-30
	Minocycline	High	90-100	No change	Hepatic	16	11-23

*Percent absorbed when taken on an empty stomach.

†Do not use in patients with renal impairment because the drug could accumulate to toxic levels.

Peptic Ulcer Disease. *Helicobacter pylori*, a bacterium that lives in the stomach, is a major contributing factor to peptic ulcer disease. Tetracyclines, in combination with metronidazole and bismuth subsalicylate, are a treatment of choice for eradicating this bug. The role of *H. pylori* in ulcer formation is discussed in Chapter 78 (Drugs for Peptic Ulcer Disease).

Periodontal Disease. Two tetracyclines—doxycycline and minocycline—are used for periodontal disease. Doxycycline is used orally and topically, whereas minocycline is used only topically.

Oral Therapy. Benefits of oral doxycycline [Periostat] result from inhibiting collagenase, an enzyme that destroys connective tissue in the gums. The small doses employed—20 mg twice daily—are too low to harm bacteria.

Topical Therapy. Topical minocycline [Arestin] and doxycycline [Atridox] are employed as adjuncts to scaling and root planing. The objective is to reduce pocket depth and bleeding in adults with periodontitis. Benefits derive from suppressing bacterial growth. Both products are applied directly to the site of periodontal disease.

Rheumatoid Arthritis. Minocycline can reduce symptoms in patients with rheumatoid arthritis, suggesting a possible infectious component to the disease.

Pharmacokinetics

Individual tetracyclines differ significantly in their pharmacokinetic properties. Of particular significance are differences in half-life and route of elimination. Also important is the degree to which food decreases absorption. The pharmacokinetic properties of individual tetracyclines are summarized in Table 86-1.

Duration of Action. The tetracyclines can be divided into three groups: short acting, intermediate acting, and long acting (see Table 86-1). These differences are related to differences in lipid solubility: The only short-acting tetracycline (tetracycline) has relatively low lipid solubility, whereas the long-acting agents (doxycycline, minocycline) have relatively high lipid solubility.

Absorption. All of the tetracyclines are orally effective, although the extent of absorption differs among individual agents (see Table 86-1). Absorption of three agents—tetracycline, demeclocycline, and doxycycline—is reduced by food, whereas absorption of minocycline is not.

The tetracyclines form insoluble chelates with calcium, iron, magnesium, aluminum, and zinc. The result is decreased absorption. Accordingly, *tetracyclines should not be adminis-*

tered together with (1) calcium supplements, (2) milk products (because they contain calcium), (3) iron supplements, (4) magnesium-containing laxatives, and (5) most antacids (because they contain magnesium, aluminum, or both).

Distribution. Tetracyclines are widely distributed to most tissues and body fluids. However, penetration to the cerebrospinal fluid (CSF) is poor, and hence levels in the CSF are too low to treat meningeal infections. Tetracyclines readily cross the placenta and enter the fetal circulation.

Elimination. Tetracyclines are eliminated by the kidneys and liver. All tetracyclines are excreted by the liver into the bile. After the bile enters the intestine, most tetracyclines are reabsorbed.

Ultimate elimination of short- and intermediate-acting tetracyclines—tetracycline and demeclocycline—is in the urine, largely as the unchanged drug (see Table 86-1). Because these agents undergo renal elimination, they can accumulate to toxic levels if the kidneys fail. Consequently, *tetracycline and demeclocycline should not be given to patients with significant renal impairment.*

Long-acting tetracyclines are eliminated by the liver, primarily as metabolites. Because these agents are excreted by the liver, their half-lives are unaffected by kidney dysfunction. Accordingly, *the long-acting agents (doxycycline and minocycline) are drugs of choice for tetracycline-responsive infections in patients with renal impairment.*

Adverse Effects

Gastrointestinal Irritation. Tetracyclines irritate the GI tract. As a result, oral therapy is frequently associated with epigastric burning, cramps, nausea, vomiting, and diarrhea. These reactions can be reduced by giving tetracyclines with meals—although food may decrease absorption. Occasionally, tetracyclines cause esophageal ulceration. Risk can be minimized by avoiding dosing at bedtime. Because diarrhea may result from suprainfection of the bowel (in addition to nonspecific irritation), it is important that the cause of diarrhea be determined.

Effects on Bones and Teeth. Tetracyclines bind to calcium in developing teeth, resulting in yellow or brown discoloration; hypoplasia of the enamel may also occur. The intensity of tooth discoloration is related to the total cumulative dose: Staining is darker with prolonged and repeated treatment. When taken after the fourth month of gestation, tetracyclines can cause staining of deciduous teeth of the infant. However, use during pregnancy will not affect permanent teeth. Discoloration of permanent teeth occurs when tetracyclines are taken by patients ages 4 months to 8 years, the

interval during which tooth enamel is being formed. Accordingly, these drugs should be avoided by children under 8 years old. The risk of tooth discoloration with *doxycycline* may be less than with other tetracyclines.

Tetracyclines can suppress long-bone growth in premature infants. This effect is reversible upon discontinuation of treatment.

Suprainfection. As discussed in Chapter 83, a suprainfection is an overgrowth with drug-resistant microbes, which occurs secondary to suppression of drug-sensitive organisms. Because the tetracyclines are broad-spectrum agents, and therefore can decrease viability of a wide variety of microbes, the risk of suprainfection is greater than with antibiotics that have a more narrow spectrum.

Suprainfection of the bowel with staphylococci or with *Clostridium difficile* produces severe diarrhea and can be life threatening. The infection caused by *C. difficile* is known as *C. difficile*-associated diarrhea (CDAD), also known as *antibiotic-associated pseudomembranous colitis* (AAPMC). Patients should notify the prescriber if significant diarrhea occurs, so that the possibility of bacterial suprainfection can be evaluated. If a diagnosis of suprainfection with staphylococci or *C. difficile* is made, tetracyclines should be discontinued immediately. Treatment of CDAD consists of oral *vancomycin* or *metronidazole* plus vigorous fluid and electrolyte replacement.

Overgrowth with fungi (commonly *Candida albicans*) may occur in the mouth, pharynx, vagina, and bowel. Symptoms include vaginal or anal itching; inflammatory lesions of the anogenital region; and a black, furry appearance of the tongue. Suprainfection with *Candida* can be managed by discontinuing tetracyclines. When this is not possible, antifungal therapy is indicated.

Hepatotoxicity. Tetracyclines can cause fatty infiltration of the liver. Hepatotoxicity manifests clinically as lethargy and jaundice. Rarely, the condition progresses to massive liver failure. Liver damage is most likely when tetracyclines are administered intravenously in high doses (greater than 2 gm/day). Pregnant and postpartum women with kidney disease are at especially high risk.

Renal Toxicity. Tetracyclines may exacerbate renal impairment in patients with pre-existing kidney disease. Because *tetracycline* and *demeclocycline* are eliminated by the kidneys, these agents should not be given to patients with renal impairment. If a patient with renal impairment requires a tetracycline, either *doxycycline* or *minocycline* should be used, since these drugs are eliminated primarily by the liver.

Photosensitivity. All tetracyclines can increase the sensitivity of the skin to ultraviolet light. The most common result is exaggerated sunburn. Advise patients to avoid prolonged exposure to sunlight, wear protective clothing, and apply a sunscreen to exposed skin.

Other Adverse Effects. Vestibular toxicity—manifesting as dizziness, lightheadedness, and unsteadiness—has occurred with *minocycline*. Rarely, tetracyclines have produced pseudotumor cerebri (a benign elevation in intracranial pressure). In a few patients, *demeclocycline* has produced nephrogenic diabetes insipidus, a syndrome characterized by thirst, increased frequency of urination, and unusual weakness or tiredness. Because of their unusual properties, tetracyclines can cause pain at sites of IM injection and thrombophlebitis when administered intravenously.

Drug and Food Interactions

As noted, tetracyclines can form nonabsorbable chelates with certain metal ions (calcium, iron, magnesium, aluminum, zinc). Substances that contain these ions include *milk prod-*

ucts, calcium supplements, iron supplements, magnesium-containing laxatives, and most antacids. If a tetracycline is administered with these agents, its absorption will be decreased. To minimize interference with absorption, tetracyclines should be administered at least 1 hour before or 2 hours after ingestion of chelating agents.

Dosage and Administration

Administration. For systemic therapy, tetracyclines may be administered orally, intravenously, and by IM injection. Oral administration is preferred, and all tetracyclines are available in oral formulations. As a rule, oral tetracyclines should be taken on an empty stomach (1 hour before meals or 2 hours after) and with a full glass of water. An interval of at least 2 hours should separate tetracycline ingestion and ingestion of products that can chelate these drugs (eg, milk, calcium or iron supplements, antacids). Three tetracyclines can be given IV (Table 86-2), but this route should be employed only when oral therapy cannot be tolerated or has proved inadequate. Intramuscular injection is extremely painful and used rarely.

In addition to their systemic use, two agents—*doxycycline* and *minocycline*—are available in formulations for topical therapy of periodontal disease (see above).

Dosage. Dosage is determined by the nature and intensity of the infection. Typical systemic doses for adults and children are summarized in Table 86-2.

Summary of Major Precautions

Two tetracyclines—*tetracycline* and *demeclocycline*—are eliminated primarily in the urine, and hence will accumulate to toxic levels in patients with kidney disease. Accordingly, patients with kidney disease should not use these drugs.

Tetracyclines can cause discoloration of deciduous and permanent teeth. Tooth discoloration can be avoided by withholding these drugs from pregnant women and from children under 8 years of age.

Diarrhea may indicate a potentially life-threatening suprainfection of the bowel. Advise patients to notify the prescriber if diarrhea occurs.

High-dose IV therapy has been associated with severe liver damage, particularly in pregnant and postpartum women with kidney disease. As a rule, these women should not receive tetracyclines.

Summary of Unique Properties of Individual Tetracyclines

Tetracycline. Tetracycline hydrochloride is the least expensive and most widely used member of the family. When employed systemically, the drug has the indications, pharmacokinetics, adverse effects, and drug interactions described for the tetracyclines as a group. Like most tetracyclines, *tetracycline* hydrochloride should not be administered with food, and is contraindicated for patients with renal impairment. This agent and all other tetracyclines should not be given to pregnant women or to children less than 8 years old.

Demeclocycline. *Demeclocycline* [Declomycin] shares the actions, indications, and adverse effects described above for the tetracyclines as a group. Because of its intermediate duration of action, *demeclocycline* can be administered at dosing intervals that are longer than those used for *tetracycline*. Like *tetracycline*, *demeclocycline* should not be administered with food.

Demeclocycline is unique among the tetracyclines in that it stimulates urine flow. This side effect can lead to excessive urination, thirst, and tiredness. Interestingly, because of its effect on renal function, *demeclocycline* has been employed therapeutically to promote urine production in patients suffering from the syndrome of inappropriate (excessive) secretion of antidiuretic hormone.

TABLE 86-2 ■ Tetracyclines: Routes of Administration, Dosing Interval, and Dosage

Class	Drug	Trade Names	Route	Usual Dosing Interval (hr)	Total Daily Dose	
					Adult (mg)	Pediatric (mg/kg) ^a
Short Acting	Tetracycline	generic only	PO	6	1000–2000	25–50
			IV ^b	12	500–1000	10–20
			IM ^c	12	300	15–25
Intermediate Acting	Demeclocycline	Declomycin	PO	12	600	6–12
Long Acting	Doxycycline	Vibramycin, others	PO	24	100 ^d	2.2 ^e
			IV ^b	24	100–200 ^f	2.2–4.4 ^g
	Minocycline	Minocin, others	PO	12	200 ^h	4 ⁱ
			IV ^b	12	200 ^h	4 ⁱ

^aDoses presented are for children over the age of 8 years. Use in children below this age may cause permanent staining of teeth.

^bThe intravenous route is used only if oral therapy cannot be tolerated or is inadequate.

^cIntramuscular injection is extremely painful and used only rarely.

^dFirst-day regimen is 100 mg initially, followed by 100 mg 12 hours later.

^eFirst-day regimen is 2.2 mg/kg initially, followed by 2.2 mg/kg 12 hours later.

^fFirst-day regimen is 200 mg in one or two slow infusions (1 to 4 hours).

^gFirst-day regimen is 4.4 mg/kg in one or two slow infusions (1 to 4 hours).

^hFirst-day regimen is 200 mg initially, followed by 100 mg 12 hours later.

ⁱFirst-day regimen is 4 mg/kg initially, followed by 2 mg/kg 12 hours later.

Doxycycline. Doxycycline [Vibramycin, others] is a long-acting agent that shares the actions and adverse effects described for the tetracyclines as a group. Because of its extended half-life, doxycycline can be administered once daily. Absorption of oral doxycycline is greater than that of tetracycline. However, food can still reduce the absorption of doxycycline somewhat, and hence it is best to give this drug on an empty stomach. Doxycycline is eliminated primarily by nonrenal mechanisms. As a result, it is safe for patients with renal failure. Doxycycline is a first-line drug for Lyme disease, anthrax, chlamydial infections (urethritis, cervicitis, and lymphogranuloma venereum), and sexually acquired proctitis (in combination with ceftriaxone). A topical formulation [Atridox] is used for periodontal disease, as is a low-dose oral formulation [Periostat]. Another low-dose oral formulation [Oracea] is used for acne (see Chapter 105).

Minocycline. Minocycline [Minocin, Dynacin, others] is a long-acting agent similar to doxycycline. Unlike other tetracyclines, minocycline can be taken with food. Like doxycycline, and unlike tetracycline and demeclocycline, minocycline is safe for patients with kidney disease. Minocycline is unique among the tetracyclines in that it can damage the vestibular system, causing unsteadiness, lightheadedness, and dizziness. This toxicity limits its use. Minocycline is expensive, costing significantly more than tetracycline. In addition to fighting systemic infection, minocycline can reduce symptoms of arthritis (see Chapter 73), and is available in an extended-release formulation [Solodyn] for acne, and a topical formulation [Arestin] for periodontal disease.

MACROLIDES

The macrolides are broad-spectrum antibiotics that inhibit bacterial protein synthesis. Why are they called macrolides? Because they are big. Erythromycin is the oldest member of the family. The newer macrolides—azithromycin and clarithromycin—are derivatives of erythromycin.

Erythromycin

Erythromycin has a relatively broad antimicrobial spectrum and is a preferred or alternative treatment for a number of infections. The drug is one of our safest antibiotics and will serve as our prototype for the macrolide family.

Mechanism of Action

Antibacterial effects result from inhibition of protein synthesis: Erythromycin binds to the 50S ribosomal subunit and thereby blocks addition of new amino acids to the growing peptide chain. The drug is usually bacteriostatic, but can be bactericidal against highly susceptible organisms, or when present in high concentration. Erythromycin is selectively toxic to bacteria because ribosomes in the cytoplasm of mammalian cells do not bind the drug. Also, in contrast to chloramphenicol (see below), erythromycin cannot cross the mitochondrial membrane, and therefore does not inhibit protein synthesis in host mitochondria.

Acquired Resistance

Bacteria can become resistant by two mechanisms: (1) production of a pump that exports the drug and (2) modification (by methylation) of target ribosomes so that binding of erythromycin is impaired.

Antimicrobial Spectrum

Erythromycin has an antibacterial spectrum similar to that of penicillin. The drug is active against most gram-positive bacteria as well as some gram-negative bacteria. Bacterial sensitivity is determined in large part by the ability of erythromycin to gain access to the cell interior.

Therapeutic Uses

Erythromycin is a commonly used antibiotic. *The drug is a treatment of first choice for several infections and may be used as an alternative to penicillin G in patients with penicillin allergy.*

Erythromycin is a preferred treatment for pneumonia caused by *Legionella pneumophila* (legionnaires' disease).

Erythromycin is considered the drug of first choice for individuals infected with *Bordetella pertussis*, the causative agent of whooping cough. Because symptoms are

caused by a toxin produced by *B. pertussis*, erythromycin does little to alter the course of the disease. However, by eliminating *B. pertussis* from the nasopharynx, treatment does lower infectivity.

Corynebacterium diphtheriae is highly sensitive to erythromycin. Accordingly, erythromycin is the treatment of choice for acute diphtheria and eliminating the diphtheria carrier state.

Several infections respond equally well to erythromycin and tetracyclines. Both are drugs of first choice for certain chlamydial infections (urethritis, cervicitis) and for pneumonia caused by *M. pneumoniae*.

Erythromycin may be employed as an alternative to penicillin G in patients with penicillin allergy. The drug is used most frequently as a substitute for penicillin to treat respiratory tract infections caused by *Streptococcus pneumoniae* and by group A *Streptococcus pyogenes*. Erythromycin can also be employed as an alternative to penicillin for preventing recurrences of rheumatic fever and bacterial endocarditis.

Pharmacokinetics

Absorption and Bioavailability. Erythromycin for oral administration is available in three forms: *erythromycin base* and two derivatives of the base: *erythromycin stearate* and *erythromycin ethylsuccinate*. The base is unstable in stomach acid, and its absorption can be variable; the derivatives were synthesized to improve bioavailability. Bioavailability has also been enhanced by formulating tablets with an acid-resistant coating, which protects erythromycin while in the stomach and then dissolves in the duodenum, thereby permitting absorption from the small intestine. As a rule, *food decreases the absorption of erythromycin base and erythromycin stearate*, whereas absorption of erythromycin ethylsuccinate is not affected. Only erythromycin base is biologically active; the derivatives must be converted to the base (either in the intestine or following absorption) in order to work. When used properly (ie, when dosage is correct and the effects of food are accounted for), all of the oral erythromycins produce equivalent responses.

In addition to its oral forms, erythromycin is available as *erythromycin lactobionate* for IV use. Intravenous dosing produces drug levels that are higher than those achieved with oral dosing.

Distribution. Erythromycin readily distributes to most tissues and body fluids. Penetration to the CSF, however, is poor. Erythromycin crosses the placenta, but adverse effects on the fetus have not been observed.

Elimination. Erythromycin is eliminated primarily by hepatic mechanisms, including metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450). Erythromycin is concentrated in the liver and then excreted in the bile. A small amount (10% to 15%) is excreted unchanged in the urine.

Adverse Effects

Erythromycin is generally free of serious toxicity and is considered one of our safest antibiotics. However, the drug does carry a very small risk of sudden cardiac death.

Gastrointestinal Effects. Gastrointestinal disturbances (epigastric pain, nausea, vomiting, diarrhea) are the most common side effects. These can be reduced by administering erythromycin with meals. However, this should be done only when using erythromycin products whose absorption is unaffected by food (erythromycin ethylsuccinate, certain enteric-

coated formulations of erythromycin base). Patients who experience persistent or severe GI reactions should notify the prescriber.

QT Prolongation and Sudden Cardiac Death. A study published in 2004 raised concerns about cardiotoxicity, especially when erythromycin is combined with drugs that can raise its plasma level. When present in high concentrations, erythromycin can prolong the QT interval, thereby posing a risk of torsades de pointes, a potentially fatal ventricular dysrhythmia. Sudden death can result. The 2004 study revealed that, when erythromycin is combined with a CYP3A4 inhibitor, there is a fivefold increase in the risk of sudden cardiac death—or 6 extra deaths for every 100,000 patients using the drug. To minimize risk, erythromycin should be avoided by patients with congenital QT prolongation and by those taking class IA or class III antidysrhythmic drugs. Also, the drug should be avoided by patients taking CYP3A4 inhibitors, including certain calcium channel blockers (verapamil and diltiazem), azole antifungal drugs (eg, ketoconazole, itraconazole), HIV protease inhibitors (eg, ritonavir, saquinavir), and nefazodone (an antidepressant).

Other Adverse Effects. By killing off sensitive gut flora, erythromycin can promote *suprainfection of the bowel*. *Thrombophlebitis* can occur with IV administration; this reaction can be minimized by infusing the drug slowly in dilute solution. *Transient hearing loss* occurs rarely with high-dose therapy. There is evidence that erythromycin may cause *hypertrophic pyloric stenosis in infants*, especially those under 2 weeks of age.

Drug Interactions

Erythromycin can increase the plasma levels and half-lives of several drugs, thereby posing a risk of toxicity. The mechanism is inhibition of hepatic P450 drug-metabolizing enzymes. Elevated levels are a concern with *theophylline* (used for asthma), *carbamazepine* (used for seizures and bipolar disorder), and *warfarin* (an anticoagulant). Accordingly, when these agents are combined with erythromycin, the patient should be monitored closely for signs of toxicity.

Erythromycin prevents binding of *chloramphenicol* and *clindamycin* to bacterial ribosomes, thereby antagonizing their antibacterial effects. Accordingly, concurrent use of erythromycin with these two drugs is not recommended.

As noted, erythromycin should not be combined with drugs that can inhibit erythromycin metabolism. Among these are verapamil, diltiazem, HIV protease inhibitors, and azole antifungal drugs.

Preparations, Dosage, and Administration

Preparations. For treating systemic infections, erythromycin is available in oral and IV formulations. All preparations have the same indications, antimicrobial spectrum, and adverse effects. Erythromycin is also available in topical formulations [Eryderm, others] to treat acne (see Chapter 105).

Oral Dosage and Administration. Oral erythromycin should be administered on an empty stomach and with a full glass of water. If necessary, some preparations (erythromycin ethylsuccinate, certain enteric-coated preparations of erythromycin base) can be administered with food to decrease GI reactions. The usual *adult* dosage for *erythromycin base* and *erythromycin stearate* is 250 to 500 mg every 6 hours; the adult dosage for *erythromycin ethylsuccinate* is 400 to 800 mg every 6 hours. The usual *pediatric* dosage for all oral erythromycins is 7.5 to 12.5 mg/kg every 6 hours.

Trade names for oral erythromycins are Ery-Tab, PCE Dispertab, Erythromycin Filmtabs, and Erybid (for erythromycin base), and E.E.S., EryPed, and Erythro ES (for erythromycin ethylsuccinate). Erythromycin stearate is available only as a generic product.

Intravenous Dosage and Administration. Intravenous dosing is reserved for severe infections and is used rarely. Continuous infusion is

preferred to intermittent dosing. Only erythromycin lactobionate [Erythrocin Lactobionate] is given IV. The usual adult dosage is 1 to 4 gm daily. The usual pediatric dosage is 15 to 50 mg/kg/day. Erythromycin should be infused slowly and in dilute solution (to minimize the risk of thrombophlebitis). For instruction on preparation and storage of IV solutions, consult the manufacturer's literature.

Clarithromycin

Actions and Therapeutic Uses. Like erythromycin, clarithromycin [Biaxin, Biaxin XL] binds the 50S subunit of bacterial ribosomes, causing inhibition of protein synthesis. The drug is approved for respiratory tract infections, uncomplicated infections of the skin and skin structures, and prevention of disseminated *Mycobacterium avium* complex infections in patients with advanced HIV infection. It is also used for *H. pylori* infection and as a substitute for penicillin G in penicillin-allergic patients.

Pharmacokinetics. Clarithromycin is available in three oral formulations: immediate-release (IR) tablets, extended-release (ER) tablets, and granules. The IR tablets and granules are well absorbed, in the presence and absence of food. In contrast, the ER tablets are absorbed poorly if food is absent. Following absorption, clarithromycin is widely distributed and readily penetrates cells. Elimination is by hepatic metabolism and renal excretion. A reduction in dosage may be needed for patients with severe renal impairment.

Adverse Effects and Interactions. Clarithromycin is well tolerated and does not produce the intense nausea seen with erythromycin. The most common reactions (3%) have been diarrhea, nausea, and distorted taste—all described as mild to moderate. In clinical trials, only 3% of patients withdrew because of side effects, compared with 20% of those taking erythromycin. High doses of clarithromycin have caused fetal abnormalities in laboratory animals; possible effects on the human fetus are unknown. Like erythromycin, clarithromycin may prolong the QT interval, and hence may pose a risk of serious dysrhythmias.

Like erythromycin, clarithromycin can inhibit hepatic metabolism of other drugs, and can thereby elevate their levels. Affected drugs include warfarin, carbamazepine, and theophylline. Dosages of these drugs may need to be reduced.

Preparations, Dosage, and Administration. Clarithromycin is available in IR tablets (250 and 500 mg), sold as Biaxin; ER tablets (500 mg), sold as Biaxin XL; and granules for oral suspension (25 and 50 mg/mL), sold as Biaxin. With the IR tablets and granules, the recommended dosage is 250 or 500 mg every 12 hours for 7 to 14 days; the exact dosage size and duration depend on the infection being treated. With the ER tablets, the recommended dosage is 500 mg once a day for 7 to 14 days. The IR tablets and granules may be taken without regard to meals. The ER tablets should be taken with food.

Azithromycin

Actions and Therapeutic Uses. Like erythromycin, azithromycin [Zithromax, Zmax] binds the 50S subunit of bacterial ribosomes, causing inhibition of protein synthesis. The drug is used for respiratory tract infections, cholera, chancroid, otitis media, uncomplicated infections of the skin and skin structures, disseminated *M. avium* complex disease, and infections caused by *Chlamydia trachomatis*, for which it is a drug of choice. It may also be used as a substitute for penicillin G in penicillin-allergic patients.

Pharmacokinetics. Absorption of azithromycin is increased by food, and hence dosing may be done with meals. Following absorption, azithromycin is widely distributed to tissues and becomes concentrated in cells. Elimination is via the bile, as metabolites and parent drug.

Adverse Effects and Interactions. Like clarithromycin, azithromycin is well tolerated and does not produce the intense nausea seen with erythromycin. The most common reactions are diarrhea (5%), and nausea and abdominal pain (3%). In one trial, only 0.7% of patients withdrew because of side effects. Aluminum- and magnesium-containing antacids reduce the rate (but not the extent) of absorption. In contrast to erythromycin and clarithromycin, azithromycin does not inhibit the metabolism of other drugs. However, there is concern that azithromycin may enhance the effects of warfarin (an anticoagulant), and may thereby pose a risk of bleeding. In patients taking both drugs, prothrombin time should be closely monitored, to ensure that anticoagulation remains at a safe level.

Preparations, Dosage, and Administration. Oral, Immediate Release. Azithromycin [Zithromax] is available in three IR oral formulations: tablets (250, 500, and 600 mg), a suspension (20 and 40 mg/mL), and a 1-gm packet for dissolution in 60 mL of water. The usual dosing schedule is 500 mg once on the first day, followed by 250 mg once daily on the follow-

ing 4 days. Dosing may be done with or without food, but not with aluminum- or magnesium-containing antacids.

Oral, Extended Release. Extended-release azithromycin [Zmax] is formulated as a powder composed of ER microspheres, designed to dissolve in the small intestine. The rationale is to reduce GI upset. The powder, sold in 2-gm, single-dose bottles, must be suspended in 60 mL of water before ingestion. Dosing is done just once a day.

Intravenous. Azithromycin [Zithromax] is supplied as powder (500 mg) to be reconstituted for IV infusion. The usual dosage is 500 mg infused slowly (over 60 minutes or more) on 2 or more days. Intravenous therapy is followed by oral therapy. A complete course of treatment takes 7 days.

OTHER BACTERIOSTATIC INHIBITORS OF PROTEIN SYNTHESIS

Clindamycin

Clindamycin [Cleocin, Dalacin C⁺, others] can promote severe *C. difficile*-associated diarrhea (CDAD), a condition that can be fatal. Because of the risk of CDAD, indications for clindamycin are limited. Currently, systemic use is indicated only for certain anaerobic infections located outside the central nervous system (CNS).

Mechanism of Action

Clindamycin binds to the 50S subunit of bacterial ribosomes and thereby inhibits protein synthesis. The site at which clindamycin binds overlaps the binding sites for erythromycin and chloramphenicol. As a result, these agents may antagonize each other's effects. Accordingly, there are no indications for concurrent use of clindamycin with these other antibiotics.

Antimicrobial Spectrum

Clindamycin is active against most anaerobic bacteria (gram positive and gram negative) and most gram-positive aerobes. Gram-negative aerobes are generally resistant. Susceptible anaerobes include *Bacteroides fragilis*, *Fusobacterium*, *Clostridium perfringens*, and anaerobic streptococci. Clindamycin is usually bacteriostatic. However, it can be bactericidal if the target organism is especially sensitive. Resistance can be a significant problem with *B. fragilis*.

Therapeutic Use

Because of its efficacy against gram-positive cocci, clindamycin has been used widely as an alternative to penicillin. The drug is employed primarily for anaerobic infections outside the CNS (it doesn't cross the blood-brain barrier). Clindamycin is the drug of choice for severe group A streptococcal infection and for gas gangrene (an infection caused by *C. perfringens*), owing to its ability to rapidly suppress synthesis of bacterial toxins. In addition, clindamycin is a preferred drug for abdominal and pelvic infections caused by *B. fragilis*.

Pharmacokinetics

Absorption and Distribution. Clindamycin may be administered orally, IM, or IV. Absorption from the GI tract is nearly complete and not affected by food. The drug is widely distributed to most body fluids and tissues, including synovial fluid and bone. However, penetration to the CSF is poor.

Elimination. Clindamycin undergoes hepatic metabolism to active and inactive products, which are later excreted in the urine and bile. Only 10% of the drug is eliminated unchanged by the kidneys. The half-life is approximately 3 hours. In patients with substantial reductions in liver function or kidney function, the half-life increases slightly, but adjustments in dosage are not needed. However, in patients with combined hepatic and renal disease, the half-life increases significantly, and hence the drug may accumulate to toxic levels if dosage is not reduced.

Adverse Effects

Clostridium difficile-associated Diarrhea. *C. difficile*-associated diarrhea (CDAD), formerly known as *antibiotic-associated pseudomembranous colitis* (AAPMC), is the most severe toxicity of clindamycin. The cause is suprainfection of the bowel with *C. difficile*, an anaerobic gram-positive bacillus. CDAD is characterized by profuse, watery diarrhea (10 to 20 watery stools per day), abdominal pain, fever, and leukocytosis. Stools often contain mucus and blood. Symptoms usually begin during the first week of treatment, but may develop as long as 4 to 6 weeks after clindamycin withdrawal. Left untreated, the condition can be fatal. CDAD occurs with parenteral and oral therapy. Because of the risk of CDAD, patients should be instructed to report significant diarrhea (more than five watery stools per day). If suprainfection with *C. difficile* is diagnosed, clindamycin should be discontinued and the patient given oral vancomycin or metronidazole, which are drugs of choice for eliminating *C. difficile* from the bowel. Diarrhea usually ceases 3 to 5 days after starting vancomycin. Vigorous replacement therapy with fluids and electrolytes is usually indicated. Drugs that decrease bowel motility (eg, opioids, anticholinergics) may worsen symptoms and should not be used. CDAD is discussed further in Box 85-1, Chapter 85.

Other Adverse Effects. Diarrhea (unrelated to CDAD) is relatively common. Hypersensitivity reactions (especially rashes) occur frequently. Hepatotoxicity and blood dyscrasias (agranulocytosis, leukopenia, thrombocytopenia) develop rarely. Rapid IV administration can cause electrocardiographic changes, hypotension, and cardiac arrest.

Preparations, Dosage, and Administration

Preparations. Clindamycin is available as *clindamycin hydrochloride* and *clindamycin palmitate* for oral dosing, and as *clindamycin phosphate* for IM, IV, or topical (vaginal) dosing. Clindamycin hydrochloride [Cleocin] is supplied in capsules (75, 150, and 300 mg). Clindamycin palmitate [Cleocin Pediatric] is supplied in flavored granules, which are reconstituted with fluid to make an oral solution containing 15 mg of clindamycin per milliliter. Clindamycin phosphate is supplied in concentrated solution (150 mg/mL) and dilute solution (6, 12, and 18 mg/mL) sold as Cleocin Phosphate for parenteral therapy, and in a 2% cream [Cleocin, Clindesse, ClindaMax] and 100-mg suppositories [Cleocin] for intravaginal dosing.

Oral Dosage and Administration. For *clindamycin hydrochloride*, the adult dosage range is 150 to 450 mg every 6 hours; the pediatric dosage range is 8 to 20 mg/kg daily in three or four divided doses. For *clindamycin palmitate*, adult and pediatric dosages range from 8 to 25 mg/kg/day administered in three or four divided doses. Oral clindamycin should be taken with a full glass of water. The drug may be administered with meals.

Parenteral Dosage and Administration. For parenteral (IM or IV) therapy, *clindamycin phosphate* is employed. Intramuscular and IV dosages are the same. The usual adult dosage is 0.6 to 3.6 gm/day administered in three or four divided doses. The usual pediatric dosage is 15 to 40 mg/kg/day in three or four divided doses.

Intravaginal Administration. Intravaginal clindamycin (suppositories or cream) is indicated for bacterial vaginosis. The suppositories are approved only for nonpregnant women; the cream can be used by pregnant women, but only during the second and third trimesters. Women using clindamycin cream should apply 1 applicatorful (5 gm containing 100 mg clindamycin) nightly for 7 days (if pregnant) or for 3 to 7 days (if nonpregnant). Women using clindamycin suppositories should insert 1 suppository (100 mg) on three consecutive evenings.

Linezolid

Linezolid [Zyvox] is a first-in-class *oxazolidinone* antibiotic. The drug is important because it has activity against multidrug-resistant gram-positive pathogens, including vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staph. aureus* (MRSA). For treatment of MRSA, the drug is at least as

effective as vancomycin. To delay the emergence of resistance, linezolid should generally be reserved for infections caused by VRE or MRSA, even though it has additional approved uses.

Mechanism, Resistance, and Antimicrobial Spectrum

Linezolid is a bacteriostatic inhibitor of protein synthesis. The drug binds to the 23S portion of the 50S ribosomal subunit, and thereby blocks formation of the initiation complex. No other antibiotic works quite this way. As a result, cross-resistance with other agents is unlikely. In clinical trials, development of resistance to linezolid was rare, and occurred only in association with prolonged treatment of VRE infections and the presence of a prosthetic implant or undrained abscess. In real practice, resistance has been reported in association with extensive linezolid use.

Linezolid is active primarily against aerobic and facultative gram-positive bacteria. Susceptible pathogens include *Enterococcus faecium* (vancomycin-sensitive and vancomycin-resistant strains), *Enterococcus faecalis* (vancomycin-resistant strains), *Staph. aureus* (methicillin-sensitive and methicillin-resistant strains), *Staphylococcus epidermidis* (including methicillin-resistant strains), and *Strep. pneumoniae* (penicillin-sensitive and penicillin-resistant strains). Linezolid is not active against gram-negative bacteria, which readily export the drug.

Therapeutic Use

Linezolid has five approved indications:

- Infections cause by VRE
- Nosocomial pneumonia caused by *Staph. aureus* (methicillin-susceptible and methicillin-resistant strains) or *Streptococcus pneumoniae* (penicillin-susceptible strains only)
- Community-acquired pneumonia caused by *Strep. pneumoniae* (penicillin-susceptible strains only)
- Complicated skin and skin structure infections caused by *Staph. aureus* (methicillin-susceptible and methicillin-resistant strains), *Strep. pyogenes*, or *Strep. agalactiae*
- Uncomplicated skin and skin structure infections caused by *Staph. aureus* (methicillin-susceptible strains only) or *Strep. pyogenes*

As noted above, to delay the emergence of resistance, linezolid should generally be reserved for infections caused by VRE or MRSA, even though it has other approved uses.

Pharmacokinetics

Oral linezolid is rapidly and completely absorbed. Food decreases the rate of absorption but not the extent. Linezolid is eliminated by hepatic metabolism and renal excretion. Its half-life is about 5 hours.

Adverse Effects

Linezolid is generally well tolerated. The most common side effects are diarrhea (5.3%), nausea (3.5%), and headache (2.7%). Linezolid oral suspension contains phenylalanine, and hence must not be used by patients with phenylketonuria.

Linezolid can cause reversible *myelosuppression*, manifesting as anemia, leukopenia, thrombocytopenia, or even pancytopenia. Risk is related to duration of use. Complete blood counts should be done weekly. Special caution is needed in patients with pre-existing myelosuppression, those

taking other myelosuppressive drugs, and those receiving linezolid for more than 2 weeks. If existing myelosuppression worsens or new myelosuppression develops, discontinuing linezolid should be considered.

Rarely, prolonged therapy has been associated with *neuropathy*. Patients taking the drug for more than 5 months have developed reversible optic neuropathy and irreversible peripheral neuropathy.

Drug Interactions

Linezolid is a weak inhibitor of monoamine oxidase (MAO), and hence poses a risk of hypertensive crisis. As discussed in Chapter 32, MAO inhibitors can cause severe hypertension if combined with *indirect-acting sympathomimetics* (eg, ephedrine, pseudoephedrine, methylphenidate, cocaine) or with foods that contain large amounts of *tyramine*. Accordingly, patients using linezolid should be warned to avoid these agents.

Combining linezolid with a *selective serotonin reuptake inhibitor* (SSRI) can increase the risk of serotonin syndrome (because inhibition of MAO increases the serotonin content of CNS neurons). Deaths have been reported. Patients using SSRIs (eg, paroxetine [Paxil, Paxeva], duloxetine [Cymbalta]) should not take linezolid.

Preparations, Dosage, and Administration

Linezolid is available in three formulations: (1) 600-mg *tablets*, (2) a powder for reconstitution to a 20-mg/mL *oral suspension*, and (3) a 2-mg/mL *intravenous solution* supplied in single-use bags (100 and 300 mL). Oral linezolid can be taken with or without food. Intravenous linezolid is infused over 30 to 120 minutes, and should not be combined with additives or other drugs. Adult dosages for specific infections are as follows:

- *VRE infections*—600 mg PO or IV every 12 hours for 14 to 28 days
- *Pneumonia (nosocomial or community acquired)*—600 mg PO or IV every 12 hours for 10 to 14 days
- *Complicated skin and skin structure infections (including MRSA infections)*—same as pneumonia
- *Uncomplicated skin and skin structure infections*—400 mg PO every 12 hours for 10 to 14 days

Telithromycin

Therapeutic Use. Telithromycin [Ketek], a close relative of erythromycin and other macrolides, is a first-in-class *ketolide* antibiotic. Antibacterial activity is similar to that of the macrolides, with one important exception: telithromycin has significant activity against strains of *Strep. pneumoniae* that are penicillin and macrolide resistant. The Food and Drug Administration (FDA) initially approved the drug for three indications, but has since withdrawn approval for two of them. Currently, the only approved indication is community-acquired pneumonia (CAP) caused by *Strep. pneumoniae* (including multidrug-resistant isolates), *H. influenzae*, *M. catarrhalis*, *Chlamydia pneumoniae*, or *Mycoplasma pneumoniae*.

Unfortunately, although telithromycin is an effective antibiotic, it carries a significant risk of adverse effects (especially severe liver injury) and drug interactions. As a result, it should be reserved for infections caused by multidrug-resistant *Strep. pneumoniae* (MDRSP) that cannot be treated with other agents.

Mechanism of Action. Like the macrolides, telithromycin binds to the 50S ribosomal subunit, and thereby inhibits bacterial protein synthesis. However, in contrast to the macrolides, telithromycin has properties that give it activity against bacteria that are macrolide resistant. Among respiratory tract pathogens, macrolide resistance occurs by two mechanisms: (1) removal of the macrolide with export pumps and (2) modification (by methylation) of the bacterial ribosome in a way that decreases macrolide binding. Because telithromycin differs in structure from the macrolides, the drug is less subject to removal by bacterial export pumps, and can bind strongly to bacterial ribosomes even if they are methylated.

Pharmacokinetics. Telithromycin undergoes rapid but incomplete absorption following oral administration. Bioavailability is about 57%, both in the presence and absence of food. Once in the blood, telithromycin becomes concentrated in white cells. About 70% of absorbed drug is metabolized in

the liver—half by CYP3A4 (the 3A4 isozyme of cytochrome P450) and half by P450-independent pathways. Excretion of parent drug and metabolites occurs in the urine and feces. The half-life is 10 hours.

Adverse Effects. Although telithromycin is generally well tolerated, the drug can cause serious adverse effects, especially injury to the liver (see below). As a result, telithromycin should be used only when absolutely necessary.

In clinical trials, most adverse effects were mild to moderate. Furthermore, the rate of discontinuation because of adverse effects was nearly the same as with a comparator antibiotic (4.4% vs. 4.3%). The most common adverse effects are *gastrointestinal disturbances*, including diarrhea (10% vs. 8% with a comparator antibiotic), nausea (7% vs. 4.1%), vomiting (2.4% vs. 1.4%), and loose stools (2.1% vs. 1.4%).

Telithromycin can cause *severe liver injury* (fulminant hepatitis, hepatic necrosis) and acute hepatic failure. Liver transplants have been required and deaths have occurred. Liver damage can develop early in telithromycin treatment and can progress rapidly. Patients should be monitored for signs of hepatitis (eg, jaundice, fatigue, abdominal pain, dark urine). If liver injury is diagnosed, telithromycin should be discontinued and never used again.

In patients with *myasthenia gravis*, telithromycin can make muscle weakness much worse, sometimes within hours of taking the first dose. Some patients have died from respiratory failure. Accordingly, telithromycin is contraindicated for patients with this disorder.

About 1% of patients experience *visual disturbances*, including blurred vision, double vision, and difficulty focusing. Females and patients under 40 years old are at highest risk. These disturbances usually develop after the first or second dose, and can persist for several hours. Symptoms may or may not recur with subsequent doses.

Like erythromycin and clarithromycin, telithromycin can *prolong the QT interval*, and hence may pose a risk of adverse cardiac events. However, QT prolongation was not observed in clinical trials, and there have been no reports of torsades de pointes or other ventricular dysrhythmias. Nonetheless, telithromycin should be avoided by patients with congenital QT prolongation and by those taking class IA or class III antidysrhythmics.

Drug Interactions. Telithromycin is both a substrate for and inhibitor of CYP3A4, and hence has the potential for numerous drug interactions.

Because telithromycin is a substrate for CYP3A4, agents that inhibit the enzyme (eg, itraconazole, ketoconazole) can elevate telithromycin levels. Conversely, agents that induce CYP3A4 (eg, rifampin, phenytoin, carbamazepine, phenobarbital) can decrease telithromycin levels, possibly resulting in therapeutic failure.

By inhibiting CYP3A4, telithromycin can increase levels of many drugs that are substrates for the enzyme, thereby posing a risk of toxicity. Two such substrates—cisapride [Propulsid] and pimozide [Orap]—are contraindicated for use with telithromycin. Similarly, use of three statin-type cholesterol-lowering agents—simvastatin [Zocor], lovastatin [Mevacor], and atorvastatin [Lipitor]—should be interrupted during telithromycin therapy. However, use of two other statins—pravastatin [Pravachol] and fluvastatin [Lescol]—may continue. Telithromycin is likely to increase levels of ergotamine and dihydroergotamine (ergot alkaloids used for migraine), and may thereby cause severe peripheral vasospasm. Accordingly, use of these alkaloids must be avoided. Telithromycin increases peak levels of digoxin [Lanoxin] by 73%. Accordingly, digoxin levels and side effects should be monitored closely. Other CYP3A4 substrates whose levels can be increased include midazolam [Versed], ritonavir [Norvir], sirolimus [Rapamune], and tacrolimus [Prograf]. Finally, telithromycin can increase levels of metoprolol [Lopressor], a substrate for CYP2D6. Patients with heart failure who are using metoprolol should be monitored closely.

Preparations, Dosage, and Administration. Telithromycin [Ketek] is available in 300- and 400-mg tablets for oral dosing, with or without food. The dosage for CAP is 800 mg once a day for 7 to 10 days. Dosage reduction may be needed for patients with severe renal impairment, but not for patients with mild to moderate renal impairment or those with hepatic impairment.

Dalfopristin/Quinupristin

Dalfopristin and quinupristin are first-in-class *streptogramin* antibiotics. The two drugs are available in a fixed-dose combination (70 parts dalfopristin 30 parts quinupristin) under the trade name *Synercid*.

Mechanism of Action. Dalfopristin and quinupristin inhibit bacterial protein synthesis. When used separately, dalfopristin and quinupristin are bacteriostatic. However, in combination they are bactericidal.

Therapeutic Use. The principal indication for dalfopristin/quinupristin is vancomycin-resistant *E. faecium*. (The drugs are not active against *E. faecalis*.) To delay emergence of resistance, dalfopristin/quinupristin should be reserved for infections that have not responded to vancomycin. Other indications

include MRSA, methicillin-resistant *Staph. epidermidis*, and drug-resistant *Strep. pneumoniae*. Dalfopristin/quinupristin is safe for patients who are allergic to penicillins and cephalosporins.

Adverse Effects. *Hepatotoxicity* is the major concern. Blood should be tested for liver enzymes and bilirubin at least twice during the first week of therapy and weekly thereafter. About 50% of patients develop infusion-related thrombophlebitis. When this occurs, administration must be switched to a central venous line. Other adverse effects include joint and muscle pain, rash, pruritus, vomiting, and diarrhea.

Drug Interactions. Dalfopristin and quinupristin inhibit hepatic drug-metabolizing enzymes, specifically CYP3A4. Accordingly, the combination is likely to inhibit the metabolism of many other drugs, including cyclosporine, tacrolimus, and cisapride.

Preparations, Dosage, and Administration. Dalfopristin/quinupristin [Synercid] is supplied as a powder in 500-mg vials to be reconstituted for IV administration. The usual dosage is 7.5 mg/kg infused slowly (over 1 hour) 2 or 3 times a day. To minimize venous irritation, flush the vein with 0.5% dextrose after the infusion. If irritation occurs despite flushing, the drug should be infused through a central venous line. Because dalfopristin and quinupristin are eliminated by hepatic metabolism, dosage should be reduced in patients with liver impairment.

Chloramphenicol

Chloramphenicol (formerly available as Chloromycetin) is a broad-spectrum antibiotic with the potential for causing *fatal aplastic anemia* and other blood dyscrasias. Because of the risk of severe blood disorders, use of chloramphenicol is limited to serious infections for which less toxic drugs are not effective.

Mechanism of Action

Chloramphenicol inhibits bacterial protein synthesis. The drug binds reversibly to the 50S subunit of bacterial ribosomes and thereby prevents addition of new amino acids to the growing peptide chain. Chloramphenicol is usually bacteriostatic, but can be bactericidal against highly susceptible organisms or when its concentration is high.

Since most protein synthesis in mammalian cells is carried out in the cytoplasm employing ribosomes that are insensitive to chloramphenicol, toxic effects are restricted largely to bacteria. However, because the ribosomes of mammalian *mitochondria* are very similar to those of bacteria, chloramphenicol can decrease mitochondrial protein synthesis in the host. This action may underlie certain adverse effects (eg, dose-dependent bone marrow suppression, gray syndrome in infants).

Antimicrobial Spectrum

Chloramphenicol is active against a broad spectrum of bacteria. A large number of gram-positive and gram-negative aerobic organisms are sensitive. Among these are *Salmonella typhi*, *H. influenzae*, *Neisseria meningitidis*, and *Strep. pneumoniae*. Most anaerobic bacteria (eg, *B. fragilis*) are also susceptible. In addition, chloramphenicol is active against rickettsiae, chlamydiae, mycoplasmas, and treponemes.

Resistance

Resistance among gram-negative bacteria results from acquisition of an R factor that codes for acetyltransferase, an enzyme that inactivates chloramphenicol. This same R factor also codes for resistance to tetracyclines, and frequently confers resistance to penicillins too.

Pharmacokinetics

Chloramphenicol is available as an inactive prodrug—*chloramphenicol sodium succinate*—for IV dosing. Conversion to the active form (free chloramphenicol) is variable and incomplete. Production of active drug is especially erratic in newborns, infants, and young children.

Chloramphenicol is highly lipid soluble and widely distributed to body tissues and fluids. Therapeutic concentrations are readily achieved in the CSF, and drug levels in the brain may be as much as 9 times those in plasma. As a result, chloramphenicol is of special value for treating meningitis and brain abscesses caused by susceptible bacteria. The drug crosses the placenta and is secreted in breast milk.

Chloramphenicol is eliminated primarily by hepatic metabolism. Inactive metabolites are excreted in the urine. In patients with liver impairment, the half-life is prolonged and accumulation can occur. Accordingly, dosage should be reduced. Because the kidneys serve only to excrete inactive metabolites, there is no need for dosage reduction in patients with renal impairment. In neonates, hepatic metabolism is not fully developed and hence the half-life of chloramphenicol is prolonged.

Because chloramphenicol has a low therapeutic index, and because serum levels of the drug can vary substantially among patients, monitoring drug levels is frequently indicated. Monitoring is especially important for neonates, infants, and young children, because chloramphenicol levels in these patients can be especially variable. For most infections, effective therapy is achieved with peak serum drug levels of 10 to 20 mcg/mL and trough levels of 5 to 10 mcg/mL. The risk of dose-dependent bone marrow suppression is significantly increased when peak levels rise above 25 mcg/mL.

Therapeutic Use

When first introduced, chloramphenicol was employed widely. However, use dropped sharply when its ability to cause fatal aplastic anemia became evident. Today, chloramphenicol is indicated only for life-threatening infections for which safer drugs are ineffective or contraindicated.

Adverse Effects

The most important adverse effects are gray syndrome and toxicities related to the blood. Because of these toxicities, indications for chloramphenicol are limited.

Gray Syndrome. Gray syndrome, originally known as gray baby syndrome, is a potentially fatal toxicity observed most commonly in newborns. Initial symptoms are vomiting, abdominal distention, cyanosis, and gray discoloration of the skin. These may be followed by vasomotor collapse and death. The syndrome results from accumulation of chloramphenicol to high levels. Newborns are especially vulnerable to gray syndrome because (1) hepatic function is insufficient to detoxify chloramphenicol and (2) renal function is insufficient to excrete active drug. Although gray syndrome is usually observed in neonates, it can occur in older children and adults if dosage is excessive. If drug use is discontinued immediately when early symptoms appear, the syndrome is usually reversible. The risk of gray syndrome in infants can be reduced by using low doses and by monitoring chloramphenicol levels in serum.

Reversible Bone Marrow Suppression. Chloramphenicol can produce dose-related suppression of the bone marrow, resulting in anemia, and sometimes leukopenia and thrombocytopenia. Marrow suppression occurs most commonly when plasma drug levels exceed 25 mcg/mL. The cause of bone marrow suppression appears to be inhibition of protein synthesis in host mitochondria. To promote early detection of bone marrow suppression, complete blood counts should be performed prior to therapy and every 2 days thereafter. Advise patients to notify the prescriber if signs of blood disorders develop (eg, sore throat, fever, unusual bleeding or bruising). Chloramphenicol should be withdrawn if evidence of bone marrow suppression is detected. Suppression of bone marrow usually reverses within 1 to 3 weeks following drug withdrawal. The anemia associated with toxic bone marrow suppression is not related to aplastic anemia (discussed next).

Aplastic Anemia. Rarely, chloramphenicol produces aplastic anemia, a condition characterized by pancytopenia and bone marrow aplasia. The reaction is usually fatal. Aplastic anemia develops in 1 of 35,000 patients, and is not related to dosage. As a rule, the reaction develops weeks or months after termination of treatment. Aplastic anemia can occur with oral, IV, or even topical (ophthalmic) use of the drug. The mechanism underlying aplastic anemia has not been determined, but toxicity may result from a genetic predisposition. Unfortunately, aplastic anemia cannot be predicted by monitoring the blood.

Other Adverse Effects. Gastrointestinal effects (vomiting, diarrhea, glossitis) occur occasionally. Herxheimer reactions have occurred during treatment of typhoid fever. Neurologic effects (peripheral neuropathy, optic neuritis, confusion, delirium) develop rarely, usually in association with prolonged treatment. Other rare toxicities include suprainfection of the bowel, allergic reactions, and fever.

Drug Interactions

Chloramphenicol can inhibit hepatic drug-metabolizing enzymes, thereby prolonging the half-lives of other drugs. Agents that may be affected include *phenytoin* (an anticonvulsant), *warfarin* (an anticoagulant), and two oral hypoglycemics: *tolbutamide* and *chlorpropamide*. If any of these drugs are taken concurrently with chloramphenicol, their dosages should be reduced.

Preparations, Dosage, and Administration

Chloramphenicol sodium succinate is available as a powder for reconstitution to a 100-mg/mL solution. Administration is by slow IV injection, over 1 minute or longer. As a rule, the dosing objective is to produce peak chloramphenicol plasma levels that range between 10 and 20 mcg/mL. The usual IV dosage for adults and children is 12.5 to 25 mg/kg every 6 hours. For infants 7 days old or younger, the usual dosage is 25 mg/kg once a day. For

infants more than 7 days old, the recommended dosage is 25 mg/kg every 12 hours. Dosage should be reduced for patients with liver dysfunction.

Tigecycline

Tigecycline [Tygacil], approved in 2005, is a first-in-class *glycylcycline* antibiotic. The drug is a tetracycline derivative designed to overcome drug resistance. Tigecycline is active against a broad spectrum of bacteria, including many drug-resistant strains. Unfortunately, tigecycline is associated with an increased mortality (see below), and hence using another antibiotic drug should be considered.

Mechanism of Action and Resistance. Tigecycline is a *bacteriostatic* inhibitor of protein synthesis. Like the tetracyclines, tigecycline binds to the 30S ribosomal subunit and thereby inhibits binding of transfer RNA to the messenger RNA-ribosome complex. As a result, addition of amino acids to the growing peptide chain is stopped.

Bacterial resistance to tigecycline is much less than with the tetracyclines. Why? First, bacteria are unable to extrude tigecycline. Second, bacteria cannot block binding of tigecycline to ribosomes.

Antimicrobial Spectrum. Tigecycline is a broad-spectrum antibiotic with activity against gram-positive and gram-negative bacteria, including many strains that are drug resistant. Susceptible gram-positive organisms include *Staph. aureus* (vancomycin sensitive, methicillin sensitive, and methicillin resistant), vancomycin-resistant enterococci, penicillin-resistant *Strep. pneumoniae*, *C. perfringens*, and *C. difficile*. Susceptible gram-negative organisms include *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *B. fragilis*, *Escherichia coli*, and *Enterobacter* species. Of note, tigecycline is not active against *Pseudomonas aeruginosa* or *Proteus* species.

Therapeutic Use. Tigecycline was originally approved only for complicated intra-abdominal infections and complicated skin infections that need broad empiric coverage, and was later approved for community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates). To delay emergence of resistance, tigecycline should be used only when other drugs are considered likely to fail.

Pharmacokinetics. Tigecycline is administered IV and undergoes moderate binding to plasma proteins (about 80%). Very little of the drug is metabolized. Excretion occurs in the bile (59%) and urine (33%), mainly as unchanged drug. The plasma half-life is 42 hours.

Adverse Effects. Tigecycline is a tetracycline analog, and hence may have adverse effects like those of the tetracyclines. In clinical trials, the most common reactions were nausea (30%) and vomiting (20%). Like the tetracyclines, tigecycline may pose a risk of pseudotumor cerebri (a benign elevation of intracranial pressure) and may increase sensitivity to ultraviolet light, thereby increasing the risk of sunburn. Tigecycline may stain developing teeth, and hence should not be used by children under 8 years old. Being a broad-spectrum antibiotic, tigecycline may pose a risk of suprainfection, including *Clostridium difficile*-associated diarrhea. Acute pancreatitis, including fatal cases, has occurred during tigecycline treatment. If pancreatitis is suspected, withdrawal of the drug should be considered. Tigecycline is in FDA Pregnancy Risk Category D, and hence should be avoided by pregnant women.

Among patients treated for severe infections, mortality is higher for those receiving tigecycline than for those receiving other antibiotics. Why? Probably because tigecycline is less effective than the options. Accordingly, the FDA recommends considering an alternative to tigecycline for patients with severe infections.

Drug Interactions. Drug interactions appear minimal. Tigecycline does not affect the cytochrome P450 system, and hence will not alter the ki-

netics of drugs metabolized by P450. Similarly, because tigecycline undergoes very little metabolism, drugs that alter P450 activity should not alter the kinetics of tigecycline. Tigecycline can delay the clearance of warfarin (an anticoagulant). Accordingly, if the drugs are used concurrently, coagulation status should be monitored.

Preparations, Dosage, and Administration. Tigecycline [Tygacil] is supplied as a lyophilized powder in single-dose 50-mg vials, to be reconstituted for IV infusion. The powder should be dissolved in 5.3 mL of sodium chloride injection or 5% dextrose injection, to produce a 10-mg/mL solution. This concentrated solution is then added to a 100-mL IV bag for infusion over 30 to 60 minutes. For adults, treatment consists of a 100-mg initial dose followed by 50 mg every 12 hours for 5 to 14 days. No adjustment in dosage is needed for patients with renal impairment or with mild to moderate hepatic impairment. For patients with severe hepatic impairment, the initial dose is unchanged, but maintenance dosing should be reduced to 25 mg every 12 hours.

Retapamulin and Mupirocin

Retapamulin and mupirocin are topical antibiotics. Both drugs are indicated for impetigo; mupirocin is also indicated for clearing the nostrils of methicillin-resistant *Staph. aureus* (MRSA). For impetigo therapy, retapamulin is more convenient than mupirocin, but generic mupirocin is cheaper.

Retapamulin

Retapamulin [Altobax] is a first-in-class *pleuromutalin* antibiotic. The drug binds to the 50S bacterial ribosomal subunit, and thereby inhibits protein synthesis. However, the 50S binding site is different from that of other antibiotics, and hence cross-resistance with other antibiotics is not expected. Retapamulin is bacteriostatic at therapeutic concentrations. At this time, the drug is approved only for topical therapy of impetigo caused by *Strep. pyogenes* or methicillin-susceptible *Staph. aureus*. However, *in vitro* data indicate that the drug may be effective against methicillin- and mupirocin-resistant *Staph. aureus*. Significant resistance among *Staph. aureus* has not been observed, and is considered unlikely. The principal adverse effect is local irritation, which only 2% of users experience. Systemic toxicity does not occur, owing to minimal absorption from topical sites. Retapamulin is available as a 1% ointment in 5-, 10-, and 15-gm tubes. Application is done twice daily for 5 days.

Mupirocin

Mupirocin [Bactroban, Bactroban Nasal] is a topical antibiotic with two indications: (1) impetigo caused by *Staph. aureus*, *Strep. pyogenes*, or beta-hemolytic streptococci; and (2) elimination of nasal colonization by MRSA. Mupirocin has a unique mechanism: The drug binds with bacterial isoleucyl transfer-RNA synthetase, and thereby blocks protein synthesis. The drug is bactericidal at therapeutic concentrations. Resistance has developed owing to production of a modified form of isoleucyl transfer-RNA synthetase, but cross-resistance with other antibiotics has not been reported.

Adverse effects depend on the application site. With application to the skin, local irritation can occur, but systemic effects occur rarely, if at all. (Absorption from intact skin is minimal, and any absorbed drug undergoes rapid conversion to inactive products.) With intranasal application, the most common side effects are headache (9%), rhinitis (6%), upper respiratory congestion (5%), and pharyngitis (4%).

Mupirocin is available as a 2% cream and a 2% ointment. For impetigo, the cream or ointment is applied 3 times a day for 10 to 12 days. To eradicate MRSA nasal colonization, the ointment is applied twice daily for 5 days.

KEY POINTS

- Tetracyclines are broad-spectrum, bacteriostatic antibiotics that inhibit bacterial protein synthesis.
- Tetracyclines are first-choice drugs for just a few infections, including those caused by *Chlamydia trachomatis*, rickettsia (eg, Rocky Mountain spotted fever), *H. pylori* (ie, peptic ulcer disease), *B. anthracis* (anthrax), *Borrelia burgdorferi* (Lyme disease), and *M. pneumoniae*.
- Tetracyclines form insoluble chelates with calcium, iron, magnesium, aluminum, and zinc. Accordingly, they must not be administered with calcium supplements, milk products, iron supplements, magnesium-containing laxatives, and most antacids.
- Three oral tetracyclines—tetracycline, demeclocycline, and doxycycline—should be administered on an

empty stomach. Minocycline can be administered with meals.

- Tetracycline and demeclocycline should not be given to patients with renal failure.
- Tetracyclines can stain developing teeth, and therefore should not be given to pregnant women or children under 8 years old.
- Because they are broad-spectrum antibiotics, tetracyclines can cause suprainfections, especially *C. difficile*-associated diarrhea (CDAD) and overgrowth of the mouth, pharynx, vagina, or bowel with *Candida albicans*.
- High doses of tetracyclines can cause severe liver damage, especially in pregnant and postpartum women who have renal impairment.
- Erythromycin, the prototype of the macrolide antibiotics, is a bacteriostatic drug that inhibits bacterial protein synthesis.

- Erythromycin has an antimicrobial spectrum similar to that of penicillin G, and hence can be used in place of penicillin G in patients with penicillin allergy.
- Erythromycin is generally very safe. However, combined use of erythromycin with inhibitors of CYP3A4 increases the risk of QT prolongation and sudden cardiac death.
- Clindamycin is used primarily as an alternative to penicillin for serious gram-positive anaerobic infections.
- Clindamycin causes a high incidence of CDAD.
- Linezolid is important because it can suppress multidrug-resistant gram-positive pathogens, including vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staph. aureus* (MRSA).

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Summary of Major Nursing Implications*

TETRACYCLINES

Demeclocycline
Doxycycline
Minocycline
Tetracycline

Except where stated otherwise, the implications summarized below pertain to all tetracyclines.

Preadministration Assessment

Therapeutic Goal

Treatment of tetracycline-sensitive infections, acne, and periodontal disease.

Identifying High-Risk Patients

Tetracyclines are *contraindicated* in pregnant women and children under 8 years of age.

Tetracycline and *demeclocycline* must be used with great *caution* in patients with significant renal impairment.

Implementation: Administration

Routes

Systemic. All tetracyclines are used systemically. Specific routes for individual agents are shown in Table 86-2.

Topical. *Doxycycline* and *minocycline* are used topically to treat periodontal disease.

Administration

Oral. Advise patients to take most oral tetracyclines on an empty stomach (1 hour before meals or 2 hours after) and with a full glass of water. *Minocycline* may be taken with food.

Instruct patients to allow at least 2 hours between ingestion of tetracyclines and these chelators: milk products, calcium supplements, iron supplements, magnesium-containing laxatives, and most antacids.

Instruct patients to complete the prescribed course of treatment, even though symptoms may abate before the full course is over.

Parenteral. *Intravenous* administration is performed only when oral administration is ineffective or cannot be tolerated. *Intramuscular* injection is painful and used rarely.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Gastrointestinal Irritation. Inform patients that GI distress (epigastric burning, cramps, nausea, vomiting, diarrhea) can be reduced by taking tetracyclines with meals, although absorption may be reduced.

Effects on Teeth. Tetracyclines can discolor developing teeth. To prevent this, avoid tetracyclines in pregnant women and children under 8 years of age.

Suprainfection. Tetracyclines can promote bacterial suprainfection of the bowel, resulting in severe diarrhea. **Instruct patients to notify the prescriber if significant diarrhea develops.** If suprainfection is diagnosed, discontinue tetracyclines immediately. Treatment of *C. difficile*-associated diarrhea (CDAD) consists of oral vancomycin or metronidazole, plus fluid and electrolyte replacement.

Fungal overgrowth may occur in the mouth, pharynx, vagina, and bowel. **Inform patients about symptoms of fungal infection (vaginal or anal itching; inflammatory lesions of the anogenital region; black, furry appearance of the tongue), and advise them to notify the prescriber if these occur.** Suprainfection caused by *Candida* can be managed by discontinuing the tetracycline or by giving an antifungal drug.

Hepatotoxicity. Tetracyclines can cause fatty infiltration of the liver, resulting in jaundice and, rarely, massive liver failure. The risk of liver injury can be reduced by avoiding high-dose IV therapy and by withholding tetracyclines from pregnant and postpartum women who have kidney disease.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Renal Toxicity. Tetracyclines can exacerbate pre-existing renal impairment. *Tetracycline* and *demeclocycline* should not be used by patients with kidney disease.

Photosensitivity. Tetracyclines can increase the sensitivity of the skin to ultraviolet light, thereby increasing the risk of sunburn. Advise patients to avoid prolonged exposure to sunlight, wear protective clothing, and apply a sunscreen to exposed skin.

ERYTHROMYCIN

The implications summarized below apply to all forms of erythromycin, except where noted otherwise.

Preadministration Assessment

Therapeutic Goal

Erythromycin is indicated for legionnaires' disease, whooping cough, diphtheria, chancroid, chlamydial infections, and other infections caused by erythromycin-sensitive organisms. The drug is also used as a substitute for penicillin G in penicillin-allergic patients.

Identifying High-Risk Patients

All forms of erythromycin should be avoided by patients with QT prolongation and by those taking inhibitors of CYP3A4.

Implementation: Administration

Routes

Oral. Erythromycin base, erythromycin ethylsuccinate, and erythromycin stearate.

Intravenous. Erythromycin lactobionate.

Administration

Oral. Advise patients to take oral preparations on an empty stomach (1 hour before meals or 2 hours after) and with a full glass of water. However, if GI upset occurs, administration may be done with meals.

Inform patients using erythromycin ethylsuccinate and enteric-coated formulations of erythromycin base that they may take these drugs without regard to meals.

Instruct patients to complete the prescribed course of treatment, even though symptoms may abate before the full course is over.

Intravenous. Administer by slow infusion and in dilute solution to minimize thrombophlebitis.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Gastrointestinal Effects. Gastrointestinal disturbances (epigastric pain, nausea, vomiting, diarrhea) can be reduced by administering erythromycin with meals. Advise patients to notify the prescriber if GI reactions are severe or persistent.

QT Prolongation and Sudden Cardiac Death. High levels of erythromycin can prolong the QT interval, thereby posing a risk of a potentially fatal cardiac dysrhythmia. Avoid erythromycin in patients with pre-existing QT prolongation, and in those taking drugs that can increase erythromycin levels.

Minimizing Adverse Interactions

Erythromycin can increase the half-lives and plasma levels of several drugs. When erythromycin is combined with *theophylline*, *carbamazepine*, or *warfarin*, patients should be monitored closely for toxicity.

Erythromycin can antagonize the antibacterial actions of *clindamycin* and *chloramphenicol*. Concurrent use of erythromycin with these agents is not recommended.

Drugs that inhibit CYP3A4 (eg, verapamil, diltiazem, HIV protease inhibitors, azole antifungal drugs) can increase erythromycin levels, thereby posing a risk of QT prolongation and sudden cardiac death. People using these drugs should not use erythromycin.

CLINDAMYCIN

Preadministration Assessment

Therapeutic Goal

Treatment of anaerobic infections outside the CNS.

Implementation: Administration

Routes

Oral, IM, IV, intravaginal.

Administration

Instruct patients to take oral clindamycin with a full glass of water.

Instruct patients to complete the prescribed course of treatment, even though symptoms may abate before the full course is over.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Clostridium difficile-Associated Diarrhea. Clindamycin can promote CDAD, a potentially fatal suprainfection. Prominent symptoms are profuse watery diarrhea, abdominal pain, fever, and leukocytosis. Stools often contain mucus and blood. Instruct patients to report significant diarrhea (more than five watery stools per day). If CDAD is diagnosed, discontinue clindamycin. Treat with oral vancomycin or metronidazole and vigorous replacement of fluids and electrolytes. Drugs that decrease bowel motility (eg, opioids, anticholinergics) may worsen symptoms and should be avoided.

*Patient education information is highlighted as blue text.

Aminoglycosides: Bactericidal Inhibitors of Protein Synthesis

Basic Pharmacology of the Aminoglycosides Properties of Individual Aminoglycosides

Gentamicin

Tobramycin

Amikacin

Other Aminoglycosides

The aminoglycosides are narrow-spectrum antibiotics used primarily against aerobic gram-negative bacilli. These drugs disrupt protein synthesis, resulting in rapid bacterial death. The aminoglycosides can cause serious injury to the inner ear and kidney. Because of these toxicities, indications for these drugs are limited. All of the aminoglycosides carry multiple positive charges. As a result, they are not absorbed from the GI tract, and hence must be administered parenterally to treat systemic infections. In the United States, seven aminoglycosides are approved for clinical use. The agents employed most commonly are gentamicin, tobramycin, and amikacin.

BASIC PHARMACOLOGY OF THE AMINOGLYCOSIDES

Chemistry

The aminoglycosides are composed of two or more amino sugars connected by a glycoside linkage, hence the family name. At physiologic pH, these drugs are highly polar polycations (ie, they carry several positive charges), and therefore cannot readily cross membranes. As a result, aminoglycosides are not absorbed from the GI tract, do not enter the cerebrospinal fluid, and are rapidly excreted by the kidneys. Structural formulas for the three major aminoglycosides are shown in Figure 87-1.

Mechanism of Action

The aminoglycosides disrupt bacterial protein synthesis. As indicated in Figure 87-2, these drugs bind to the 30S ribosomal subunit, and thereby cause (1) inhibition of protein synthesis, (2) premature termination of protein synthesis, and (3) production of abnormal proteins (secondary to misreading of the genetic code).

The aminoglycosides are *bactericidal*. Cell kill is *concentration dependent*. Hence, the higher the concentration, the more rapidly the infection will clear. Of note, bactericidal activity persists for several hours *after* serum levels have dropped below the minimal bactericidal concentration, a phenomenon known as the *postantibiotic effect*.

Bacterial kill appears to result from production of abnormal proteins rather than from simple inhibition of protein synthesis. Studies suggest that abnormal proteins become inserted in the bacterial cell membrane, causing it to leak. The resultant loss of cell contents causes death. Inhibition of protein synthesis per se does not seem the likely cause of bacterial death. Why? Because complete blockade of protein synthesis by other antibiotics (eg, tetracyclines, chloramphenicol) is usually bacteriostatic—not bactericidal.

Microbial Resistance

The principal cause for bacterial resistance is production of enzymes that can inactivate aminoglycosides. Among gram-negative bacteria, the genetic information needed to synthesize these enzymes is acquired through transfer of R factors. To date, more than 20 different aminoglycoside-inactivating enzymes have been identified. Since each of the aminoglycosides can be modified by more than one of these enzymes, and since each enzyme can act on more than one aminoglycoside, patterns of bacterial resistance can be complex.

Of all the aminoglycosides, *amikacin* is least susceptible to inactivation by bacterial enzymes. As a result, resistance to amikacin is uncommon. To minimize emergence of resistant bacteria, amikacin should be reserved for infections that are unresponsive to other aminoglycosides.

Antimicrobial Spectrum

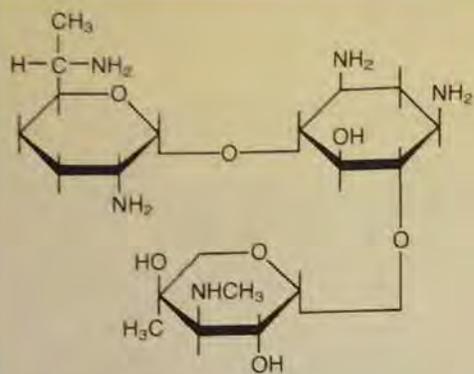
Bactericidal effects of the aminoglycosides are limited almost exclusively to *aerobic gram-negative bacilli*. Sensitive organisms include *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Aminoglycosides are inactive against most gram-positive bacteria.

Aminoglycosides *cannot kill anaerobes*. To produce antibacterial effects, aminoglycosides must be transported across the bacterial cell membrane, a process that is oxygen dependent. Since, by definition, anaerobic organisms live in the absence of oxygen, these microbes cannot take up aminoglycosides, and hence are resistant. For the same reason, aminoglycosides are inactive against facultative bacteria when these organisms are living under anaerobic conditions.

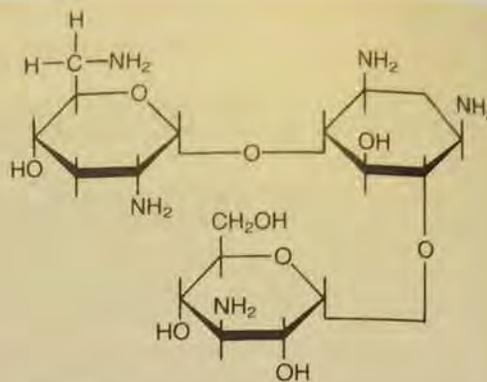
Therapeutic Use

Parenteral Therapy. The principal use for parenteral aminoglycosides is treatment of *serious infections due to aerobic gram-negative bacilli*. Primary target organisms are *Pseudomonas aeruginosa* and the Enterobacteriaceae (eg, *E. coli*, *Klebsiella*, *Serratia*, *Proteus mirabilis*).

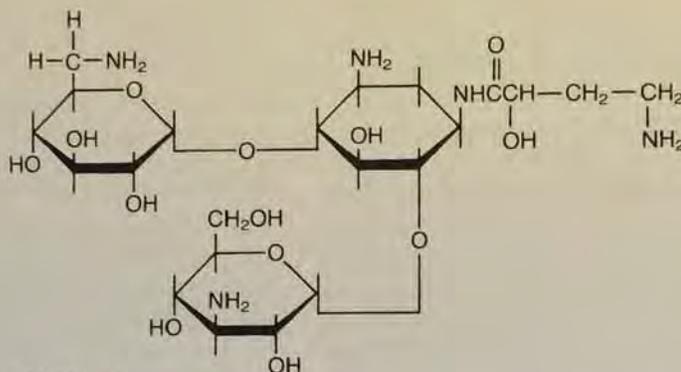
One aminoglycoside—gentamicin—is now commonly used in combination with either vancomycin or a beta-lactam antibiotic to treat *serious infections with certain gram-*



GENTAMICIN (C₁)



TOBRAMYCIN



AMIKACIN

Figure 87-1 • Structural formulas of the major aminoglycosides.

positive cocci, specifically *Enterococcus* species, some streptococci, and *Staphylococcus aureus*.

The aminoglycosides used most commonly for parenteral therapy are gentamicin, tobramycin, and amikacin. Selection among the three depends in large part on patterns of resistance in a given community or hospital. In settings where resistance to aminoglycosides is uncommon, either gentamicin or tobramycin is usually preferred. Of the two, gentamicin is less expensive and may be selected on this basis. Organisms resistant to both gentamicin and tobramycin are usually sensitive to amikacin. Accordingly, in settings where resistance to gentamicin and tobramycin is common, amikacin may be preferred for initial therapy.

Oral Therapy. Aminoglycosides are not absorbed from the GI tract, and hence oral therapy is used only for local effects within the intestine. In patients anticipating elective colorectal surgery, oral aminoglycosides have been given prophylactically to suppress bacterial growth in the bowel. One aminoglycoside—*paromomycin*—is used to treat intestinal amebiasis.

Topical Therapy. *Neomycin* is available in formulations for application to the eyes, ears, and skin. Topical preparations of *gentamicin* and *tobramycin* are used to treat conjunctivitis caused by susceptible gram-negative bacilli.

Pharmacokinetics

All of the aminoglycosides have similar pharmacokinetic profiles. Pharmacokinetic properties of the principal aminoglycosides are summarized in Table 87-1.

Absorption. Because they are polycations, the aminoglycosides cross membranes poorly. As a result, very little (about 1%) of an oral dose is absorbed. Hence, for treatment of systemic infections, aminoglycosides must be given parenterally (IM or IV). Absorption following application to the intact skin is minimal. However, when used for wound irrigation, amino-

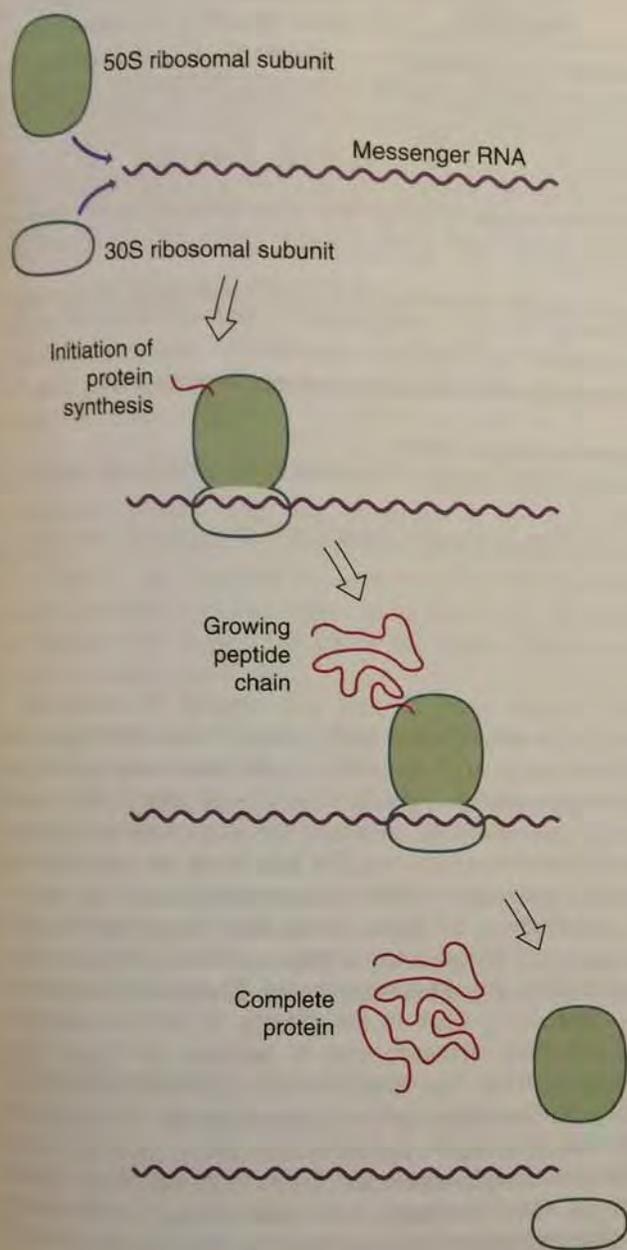
glycosides may be absorbed in amounts sufficient to produce systemic toxicity.

Distribution. Distribution of aminoglycosides is limited largely to extracellular fluid. Entry into the cerebrospinal fluid is insufficient to treat meningitis in adults. Aminoglycosides bind tightly to renal tissue, achieving levels in the kidney up to 50 times higher than levels in serum. These high levels are responsible for nephrotoxicity (see below). Aminoglycosides penetrate readily to the perilymph and endolymph of the inner ear, and can thereby cause ototoxicity (see below). Aminoglycosides can cross the placenta and may be toxic to the fetus.

Elimination. The aminoglycosides are eliminated primarily by the kidney. These drugs are not metabolized. In patients with normal renal function, half-lives of the aminoglycosides range from 2 to 3 hours. However, because elimination is almost exclusively renal, half-lives increase dramatically in patients with renal impairment (see Table 87-1). *Accordingly, to avoid serious toxicity, we must reduce dosage size or increase the dosing interval in patients with kidney disease.*

Interpatient Variation. Different patients receiving the same aminoglycoside dosage (in milligrams per kilogram of body weight) can achieve widely different serum levels of drug. This interpatient variation is caused by several factors, including age, percent body fat, and pathophysiology (eg, renal impairment, fever, edema, dehydration). Because of variability among patients, aminoglycoside dosage must be individualized. As dramatic evidence of this need, in one clinical study it was observed that, in order to produce equivalent serum drug levels, the doses required ranged from as little as

A Normal Protein Synthesis



B Effects of Aminoglycosides

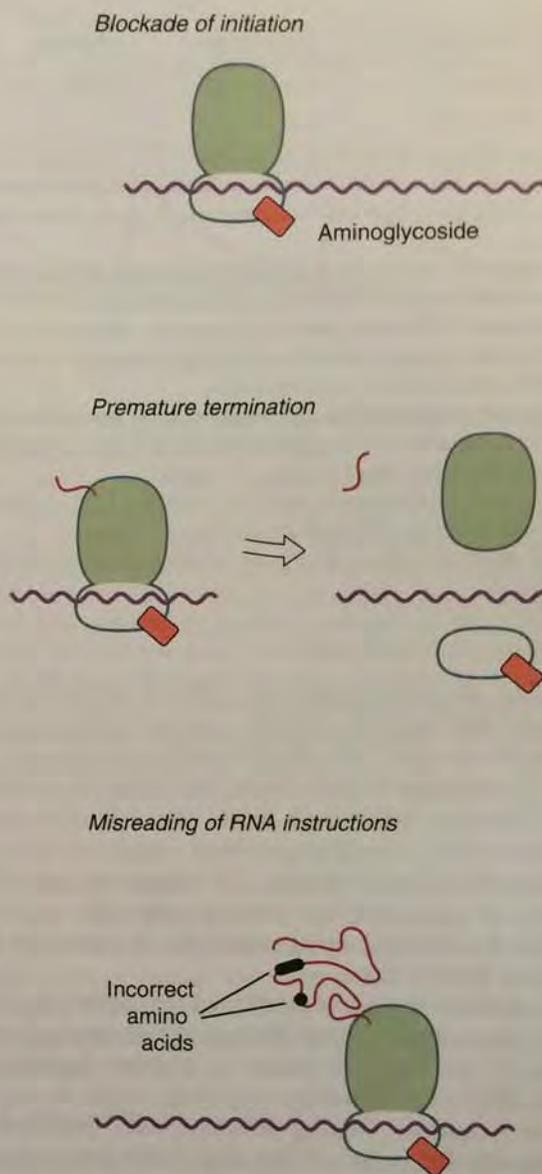


Figure 87-2 ■ Mechanism of action of aminoglycosides.

A, Protein synthesis begins with binding of the 50S and 30S ribosomal subunits to messenger RNA (mRNA), followed by attachment of the first amino acid of the new protein to the 50S subunit. As the ribosome moves down the mRNA strand, additional amino acids are added to the growing peptide chain. When the new protein is complete, it separates from the ribosome, and then the ribosomal subunits separate from the mRNA. **B**, Aminoglycosides bind to the 30S ribosomal subunit and can thereby (1) block initiation, (2) terminate synthesis before the new protein is complete, and (3) cause misreading of the genetic code, which causes synthesis of faulty proteins.

0.5 mg/kg in one patient to a high of 25.8 mg/kg in another—a difference of more than 50-fold.

Adverse Effects

The aminoglycosides can produce serious toxicity, especially to the inner ear and kidney. The inner ear and kidney are vulnerable because aminoglycosides become concentrated within cells of these structures.

Ototoxicity. All aminoglycosides can accumulate within the inner ear, causing cellular injury that can impair both

hearing and balance. *Impairment of hearing* is caused by damage to sensory hair cells in the *cochlea*. *Disruption of balance* is caused by damage to sensory hair cells of the *vestibular apparatus*.

The risk of ototoxicity is related primarily to excessive *trough levels** of drug—rather than to excessive *peak* levels. Why? Because, when trough levels remain persistently ele-

*The trough serum level is defined as the lowest level between doses, and occurs just prior to administering the next dose.

TABLE 87-1 • Dosages and Pharmacokinetics of Systemic Aminoglycosides

Generic Name	Trade Name	Total Daily Dose (mg/kg) ^{a,b}		Half-Life in Adults (hr)		Therapeutic (Peak) Level ^{c,d} (mcg/mL)	Safe Trough Level ^{e,f} (mcg/mL)
		Adults	Children	Normal	Anuric		
Amikacin	Amikin	15	15	2-3	24-60	15-30	Less than 5-10
Gentamicin	generic only	3-5 ^g	6-7.5 ^h	2	24-60	4-10 ^h	Less than 1-2
Tobramycin	generic only	3-6	6-7.5	2-2.5	24-60	4-10	Less than 1-2

^aThe total daily dose may be administered as one large dose each day, or as two or three divided doses given at equally spaced intervals around-the-clock.

^bBecause of interpatient variability, standard doses cannot be relied upon to produce appropriate serum drug levels, and hence dosage should be adjusted on the basis of serum drug measurements.

^cMeasured 30 minutes after IM injection or completing a 30-minute IV infusion.

^dThe peak values presented refer to levels obtained when the total daily dosage is given in *divided* doses, rather than as a single large daily dose.

^eMeasured just prior to the next dose.

^fTo minimize ototoxicity and nephrotoxicity, drug levels should drop *below* the listed values between doses.

^gWhen gentamicin is combined with either vancomycin or a beta-lactam antibiotic to treat certain gram-positive infections, the total daily dose is much lower (eg, about 1 mg/kg for adults).

^hThese peak values apply when gentamicin is used to treat gram-negative infections, not when gentamicin is combined with vancomycin or a beta-lactam antibiotic to treat gram-positive infections.

ⁱFor severe infections, the trough may be higher (eg, less than 2-4 mcg/mL).

vated, aminoglycosides are unable to diffuse out of inner ear cells, and hence the cells are exposed to the drug continuously for an extended time. It is this prolonged exposure, rather than brief exposure to high levels, that underlies cellular injury. In addition to high trough levels, the risk of ototoxicity is increased by (1) renal impairment (which can cause accumulation of aminoglycosides); (2) concurrent use of ethacrynic acid (a drug that has ototoxic properties of its own); and (3) administering aminoglycosides in excessive doses or for more than 10 days.

Patients should be monitored for ototoxicity. The first sign of impending *cochlear* damage is high-pitched tinnitus (ringing in the ears). As injury to cochlear hair cells proceeds, hearing in the high-frequency range begins to decline. Loss of low-frequency hearing develops with continued drug use. Because the initial decline in high-frequency hearing is subtle, audiometric testing is needed to detect it. The first sign of impending *vestibular* damage is headache, which may last for 1 or 2 days. After that, nausea, unsteadiness, dizziness, and vertigo begin to appear. Patients should be informed about the symptoms of vestibular and cochlear damage and instructed to report them.

Ototoxicity is largely *irreversible*. Accordingly, if permanent injury is to be avoided, aminoglycosides should be withdrawn at the first sign of damage (ie, tinnitus, persistent headache, or both).

The risk of ototoxicity can be minimized in several ways. Dosages should be adjusted so that trough serum drug levels do not exceed recommended values. (Aminoglycosides diffuse out of the endolymph and perilymph during the trough time, thereby decreasing exposure of sensory hair cells.) Special care should be taken to ensure safe trough levels in patients with renal impairment. When possible, aminoglycosides should be used for no more than 10 days. Concurrent use of ethacrynic acid should be avoided.

Nephrotoxicity. Aminoglycosides can injure cells of the proximal renal tubules. These drugs are taken up by

tubular cells and achieve high intracellular concentrations. Nephrotoxicity correlates with (1) the *total cumulative dose* of aminoglycosides and (2) *high trough levels*. High *peak levels* do not seem to increase toxicity. Aminoglycoside-induced nephrotoxicity usually manifests as *acute* tubular necrosis. Prominent symptoms are proteinuria, casts in the urine, production of dilute urine, and elevations in serum creatinine and blood urea nitrogen (BUN). Serum creatinine and BUN should be monitored. The risk of nephrotoxicity is especially high in the elderly, in patients with pre-existing kidney disease, and in patients receiving other nephrotoxic drugs (eg, amphotericin B, cephalothin, cyclosporine). Fortunately, cells of the proximal tubule readily regenerate. As a result, injury to the kidney usually reverses following aminoglycoside use.* The most significant consequence of renal damage is accumulation of aminoglycosides themselves, which can lead to ototoxicity and even more kidney damage.

Neuromuscular Blockade. Aminoglycosides can inhibit neuromuscular transmission, causing flaccid paralysis and potentially fatal respiratory depression. Most episodes of neuromuscular blockade have occurred following intraperitoneal or intrapleural instillation of aminoglycosides. However, neuromuscular blockade has also occurred with IV, IM, and oral dosing. The risk of paralysis is increased by concurrent use of neuromuscular blocking agents and general anesthetics. Myasthenia gravis is an additional risk. Neuromuscular blockade can be reversed with calcium; IV infusion of a calcium salt (eg, calcium gluconate) is the treatment of choice. Because of increased prescriber awareness, aminoglycoside-induced neuromuscular blockade is now rare.

Other Adverse Effects. Hypersensitivity reactions (eg, rash, pruritus, urticaria) occur occasionally. Blood dyscrasias (neutropenia, agranulocytosis, aplastic anemia) are rare. *Streptomycin* has been associated with neurologic disorders (optic nerve dysfunction, peripheral neuritis, paresthesias of the face and hands). *Oral neomycin* has caused suprainfection of the bowel and intestinal malabsorption. *Tobramycin* has caused *Clostridium difficile*-associated diarrhea. *Topical neomycin* can cause contact dermatitis.

*If interstitial fibrosis or renal tubular necrosis develops, damage to the kidney may be permanent.

Beneficial Drug Interactions

Penicillins. Penicillins and aminoglycosides are frequently employed in combination to enhance bacterial kill. The combination is effective because penicillins disrupt the cell wall, and thereby facilitate access of aminoglycosides to their site of action. Unfortunately, when present in high concentrations, penicillins can inactivate aminoglycosides by direct chemical interaction. Therefore, *penicillins and aminoglycosides should not be mixed together in the same IV solution.* (Inactivation is not likely to occur once the drugs are in the body, because drug concentrations are usually too low for significant chemical interaction.)

Cephalosporins and Vancomycin. Like the penicillins, cephalosporins and vancomycin weaken the bacterial cell wall, and can thereby act in concert with aminoglycosides to enhance bacterial kill.

Adverse Drug Interactions

Ototoxic Drugs. The risk of injury to the inner ear is significantly increased by concurrent use of *ethacrynic acid*, a loop diuretic that has ototoxic actions of its own. Combining aminoglycosides with two other loop diuretics—furosemide and bumetanide—appears to cause no more ototoxicity than aminoglycosides alone.

Nephrotoxic Drugs. The risk of renal damage is increased by concurrent therapy with other nephrotoxic agents. Additive or potentiative nephrotoxicity can occur with *amphotericin B*, *cephalosporins*, *polymyxins*, *vancomycin*, and *cyclosporine*, as well as with *aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)*.

Skeletal Muscle Relaxants. Aminoglycosides can intensify neuromuscular blockade induced by pancuronium and other skeletal muscle relaxants. If aminoglycosides are used with these agents, caution must be exercised to avoid respiratory arrest.

Dosing Schedules

Systemic aminoglycosides may be administered as a single large dose each day, or as two or three smaller doses. Traditionally, these drugs have been administered in divided doses, given at equally spaced intervals around-the-clock (eg, every 8 hours). Today, however, it is common to administer the total daily dose all at once, rather than dividing it up. Several studies have shown that once-daily doses are just as effective as divided doses, and probably safer. Because once-daily dosing is both safe and effective, and because it's easier and cheaper than giving divided doses, once-daily dosing has become the preferred schedule. Keep in mind, however, that this schedule is not appropriate for some patients, including neonates and women who are pregnant.

How can it be that giving one large daily dose is just as safe and effective as giving divided doses? The answer lies in the hypothetical data for gentamicin levels plotted in Figure 87-3. As indicated, when we give one large dose (4.5 mg/kg) once a day, we achieve a very high peak plasma level—much higher than when we give the same daily total in the form of three smaller doses (1.5 mg/kg) every 8 hours. Because of this high peak concentration, and because aminoglycosides exhibit a postantibiotic effect (see *Mechanism of Action* above), bacterial kill using a single daily dose is just as great as when we use divided doses—even though, with once-daily dosing, plasma drug levels are subtherapeutic for a prolonged time

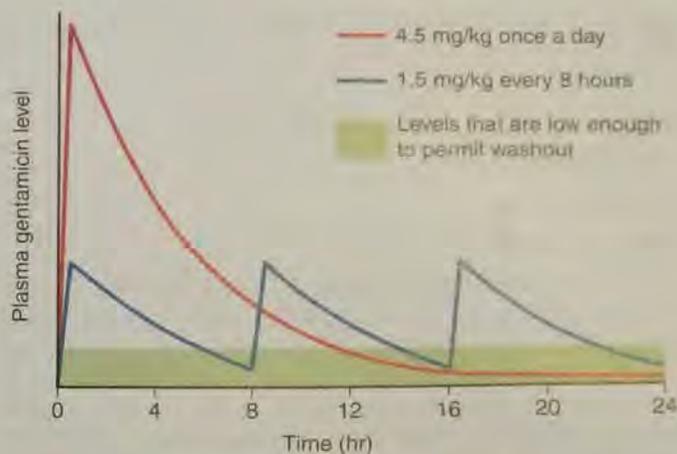


Figure 87-3 • Plasma gentamicin levels produced with once-daily doses versus divided doses.

The curves depict plasma levels of gentamicin produced with (1) a single large dose administered once a day versus (2) the same daily total given as three smaller doses spaced 8 hours apart. Plasma levels with both regimens are high enough to produce good bactericidal effects. The shaded area indicates levels that are low enough to permit washout of the drug from vulnerable cells in the inner ear. Note that, with once-daily dosing, levels are in the washout range for over 12 hours, versus a total of only 6 hours when divided doses are used. As a result, ototoxicity and nephrotoxicity are lower with the once-a-day schedule.

between doses. This prolonged period of low drug levels also explains why once-daily dosing is very safe: Because levels are low for a long time, aminoglycosides are able to wash out from vulnerable cells of the ear and kidney, thereby reducing injury. In contrast, when we use divided doses, the time during which drug levels are low enough to permit washout is quite short, and hence the risk of toxicity is high.

Monitoring Serum Drug Levels

Monitoring serum drug levels provides the best basis for adjusting aminoglycoside dosage. To produce bacterial kill, peak levels must be sufficiently high. To minimize ototoxicity and nephrotoxicity, trough levels must be sufficiently low. Therapeutic levels and trough levels for the major systemic aminoglycosides are listed in Table 87-1.

How monitoring is done depends on the dosing schedule employed (ie, once-daily dosing or use of divided doses). When once-daily dosing is employed, we only need to measure trough levels. As a rule, there is no need to measure peak levels. Why? Because, when the entire daily dose is given at once, high peak levels are guaranteed. (They're typically 3 to 4 times those achieved with divided doses.) In contrast, when divided doses are employed, we need to measure both the peak and the trough.

When drawing blood samples for aminoglycoside levels, timing is important. Samples for *peak* levels should be taken 30 minutes after giving an IM injection or after completing a 30-minute IV infusion. Sampling for *trough* levels depends on the dosing schedule. For patients receiving *divided doses*, trough samples should be taken just prior to the next dose. For patients receiving *once-daily doses*, a single sample can be

drawn 1 hour before the next dose. The value should be very low, preferably close to zero.

PROPERTIES OF INDIVIDUAL AMINOGLYCOSIDES

Gentamicin

Therapeutic Use

Gentamicin (formerly available as Garamycin) is used primarily to treat serious infections caused by aerobic gram-negative bacilli. Primary targets are *Pseudomonas aeruginosa* and the Enterobacteriaceae (eg, *E. coli*, *Klebsiella*, *Serratia*, *Proteus mirabilis*). In hospitals where resistance is not a problem, gentamicin is often the preferred aminoglycoside for use against these bacteria. Why? Because gentamicin is cheaper than the alternatives (tobramycin and amikacin). Unfortunately, resistance to gentamicin is increasing, and cross-resistance to tobramycin is common. For infections that are resistant to gentamicin and tobramycin, amikacin is usually effective.

In addition to its use against gram-negative bacilli, gentamicin can be combined with vancomycin, a cephalosporin, or a penicillin to treat serious infections caused by certain gram-positive cocci, namely, *Enterococcus* species, some streptococci, and *Staphylococcus aureus*.

Adverse Effects and Interactions

Like all other aminoglycosides, gentamicin is toxic to the kidney and inner ear. Caution must be exercised when combining gentamicin with other nephrotoxic or ototoxic drugs. Gentamicin is inactivated by direct chemical interaction with penicillins, and hence these drugs should not be mixed in the same IV solution.

Preparations, Dosage, and Administration

Treatment of Gram-Negative Infections. *Intravenous and Intramuscular.* Gentamicin sulfate (formerly available as Garamycin) is supplied in solution (0.8, 0.9, 1, 1.2, 1.4, 1.6, 10, and 40 mg/mL) and as a powder (60, 80, and 100 mg for reconstitution) for IM and IV administration. The dosage for both routes is the same. For adults, the traditional dosing scheme consists of a loading dose (2 mg/kg) followed by doses of 1 to 1.7 mg/kg every 8 hours—for a total of 3 to approximately 5 mg/kg/day. When once-daily dosing is employed, the dosage is 5 mg/kg every 24 hours; no loading dose is needed. For children, the traditional maintenance dosage is 2 to 2.5 mg/kg every 8 hours. In adults and children with renal impairment, the total daily dosage should be reduced. Duration of treatment is usually 7 to 10 days.

Because of substantial interpatient variation, it is desirable to monitor serum drug levels and to adjust dosage accordingly. Peak levels should range between 4 and 10 mcg/mL (for traditional dosing) or between 16 and 24 mcg/mL (for once-daily dosing). As a rule, the trough should not exceed 2 mcg/mL.

For IV administration, gentamicin should be diluted in either 0.9 sodium chloride injection or 5% dextrose and infused over 30 minutes or longer. The drug should not be mixed with penicillins in the same IV solution.

Intrathecal. Intrathecal therapy is done with a 2-mg/mL solution devoid of preservatives. The usual dosage for children under 3 months old is 1 to 2 mg once daily. The usual dosage for adults is 4 to 8 mg once daily. For all patients, treatment should continue for 1 day after samples of cerebrospinal fluid become negative for the infecting organism.

Treatment of Gram-Positive Infections. As noted, gentamicin may be combined with vancomycin, a penicillin, or a cephalosporin to treat serious infections caused by *Enterococcus* species, certain streptococci, and *Staph. aureus*. When gentamicin is used in this way, dosages are much lower than when the drug is used against gram-negative infections. For combination therapy, a typical dosage for adults is 1 mg/kg/day, compared with 3 to 5 mg/kg/day when the drug is used by itself.

Tobramycin

Uses, Adverse Effects, and Interactions. Tobramycin (formerly available as Nebcin) is similar to gentamicin with respect to uses, adverse effects, and interactions. The drug is more active than gentamicin against *Pseudomonas aeruginosa*, but less active against enterococci and *Serratia*. Inhaled tobramycin is used for patients with cystic fibrosis (see Chapter 107). Like all other aminoglycosides, tobramycin can injure the inner ear and kidney. If possible, concurrent therapy with other ototoxic or nephrotoxic drugs should be avoided. Tobramycin may also cause *Clostridium difficile*-associated diarrhea.

Preparations, Dosage, and Administration. *Intravenous and Intramuscular.* Tobramycin sulfate (formerly available as Nebcin) is supplied in solution (0.8, 1.2, 10, and 40 mg/mL) and as a 1.2-gm powder (40 mg/mL after reconstitution) for IM and IV administration. Dosages and serum levels are the same as those given for gentamicin. Ideally, dosages should be individualized to produce peak and trough levels within the ranges indicated in Table 87-1. In patients with renal impairment, the total daily dosage should be reduced. For IV administration, the drug should be diluted in either 0.9% sodium chloride injection or 5% dextrose and infused over 30 minutes or more. Tobramycin should not be mixed with penicillins in the same IV solution. Duration of treatment is usually 7 to 10 days.

Nebulization. For patients with cystic fibrosis, tobramycin [TOBI] is available in solution (300 mg/5 mL) for use in a nebulizer. The dosage is 300 mg twice daily administered in a repeating cycle consisting of 28 days of drug use followed by 28 days off. Cystic fibrosis is discussed in Chapter 107.

Amikacin

Uses, Adverse Effects, and Interactions. Amikacin [Amikin] has two outstanding features: (1) of all the aminoglycosides, amikacin is active against the broadest spectrum of gram-negative bacilli; and (2) of all the aminoglycosides, amikacin is the least vulnerable to inactivation by bacterial enzymes. Because most aminoglycoside-inactivating enzymes do not affect amikacin, the incidence of bacterial resistance to this agent is lower than with other major aminoglycosides (gentamicin and tobramycin). In hospitals where resistance to gentamicin and tobramycin is common, amikacin is the preferred agent for initial treatment of infections caused by aerobic gram-negative bacilli. However, in settings where resistance to the other aminoglycosides is infrequent, amikacin should be reserved for infections of proven aminoglycoside resistance. Why? Because this practice will delay emergence of organisms resistant to amikacin. Like all other aminoglycosides, amikacin is toxic to the kidney and inner ear. Caution should be exercised if amikacin is used in combination with other ototoxic or nephrotoxic drugs.

Preparations, Dosage, and Administration. Amikacin sulfate [Amikin] is available in solution (50, 100, and 250 mg/mL) for IM and IV administration. For IV use, amikacin should be diluted in 0.9% sodium chloride injection or 5% dextrose; infusion time should be 30 to 60 minutes in adults and 1 to 2 hours in infants. The recommended dosage for adults and children is 15 mg/kg/day administered either (1) as a single daily dose or (2) in equally divided doses given 8 or 12 hours apart. In patients with renal impairment, dosage should be reduced or the dosing interval increased. Dosage adjustments should be based on measurements of serum drug levels. As a rule, duration of treatment should not exceed 10 days.

Other Aminoglycosides

Neomycin

Neomycin is more ototoxic and nephrotoxic than any other aminoglycoside. As a result, neomycin is not used parenterally. Instead, the drug is employed for topical treatment of infections of the eye, ear, and skin. Neomycin is also administered orally to suppress bowel flora prior to surgery of the intestine. Because aminoglycosides are not absorbed from the GI tract, oral administration

constitutes a local (nonsystemic) use of the drug. Oral neomycin can cause suprainfection of the bowel as well as an intestinal malabsorption syndrome.

Kanamycin

Kanamycin [Kantrex] is an older aminoglycoside to which bacterial resistance is common. The drug is still active against some gram-negative bacilli, but *Serratia* and *Pseudomonas aeruginosa* are resistant. Because of resistance, systemic use of the drug has sharply declined; gentamicin, tobramycin, and amikacin are preferred. Like neomycin, kanamycin is employed to suppress bacterial flora of the bowel prior to elective colorectal surgery. Kanamycin is supplied in solution for IM and IV use. Oral capsules for sterilizing the bowel have been withdrawn.

Streptomycin

Streptomycin, discovered in 1943, was the first aminoglycoside drug. Although once employed widely, streptomycin has been largely replaced by

safer or more effective medications. As discussed in Chapter 90, streptomycin can be used in combination with other drugs to treat tuberculosis, but newer and safer agents (rifampin, isoniazid, ethambutol) are generally preferred. Streptomycin is also indicated for several uncommon infections (plague, tularemia, glanders, brucellosis). When combined with ampicillin or penicillin G, streptomycin may be used for enterococcal endocarditis.

Paromomycin

Paromomycin [Humatin] is an aminoglycoside employed only for local effects within the intestine. The drug is approved for oral therapy of intestinal amebiasis, and has been used investigational against other intestinal parasites. The dosage for amebiasis in adults and children is 8 to 12 mg/kg 3 times daily for 7 days. Principal adverse effects are nausea, cramps, and diarrhea. Paromomycin is supplied in 250-mg capsules.

KEY POINTS

- Aminoglycosides are narrow-spectrum antibiotics, used primarily against aerobic gram-negative bacilli.
- Aminoglycosides disrupt protein synthesis and cause rapid bacterial death.
- Aminoglycosides are highly polar polycations. As a result, they are not absorbed from the GI tract, do not cross the blood-brain barrier, and are excreted rapidly by the kidney.
- Aminoglycosides can cause irreversible injury to sensory cells of the inner ear, resulting in hearing loss and disturbed balance.
- The risk of ototoxicity is related primarily to persistently elevated trough drug levels, rather than to excessive peak levels.
- Aminoglycosides are nephrotoxic, but renal injury is usually reversible.
- The risk of nephrotoxicity is related to the total cumulative dose and elevated trough levels.
- Because the same aminoglycoside dose can produce very different plasma levels in different patients, monitoring serum levels is common. *Peak* levels must be high enough to cause bacterial kill; *trough* levels must be low enough to minimize toxicity to the inner ear and kidney.

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Summary of Major Nursing Implications

AMINOGLYCOSIDES

Amikacin
Gentamicin
Kanamycin
Neomycin
Paromomycin
Tobramycin

Except where noted, the implications summarized below apply to all aminoglycosides.

Preadministration Assessment

Therapeutic Goal

Parenteral Therapy. Treatment of serious infections caused by gram-negative aerobic bacilli. One aminoglycoside—*gentamicin*—is also used (in combination with vancomycin or a beta-lactam antibiotic) to treat serious infections caused by certain gram-positive cocci, namely *Enterococcus* species, some streptococci, and *Staph. aureus*.

Oral Therapy. Suppression of bowel flora prior to elective colorectal surgery.

Topical Therapy. Treatment of local infections of the eyes, ears, and skin.

Identifying High-Risk Patients

Aminoglycosides must be used with *caution* in patients with renal impairment, pre-existing hearing impairment, and myasthenia gravis, and in patients receiving ototoxic drugs (especially ethacrynic acid), nephrotoxic drugs (eg, amphotericin B, cephalosporins, vancomycin, cyclosporine, NSAIDs), and neuromuscular blocking agents.

Implementation: Administration

Routes

Intramuscular and Intravenous. Gentamicin, tobramycin, amikacin, kanamycin.

Oral. Neomycin, paromomycin.

Topical. Neomycin, tobramycin.

Dosing Schedule

Parenteral aminoglycosides may be given as one large dose each day, or in two or three divided doses administered at equally spaced intervals around-the-clock.

Summary of Major Nursing Implications*—cont'd

Administration

Aminoglycosides must be given parenterally (IV, IM) to treat systemic infections. Intravenous infusions should be done slowly (over 30 minutes or more). Do not mix aminoglycosides and penicillins in the same IV solution.

When possible, adjust the dosage on the basis of plasma drug levels. When using divided daily doses, draw blood samples for measuring peak levels 1 hour after IM injection and 30 minutes after completing an IV infusion. When using a single daily dose, measuring peak levels is unnecessary. Draw samples for trough levels just prior to the next dose (when using divided daily doses) or 1 hour before the next dose (when using a single daily dose).

In patients with renal impairment, the dosage should be reduced or the dosing interval increased.

Ongoing Evaluation and Interventions

Monitoring Summary

Monitor aminoglycoside levels (peaks and troughs), inner ear function (hearing and balance), and kidney function (creatinine clearance, BUN, and urine output).

Minimizing Adverse Effects

Ototoxicity. Aminoglycosides can damage the inner ear, causing irreversible impairment of hearing and balance. Monitor for ototoxicity, using audiometry in high-risk patients. **Instruct patients to report symptoms of ototoxicity (tinnitus, high-frequency hearing loss, persistent headache, nausea, unsteadiness, dizziness, vertigo).** If ototoxicity is detected, aminoglycosides should be withdrawn.

Nephrotoxicity. Aminoglycosides can cause acute tubular necrosis, which is usually reversible. To evaluate renal injury, monitor serum creatinine and BUN. If oliguria or anuria develops, withhold the aminoglycoside and notify the prescriber.

Neuromuscular Blockade. Aminoglycosides can inhibit neuromuscular transmission, causing potentially fatal respiratory depression. Carefully observe patients with myasthenia gravis and patients receiving skeletal muscle relaxants or general anesthetics. Aminoglycoside-induced neuromuscular blockade can be reversed with IV calcium gluconate.

Minimizing Adverse Interactions

Penicillins. Aminoglycosides can be inactivated by high concentrations of penicillins. Never mix penicillins and aminoglycosides in the same IV solution.

Ototoxic and Nephrotoxic Drugs. Exercise caution when using aminoglycosides in combination with other nephrotoxic or ototoxic drugs. Increased nephrotoxicity may occur with *amphotericin B*, *cephalosporins*, *polymyxins*, *vancomycin*, *cyclosporine*, and *NSAIDs*. Increased ototoxicity may occur with *ethacrynic acid*.

Skeletal Muscle Relaxants. Aminoglycosides can intensify neuromuscular blockade induced by pancuronium and other skeletal muscle relaxants. When aminoglycosides are used concurrently with these agents, exercise caution to avoid respiratory arrest.

*Patient education information is highlighted as **blue text**.

Sulfonamides and Trimethoprim

Sulfonamides

Basic Pharmacology

Sulfonamide Preparations

Trimethoprim

Trimethoprim/Sulfamethoxazole

The sulfonamides and trimethoprim are broad-spectrum antimicrobials that have closely related mechanisms: They all disrupt the synthesis of tetrahydrofolic acid. In approaching these drugs, we begin with the sulfonamides, followed by trimethoprim, and then conclude with trimethoprim/sulfamethoxazole, an important fixed-dose combination.

SULFONAMIDES

Sulfonamides were the first drugs available for systemic treatment of bacterial infections. Their introduction and subsequent widespread use produced a sharp decline in morbidity and mortality from susceptible infections. Until the penicillins became generally available, sulfonamides remained the mainstay of antibacterial chemotherapy. With the advent of newer antimicrobial drugs, use of sulfonamides has greatly declined. Today, only a few remain on the market. Nonetheless, the sulfonamides still have important uses, primarily against urinary tract infections. With the introduction of trimethoprim/sulfamethoxazole in the 1970s, indications for the sulfonamides expanded.

Basic Pharmacology

Similarities among the sulfonamides are more striking than the differences. Accordingly, rather than focusing on a representative prototype, we will discuss the sulfonamides as a group.

Chemistry

The general structural formula for the sulfonamides is shown in Figure 88-1. As you can see, sulfonamides are structural analogs of para-aminobenzoic acid (PABA). The antimicrobial actions of sulfonamides are based on this similarity.

Individual sulfonamides vary greatly with respect to solubility in water. Older sulfonamides had low solubility, and hence they often crystallized out in the urine, causing injury to the kidneys. The sulfonamides in current use are much more water soluble, and hence the risk of renal damage is low.

Mechanism of Action

Sulfonamides suppress bacterial growth by inhibiting synthesis of folic acid (folate), a compound required by all cells to make DNA, RNA, and proteins. The steps in folate synthesis are shown in Figure 88-2. As indicated, sulfonamides block the step in which PABA is combined with pteridine to form dihydropteroic acid. Because of their structural similarity to PABA, sulfonamides act as competitive inhibitors of this reaction. Sulfonamides are usually bacteriostatic. Accordingly, host defenses are essential for complete elimination of infection.

If all cells require folate, why don't sulfonamides harm us? The answer lies in how bacteria and mammalian cells acquire folic acid. Bacteria are unable to take up folate from their environment, and hence must synthesize folic acid from precursors. Sulfonamides disrupt this process. In contrast to bacteria, mammalian cells do not manufacture their own folate. Rather, they simply take up folic acid obtained from the diet, using a specialized transport system for uptake. Because mammalian cells use preformed folic acid rather than synthesizing it, sulfonamides are harmless to us.

Microbial Resistance

Many bacterial species have developed resistance to sulfonamides. Resistance is especially high among gonococci, meningococci, streptococci, and shigellae. Resistance may be acquired by spontaneous mutation or by transfer of R factors. Principal resistance mechanisms are (1) reduced sulfonamide uptake, (2) synthesis of PABA in amounts sufficient to overcome sulfonamide-mediated inhibition of dihydropteroate synthetase, and (3) alteration in the structure of dihydropteroate synthetase such that binding and inhibition by sulfonamides is reduced.

Antimicrobial Spectrum

The sulfonamides are active against a broad spectrum of microbes. Susceptible organisms include gram-positive cocci (including methicillin-resistant *Staphylococcus aureus*), gram-negative bacilli, *Listeria monocytogenes*, actinomycetes (eg, *Nocardia*), chlamydiae (eg, *Chlamydia trachomatis*), some protozoa (eg, *Toxoplasma*, plasmodia, *Isoospora belli*), and two fungi: *Pneumocystis jirovecii* (formerly thought to be *Pneumocystis carinii*) and *Paracoccidioides brasiliensis*.

Therapeutic Uses

Although the sulfonamides were once employed widely, their applications are now limited. Two factors explain why: (1) introduction of bactericidal antibiotics that are less toxic than the sulfonamides, and (2) development of sulfonamide resistance. Today, urinary tract infection is the principal indication for these drugs.

Urinary Tract Infections. Sulfonamides are often preferred drugs for acute infections of the urinary tract. About 90% of these infections are due to *Escherichia coli*, a bacterium that is usually sulfonamide sensitive. Of the sulfonamides available, *sulfamethoxazole* (in combination with trimethoprim) is generally favored. Sulfamethoxazole has good

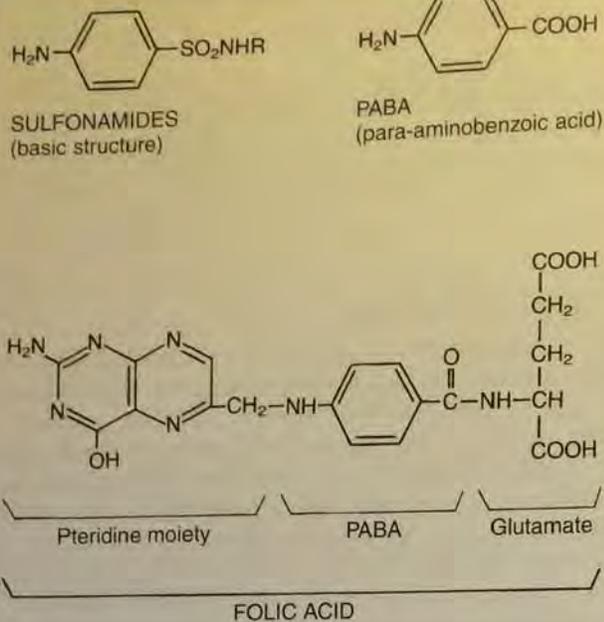


Figure 88-1 • Structural relationships among sulfonamides, PABA, and folic acid.

solubility in urine and achieves effective concentrations within the urinary tract. Urinary tract infections and their treatment are discussed in Chapter 89.

Other Uses. Sulfonamides are useful drugs for nocardiosis (infection with *Nocardia asteroides*), listeria, paracoccidioidomycosis, and infection with *Pneumocystis jirovecii*. In addition, sulfonamides are alternatives to doxycycline and erythromycin for infections caused by *C. trachomatis* (trachoma, inclusion conjunctivitis, urethritis, lymphogranuloma venereum). Sulfonamides are used in conjunction with pyrimethamine to treat two protozoal infections: toxoplasmosis and malaria caused by chloroquine-resistant *Plasmodium falciparum*. Topical sulfonamides are used to treat superficial infections of the eye and to suppress bacterial colonization in burn patients.

One sulfonamide—sulfasalazine—is used to treat *ulcerative colitis*. However, benefits in this disorder do not result from inhibiting microbial growth. *Ulcerative colitis* is discussed in Chapter 80.

Pharmacokinetics

Absorption. Sulfonamides are well absorbed following oral administration. When applied topically to the skin or mucous membranes, these drugs may be absorbed in amounts sufficient to cause systemic effects.

Distribution. Sulfonamides are well distributed to all tissues. Concentrations in pleural, peritoneal, ocular, and similar body fluids may be as much as 80% of the concentration in blood. Sulfonamides readily cross the placenta, and levels achieved in the fetus are sufficient to produce antimicrobial effects and toxicity.

Metabolism. Sulfonamides are metabolized in the liver, principally by acetylation. Acetylated derivatives lack antimicrobial activity, but are just as toxic as the parent compounds. Acetylation may decrease sulfonamide solubility, thereby increasing the risk of renal damage from crystal formation.

Excretion. Sulfonamides are excreted primarily by the kidneys. Hence, the rate of renal excretion is the principal determinant of their half-lives.

Adverse Effects

Sulfonamides can cause multiple adverse effects. Prominent among these are hypersensitivity reactions, blood dyscrasias, and kernicterus, which occurs in newborns. Renal damage from crystalluria was a problem with older sulfonamides but is of minimal concern with the sulfonamides used today.

Hypersensitivity Reactions. Sulfonamides can induce a variety of hypersensitivity reactions, which are seen in about 3%

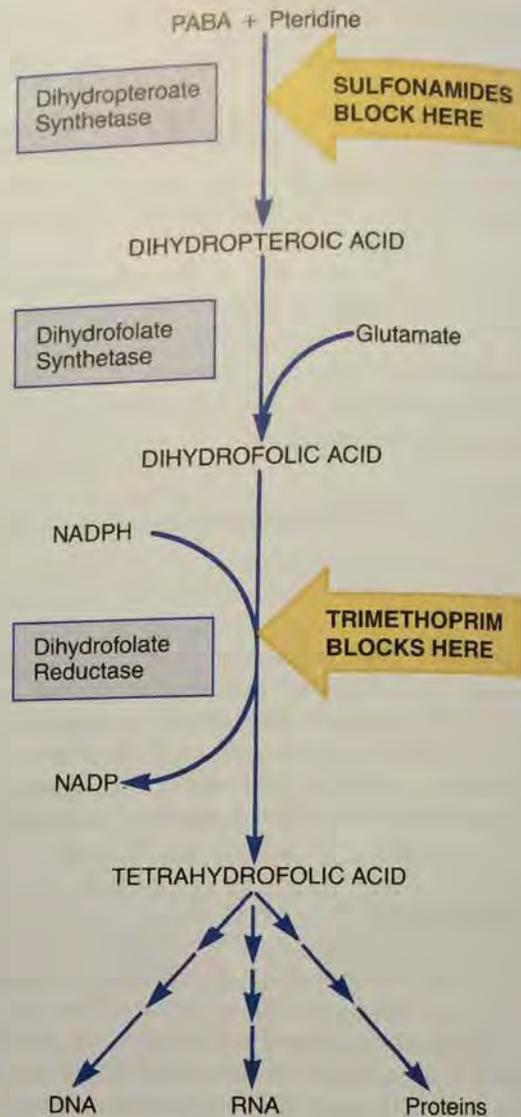


Figure 88-2 • Sites of action of sulfonamides and trimethoprim.

Sulfonamides and trimethoprim inhibit sequential steps in the synthesis of tetrahydrofolic acid (FAH₄). In the absence of FAH₄, bacteria are unable to synthesize DNA, RNA, and proteins.

of patients. Mild reactions—rash, drug fever, photosensitivity—are relatively common. To minimize photosensitivity reactions, patients should avoid prolonged exposure to sunlight, wear protective clothing, and apply a sunscreen to exposed skin.

Hypersensitivity reactions are especially frequent with topical sulfonamides. As a result, these preparations are no longer employed routinely. Rather, they are usually reserved for ophthalmic infections, burns, and bacterial vaginosis caused by *Gardnerella vaginalis* and a mixed population of anaerobic bacteria.

The most severe hypersensitivity response to sulfonamides is *Stevens-Johnson syndrome*, a rare reaction with a mortality rate of about 25%. Symptoms include widespread lesions of the skin and mucous membranes, combined with fever, malaise, and toxemia. The reaction is most likely with long-acting sulfonamides, which are now banned in the United States. Short-acting sulfonamides may also induce the syndrome, but the incidence is low. To minimize the risk of severe reactions, sulfonamides should be discontinued immediately if skin rash

of any sort is observed. In addition, sulfonamides should not be given to patients with a history of hypersensitivity to chemically related drugs, including thiazide diuretics, loop diuretics, and sulfonamide-type oral hypoglycemics—although the risk of cross-reactivity with these agents is probably low (see below, under *Drug Interactions*).

Hematologic Effects. Sulfonamides can cause *hemolytic anemia* in patients whose red blood cells have a genetically determined deficiency in glucose-6-phosphate dehydrogenase (G6PD). This inherited trait is most common among African Americans and people of Mediterranean origin. Rarely, hemolysis occurs in the absence of G6PD deficiency. Red cell lysis can produce fever, pallor, and jaundice; patients should be observed for these signs. In addition to hemolytic anemia, sulfonamides can cause agranulocytosis, leukopenia, thrombocytopenia, and, very rarely, aplastic anemia. When sulfonamides are used for a long time, periodic blood tests should be obtained.

Kernicterus. Kernicterus is a disorder in newborns caused by deposition of bilirubin in the brain. Bilirubin is neurotoxic and can cause severe neurologic deficits and even death. Under normal conditions, infants are not vulnerable to kernicterus. Why? Because any bilirubin present in their blood is tightly bound to plasma proteins, and therefore is not free to enter the central nervous system (CNS). Sulfonamides promote kernicterus by displacing bilirubin from plasma proteins. Since the blood-brain barrier of infants is poorly developed, the newly freed bilirubin has easy access to sites within the brain. *Because of the risk of kernicterus, sulfonamides should not be administered to infants under the age of 2 months. In addition, sulfonamides should not be given to pregnant women near term or to mothers who are breast-feeding.*

Renal Damage from Crystalluria. Because of their low solubility, older sulfonamides tended to come out of solution in the urine, forming crystalline aggregates in the kidneys, ureters, and bladder. These aggregates caused irritation and obstruction, sometimes resulting in anuria and even death. Renal damage is uncommon with today's sulfonamides, owing to their increased water solubility. To minimize the risk of renal damage, adults should maintain a daily urine output of 1200 mL. This can be accomplished by consuming 8 to 10 glasses of water each day. Because the solubility of sulfonamides is highest at elevated pH, alkalization of the urine (eg, with sodium bicarbonate) can further decrease the chances of crystalluria.

Drug Interactions

Metabolism-Related Interactions. Sulfonamides can intensify the effects of warfarin, phenytoin, and sulfonamide-type oral hypoglycemics (eg, glipizide, glyburide). The principal mechanism is inhibition of hepatic metabolism. When combined with sulfonamides, these drugs may require a reduction in dosage to prevent toxicity.

Cross-Hypersensitivity. There is concern that people who are hypersensitive to sulfonamide antibiotics may be cross-hypersensitive to other drugs that contain a sulfonamide moiety (eg, thiazide diuretics, loop diuretics, sulfonamide-type oral hypoglycemics). However, there are no good data to show that such cross-hypersensitivity actually exists—suggesting that patients who experience an allergic reaction when taking another sulfonamide simply have a general predisposition to drug allergy, rather than a specific cross-reactivity with sulfonamide-type drugs. In fact, clinical experience has shown that patients with documented allergy to sulfonamide antibiotics can take

other sulfonamide drugs without incident. The bottom line? For most patients allergic to sulfa antibiotics, it's safe to use other sulfonamide-type drugs, including thiazide diuretics and sulfonamide-type oral hypoglycemics. Having said that, the proper answer on your NCLEX exam is this: Patients who are allergic to sulfonamide antibiotics should avoid all other sulfonamide-type drugs. (This answer would be consistent with Food and Drug Administration recommendations, if not with current clinical reality.)

Sulfonamide Preparations

The sulfonamides fall into two major categories: (1) systemic sulfonamides and (2) topical sulfonamides. The systemic agents are used more often.

Systemic Sulfonamides

In the past, we had three groups of systemic sulfonamides: short acting, intermediate acting, and long acting. Today, the long-acting agents are no longer available, owing to a high risk of Stevens-Johnson syndrome. The remaining two groups—short acting and intermediate acting—differ primarily with regard to dosing interval, which is much shorter for the short-acting drugs.

Sulfamethoxazole. Sulfamethoxazole is the only *intermediate-acting* sulfonamide available. Because its effects are moderately prolonged, dosing can be done less often than with the short-acting agents. The risk of renal damage from crystalluria can be reduced by maintaining adequate hydration. Sulfamethoxazole is not available for use by itself—but is available in combination with trimethoprim (see below).

Sulfisoxazole. Sulfisoxazole is a *short-acting* sulfonamide. Prior to the introduction of trimethoprim/sulfamethoxazole, sulfisoxazole was the preferred sulfonamide for urinary tract infections. The drug is just as effective as other sulfonamides and less expensive. Moreover, owing to its high water solubility, sulfisoxazole poses a minimal risk of crystalluria. Because high plasma concentrations of sulfisoxazole can be achieved, the drug is useful against a variety of systemic infections (eg, nocardiosis, chancroid, trachoma). In the United States, only one formulation is available: an oral solution that contains sulfisoxazole combined with erythromycin.

Sulfadiazine. Sulfadiazine is a *short-acting* sulfonamide with lower solubility than sulfisoxazole. Accordingly, if renal damage is to be avoided, high urine flow must be maintained. Sulfadiazine crosses the blood-brain barrier with ease, and hence is the best sulfonamide for prophylaxis of meningitis (although other drugs—ciprofloxacin, ceftriaxone, rifampin—are preferred). When combined with pyrimethamine, sulfadiazine is useful against toxoplasmosis.

Sulfadiazine is supplied in 500-mg oral tablets. The dosage for *adults* is 2 to 4 gm initially, followed by 2 to 4 gm every 24 hours, given as three to six divided doses. The maintenance dosage for *children age 2 months and older* is 150 mg/kg (or 4 gm/m²) every 24 hours (6 gm max), given as four to six divided doses.

Topical Sulfonamides

Topical sulfonamides have been associated with a high incidence of hypersensitivity and are not used routinely. The preparations discussed below have proven utility and a relatively low incidence of hypersensitivity.

Sulfacetamide. Sulfacetamide [Bleph-10] is widely used for superficial infections of the eye (eg, conjunctivitis, corneal ulcer). The drug may cause blurred vision, sensitivity to bright light, headache, brow ache, and local irritation. Hypersensitivity is rare, but severe reactions have occurred. Accordingly, sulfacetamide should not be used by patients with a history of severe hypersensitivity to sulfonamides, sulfonamides, or thiazide or loop diuretics. Sulfacetamide is available in solution (1%, 10%, and 15%) for application to the eye.

In addition to its ophthalmologic use, topical sulfacetamide is used for dermatologic disorders. The drug is available as a 10% lotion for treating seborrheic dermatitis and bacterial infections of the skin.

Silver Sulfadiazine and Mafenide. Both of these sulfonamides are employed to suppress bacterial colonization in patients with second- and third-degree burns. Mafenide acts by the same mechanism as other sulfonamides. In contrast, antibacterial effects of silver sulfadiazine are due primarily to release of free silver—and not to the sulfonamide portion of the molecule. Local application of mafenide is frequently painful. In contrast, application of silver sulfadiazine is usually pain free. Following application, both agents can be absorbed in amounts sufficient to produce systemic effects. Mafenide, but not silver sulfadiazine, is metabolized to a compound that can suppress renal excretion of acid, thereby causing acidosis. Accordingly, patients receiving mafenide should be monitored for acid-base status. If acidosis becomes severe, mafenide should be discontinued for 1 to 2 days. Mafenide is marketed under the trade name Sulfamylon. Trade names for silver sulfadiazine are Silvadene, Therma-zene, SSD Cream, Flamazine \clubsuit , and Dermazin \clubsuit .

TRIMETHOPRIM

Like the sulfonamides, trimethoprim [Primsol] suppresses synthesis of tetrahydrofolic acid. Trimethoprim is active against a broad spectrum of microbes.

Mechanism of Action

As indicated in Figure 88–2, trimethoprim *inhibits dihydrofolate reductase*, the enzyme that converts dihydrofolic acid to its active form: tetrahydrofolic acid. Hence, like the sulfonamides, trimethoprim suppresses bacterial synthesis of DNA, RNA, and proteins. Depending on conditions at the site of infection, trimethoprim may be bactericidal or bacteriostatic.

Although mammalian cells also contain dihydrofolate reductase, trimethoprim is selectively toxic to bacteria. Why? Because bacterial dihydrofolate reductase differs in structure from mammalian dihydrofolate reductase. As a result, trimethoprim inhibits the bacterial enzyme at concentrations about 40,000 times lower than those required to inhibit the mammalian enzyme. This allows suppression of bacterial growth with doses that have essentially no effect on the host.

Microbial Resistance

Bacteria acquire resistance to trimethoprim in three ways: (1) synthesizing increased amounts of dihydrofolate reductase, (2) producing an altered dihydrofolate reductase that has a low affinity for trimethoprim, and (3) reduced cellular permeability to trimethoprim. Resistance has resulted from spontaneous mutation and from transfer of R factors. In the United States, bacterial resistance is uncommon.

Antimicrobial Spectrum

Trimethoprim is active against most enteric gram-negative bacilli of clinical importance, including *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Serratia marcescens*, *Salmonella*, and *Shigella*. The drug is also active against some gram-positive bacilli (eg, *Corynebacterium diphtheriae*, *Listeria monocytogenes*), as well as some pathogenic protozoa (eg, *Toxoplasma gondii*), and one fungus (*P. jiroveci*).

Therapeutic Uses

Trimethoprim is approved only for initial therapy of acute, uncomplicated urinary tract infections due to susceptible organisms (eg, *E. coli*, *Proteus mirabilis*, *K. pneumoniae*, *Enterobacter* species, and coagulase-negative *Staphylococcus* species, including *S. saprophyticus*). When combined with sulfamethoxazole, trimethoprim has considerably more applications, as discussed later in the chapter.

Pharmacokinetics

Trimethoprim is absorbed rapidly and completely from the GI tract. The drug is lipid soluble, and therefore undergoes wide distribution to body fluids and tissues. Trimethoprim readily crosses the placenta. Most of an administered dose is excreted

unchanged in the urine. Hence, in the presence of renal impairment, the drug's half-life is prolonged. The concentration of trimethoprim achieved in urine is considerably higher than the concentration in blood.

Adverse Effects and Interactions

Trimethoprim is generally well tolerated. The most frequent adverse effects are itching and rash. Gastrointestinal reactions (eg, epigastric distress, nausea, vomiting, glossitis, stomatitis) occur occasionally.

Hematologic Effects. Because mammalian dihydrofolate reductase is relatively insensitive to trimethoprim, toxicities related to impaired tetrahydrofolate production are rare. These rare effects—*megaloblastic anemia*, *thrombocytopenia*, and *neutropenia*—occur only in individuals with pre-existing folic acid deficiency. Accordingly, caution is needed when administering trimethoprim to patients in whom folate deficiency might be likely (eg, alcoholics, pregnant women, debilitated patients). If early signs of bone marrow suppression occur (eg, sore throat, fever, pallor), complete blood counts should be performed. If a significant reduction in blood cell counts is observed, trimethoprim should be discontinued. Administering folic acid (leucovorin) will restore normal hematopoiesis.

Hyperkalemia. Trimethoprim suppresses renal excretion of potassium, and can thereby promote hyperkalemia. Patients at greatest risk are those taking high doses, those with renal impairment, and those taking other drugs that can elevate potassium, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), potassium-sparing diuretics, aldosterone antagonists, and potassium supplements. Patients over the age of 65 who are taking an ACE inhibitor or ARB are at especially high risk. Risk can be reduced by checking serum potassium, preferably 4 days after starting treatment (hyperkalemia typically develops within 5 days of starting treatment).

Effects in Pregnancy and Lactation. Large doses of trimethoprim have caused fetal malformations in animals. To date, developmental abnormalities have not been observed in humans. Nonetheless, since trimethoprim readily crosses the placenta, prudence dictates avoiding routine use during pregnancy. The risk of exacerbating pregnancy-related folate deficiency is an additional reason to avoid the drug.

Trimethoprim is excreted in breast milk and may interfere with folic acid utilization by the nursing infant. Administer with caution to women who are breast-feeding.

Preparations, Dosage, and Administration

Trimethoprim is supplied in 100-mg tablets sold generically, and in solution (50 mg/5 mL) sold as Primsol. For urinary tract infections, the usual dosage is 100 mg every 12 hours or 200 mg PO every 24 hours. In patients with moderate renal impairment (creatinine clearance 15 to 30 mL/min), dosage should be reduced to 50 mg every 12 hours. In patients with more severe renal impairment (creatinine clearance below 15 mL/min), trimethoprim should be avoided. Duration of treatment is 10 days.

TRIMETHOPRIM/SULFAMETHOXAZOLE

Trimethoprim (TMP) and sulfamethoxazole (SMZ) are marketed together in a fixed-dose combination product. This combination (TMP/SMZ) is a powerful antimicrobial preparation whose components act in concert to inhibit sequential steps in tetrahydrofolic acid synthesis. Trade names for TMP/

SMZ are *Bactrim* and *Septra*. In many countries, the combination is known generically as *co-trimoxazole*.

Mechanism of Action

The antimicrobial effects of TMP/SMZ result from inhibiting consecutive steps in the synthesis of tetrahydrofolic acid: SMZ acts first to inhibit incorporation of PABA into folic acid; TMP then inhibits dihydrofolate reductase, the enzyme that converts dihydrofolic acid into tetrahydrofolate (see Fig. 88-2). As a result, the ability of the target organism to make nucleic acids and proteins is greatly suppressed. By inhibiting two reactions required for synthesis of tetrahydrofolate, TMP and SMZ potentiate each other's effects. That is, the antimicrobial effect of the combination is more powerful than the sum of the effects of TMP alone plus SMZ alone. TMP/SMZ is selectively toxic to microbes because (1) mammalian cells use preformed folic acid, and therefore are not affected by SMZ; and (2) dihydrofolate reductases of mammalian cells are relatively insensitive to inhibition by TMP.

Microbial Resistance

Resistance to TMP/SMZ is less than to either drug alone. This is logical in that the chances of an organism acquiring resistance to both drugs are less than its chances of developing resistance to just one or the other. Specific mechanisms of resistance to sulfonamides and TMP are presented earlier in the chapter.

Antimicrobial Spectrum

TMP/SMZ is active against a wide range of gram-positive and gram-negative bacteria. This should be no surprise in that TMP and SMZ by themselves are broad-spectrum antimicrobial drugs. About 80% of urinary tract pathogens are susceptible. Specific bacteria against which TMP/SMZ is consistently effective include *E. coli*, *Proteus mirabilis*, *Listeria monocytogenes*, *S. aureus* (including methicillin-resistant isolates), *Chlamydia trachomatis*, *Salmonella typhi*, *Shigella* species, *Vibrio cholerae*, *Haemophilus influenzae*, and *Yersinia pestis*. TMP/SMZ is also active against *Nocardia*, certain protozoa (eg, *T. gondii*), and two fungi (*P. jiroveci* and *Paracoccidioides brasiliensis*).

Therapeutic Uses

TMP/SMZ is a preferred or alternative medication for a variety of infectious diseases. The combination is especially valuable for urinary tract infections, otitis media, bronchitis, shigellosis, and pneumonia caused by *P. jiroveci*.

Urinary Tract Infection. TMP/SMZ is indicated for chemotherapy of uncomplicated urinary tract infection caused by susceptible strains of *E. coli*, *Klebsiella*, *Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, and *Morganella morganii*. The combination is particularly useful for chronic and recurrent infections.

Pneumocystis Pneumonia (PCP). TMP/SMZ is the treatment of choice for PCP, an infection caused by *Pneumocystis jiroveci*, formerly thought to be *Pneumocystis carinii*. *Pneumocystis jiroveci* is an opportunistic fungus that thrives in immunocompromised hosts (eg, cancer patients, organ transplant recipients, individuals with AIDS). When given to AIDS patients, TMP/SMZ produces a high incidence of adverse effects.

Gastrointestinal Infections. TMP/SMZ is a drug of choice for infections caused by several gram-negative bacilli, including *Yersinia enterocolitica* and *Aeromonas*. In addition, the combination is a preferred treatment for shigellosis caused by susceptible strains of *Shigella flexneri* and *S. sonnei*.

Other Infections. TMP/SMZ can be used for otitis media and acute exacerbations of chronic bronchitis when these infections are due to susceptible strains of *H. influenzae* or *Streptococcus pneumoniae*. The preparation is also useful against urethritis and pharyngeal infection caused by penicillinase-producing *Neisseria gonorrhoeae*. Other infections that can be treated with TMP/SMZ include whooping cough, nocardiosis, brucellosis, melioidosis, listeria, and chancroid.

Pharmacokinetics

Absorption and Distribution. TMP/SMZ may be administered orally or by IV infusion. Both components of TMP/SMZ are well distributed throughout the body. Therapeutic concentrations are achieved in tissues and body fluids (eg, vaginal secretions, cerebrospinal fluid, pleural effusions, bile, aqueous humor). Both TMP and SMZ readily cross the placenta, and both enter breast milk.

Plasma Drug Levels. Optimal antibacterial effects are produced when the ratio of TMP to SMZ is 1:20. To achieve this ratio in plasma, TMP and SMZ must be administered in a ratio of 1:5. Hence, standard tablets contain 80 mg of TMP and 400 mg of SMZ. Because the plasma half-lives of TMP and SMZ are similar (10 hours for TMP and 11 hours for SMZ), levels of both drugs decline in parallel, and the 1:20 ratio is maintained as the drugs are eliminated.

Elimination. Both TMP and SMZ are excreted primarily by the kidneys. About 70% of urinary SMZ is present as inactive metabolites. In contrast, TMP undergoes little metabolism prior to excretion. Both agents are concentrated in the urine. Hence, levels of active drug are higher in the urine than in plasma, despite some conversion to inactive products.

Adverse Effects

TMP/SMZ is generally well tolerated; toxicity from routine use is rare. The most common adverse effects are nausea, vomiting, and rash. However, although infrequent, all of the serious toxicities associated with sulfonamides alone and trimethoprim alone can occur with TMP/SMZ. Hence, like sulfonamides, the combination can cause

- Hypersensitivity reactions (including Stevens-Johnson syndrome)
- Blood dyscrasias (hemolytic anemia, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia)
- Kernicterus
- Renal damage

And like trimethoprim, the combination can cause

- Megaloblastic anemia (but only in patients who are folate deficient)
- Hyperkalemia (especially in patients on high doses, and in those with renal impairment, and in those taking other drugs that can raise potassium levels)
- Birth defects (especially during the first trimester)

TMP/SMZ may also cause adverse CNS effects (headache, depression, hallucinations). Patients suffering from AIDS are unusually susceptible to TMP/SMZ toxicity. In this group, the incidence of adverse effects (rash, recurrent fever, leukopenia) is about 55%.

Several measures can reduce the incidence and severity of adverse effects. Crystalluria can be avoided by maintaining adequate hydration. Periodic blood tests permit early detection of hematologic disorders. To avoid kernicterus, TMP/SMZ should be withheld from pregnant women near term, nursing mothers, and infants under the age of 2 months. To avoid possible birth defects, TMP/SMZ should be withheld during the first trimester. The risk of megaloblastic anemia can be reduced by withholding sulfonamides from individuals likely to be folate deficient (eg, debilitated patients, pregnant women, alcoholics). Hypersensitivity reactions can be minimized by avoiding TMP/SMZ in patients with a history of hypersensitivity to sulfonamides or to chemically related drugs, including thiazide diuretics, loop diuretics, and sulfonylurea-type oral hypoglycemics. Injury from hyperkalemia can be reduced by checking serum potassium, and by exercising caution in patients taking other drugs that can elevate potassium.

Drug Interactions

Interactions of TMP/SMZ with other drugs are due primarily to the presence of SMZ. Hence, like sulfonamides used alone, SMZ in the combination can intensify the effects of warfarin, phenytoin, and sulfonylurea-type oral hypoglycemics (eg, tolbutamide). Accordingly, when these drugs are combined with TMP/SMZ, a reduction in their dosage may be needed. TMP/SMZ may also intensify bone marrow suppression in patients receiving methotrexate. As noted, drugs that raise potassium levels can increase the risk of hyperkalemia from TMP.

Preparations, Dosage, and Administration

Preparations. Trimethoprim/sulfamethoxazole [Bactrim, Septra] is supplied in tablets and a suspension for oral use, and in solution for IV infusion. The ratio of TMP to SMZ in all preparations is 1:5. Two tablet strengths are available: *standard tablets* contain 80 mg TMP and 400 mg SMZ; *double-strength tablets* contain 160 mg TMP and 800 mg SMZ. Each milliliter of the *oral suspension* contains 8 mg TMP and 40 mg SMZ. Each milliliter of the *stock solution for IV infusion* contains 16 mg TMP and 80 mg SMZ; this stock solution must be greatly diluted before use.

Oral Dosing. For management of most infections, the usual *adult* dosage is 160 mg TMP plus 800 mg SMZ administered every 12 hours for 10 to 14 days. To treat shigellosis or traveler's diarrhea, the same dose is adminis-

tered every 12 hours for 5 days. In the presence of renal impairment (creatinine clearance 15 to 30 mL/min), the dosage should be reduced by 50%. If creatinine clearance is below 15 mL/min, TMP/SMZ should not be used.

To treat urinary tract infections and acute otitis media in *children*, the usual dosage is 4 mg/kg TMP plus 20 mg/kg SMZ administered every 12 hours for 10 days. The same dose, administered every 12 hours for 5 days, is used to treat shigellosis. As in adults, the dosage should be reduced in patients with renal impairment.

For *prophylaxis of PCP* in patients with AIDS, the usual dosage is 160 mg TMP plus 800 mg SMZ once daily.

Intravenous Dosing. Intravenous TMP/SMZ is reserved for severe infections. The following dosages are for adults and children, and are based on the TMP component of TMP/SMZ. For urinary tract infection or shigellosis, the total daily dose is 8 to 10 mg/kg. This total dose is administered in two to four divided doses given at equally spaced intervals. Duration of treatment is 14 days for urinary tract infection and 5 days for shigellosis. For treatment of PCP, the total daily dose is 15 to 20 mg/kg, administered in three or four divided doses given at equally spaced intervals. Duration of treatment is 3 weeks or more. Dosage for all indications should be reduced in patients with renal impairment. Intravenous TMP/SMZ represents a large fluid load, and hence must be used with care in patients needing fluid restriction.

KEY POINTS

- The sulfonamides and trimethoprim act by inhibiting bacterial synthesis of folic acid.
- Sulfonamides are used primarily for urinary tract infections.
- The principal adverse effects of sulfonamides are (1) hypersensitivity reactions, ranging from rash and photosensitivity to Stevens-Johnson syndrome; (2) hemolytic anemia; (3) kernicterus; and (4) renal damage.
- Trimethoprim is used primarily for urinary tract infections.
- The principal adverse effects of trimethoprim are hyperkalemia and possible birth defects.
- The combination product TMP/SMZ inhibits sequential steps in bacterial folic acid synthesis, and therefore is much more powerful than TMP or SMZ alone.
- TMP/SMZ is a preferred drug for urinary tract infections and is the drug of choice for PCP in patients with AIDS and other immunodeficiency states.
- The principal adverse effects of TMP/SMZ are like those caused by sulfonamides alone (ie, hypersensitivity reactions, hemolytic anemia, kernicterus, and renal injury) and trimethoprim alone (hyperkalemia and birth defects).

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Summary of Major Nursing Implications***SULFONAMIDES (SYSTEMIC)**

Sulfadiazine
Sulfamethoxazole[†]
Sulfisoxazole[‡]

The nursing implications summarized here apply only to systemic sulfonamides. Implications specific to topical sulfonamides are not summarized.

Preadministration Assessment**Therapeutic Goal**

Sulfonamides are used primarily for urinary tract infections caused by *E. coli* and other susceptible organisms.

Identifying High-Risk Patients

Sulfonamides are *contraindicated* for nursing mothers, pregnant women near term, and infants under 2 months old. In addition, sulfonamides are contraindicated for patients

with a history of severe hypersensitivity to sulfonamides and chemically related drugs, including thiazide diuretics, loop diuretics, and sulfonylurea-type oral hypoglycemics—even though good proof of cross-hypersensitivity is lacking.

Exercise *caution* in patients with renal impairment.

Implementation: Administration**Routes**

All currently available systemic sulfonamides are administered orally.

Administration

Instruct patients to complete the prescribed course of treatment, even though symptoms may abate before the full course is over.

Advise patients to take oral sulfonamides on an empty stomach and with a full glass of water.

*Patient education information is highlighted as blue text.

[†]Sulfamethoxazole is available only in combination with trimethoprim.

[‡]Sulfisoxazole is available only in combination with erythromycin.

Summary of Major Nursing Implications*—cont'd

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hypersensitivity Reactions. Sulfonamides can induce severe hypersensitivity reactions (eg, Stevens-Johnson syndrome). Do not give sulfonamides to patients with a history of severe hypersensitivity to sulfonamides or to chemically related drugs, including sulfonylureas, thiazide diuretics, and loop diuretics. **Instruct patients to discontinue drug use at the first sign of hypersensitivity (eg, rash).**

Photosensitivity. Photosensitivity reactions may occur. **Advise patients to avoid prolonged exposure to sunlight, wear protective clothing, and apply a sunscreen to exposed skin.**

Hematologic Effects. Sulfonamides can cause hemolytic anemia and other blood dyscrasias (agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia). Observe patients for signs of hemolysis (fever, pallor, jaundice). When sulfonamide therapy is prolonged, periodic blood cell counts should be made.

Kernicterus. Sulfonamides can cause kernicterus in newborns. Do not give these drugs to pregnant women near term, nursing mothers, or infants under 2 months old.

Renal Damage. Deposition of sulfonamide crystals can injure the kidney. To minimize crystalluria, maintain hydration sufficient to produce a daily urine flow of 1200 mL in adults. Alkalinization of urine (eg, with sodium bicarbonate) can also help. **Advise outpatients to consume 8 to 10 glasses of water per day.**

Minimizing Adverse Interactions

Metabolism-Related Interactions. Sulfonamides can intensify the effects of *warfarin*, *phenytoin*, and *sulfonylurea-type oral hypoglycemics* (eg, tolbutamide). When combined with sulfonamides, these drugs may require a reduction in dosage.

Cross-Hypersensitivity. People who are hypersensitive to sulfonamide antibiotics may also be hypersensitive to chemically related drugs—*thiazide diuretics*, *loop diuretics*, and *sulfonylurea-type oral hypoglycemics*—as well as to *penicillins* and other drugs that induce allergic reactions.

TRIMETHOPRIM

Preadministration Assessment

Therapeutic Goal

Initial treatment of uncomplicated urinary tract infections caused by *E. coli* and other susceptible organisms.

Identifying High-Risk Patients

Trimethoprim is *contraindicated* in patients with folate deficiency (manifested as megaloblastic anemia). When possible, the drug should be avoided during pregnancy and lactation.

Implementation: Administration

Route

Oral.

Dosage and Administration

Instruct patients to complete the prescribed course of treatment, even though symptoms may abate before the full course is over.

Reduce the dosage in patients with renal dysfunction.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects and Interactions

Hematologic Effects. Trimethoprim can cause blood dyscrasias (megaloblastic anemia, thrombocytopenia, neutropenia) by exacerbating pre-existing folate deficiency. Avoid trimethoprim when folate deficiency is likely (eg, in alcoholics, pregnant women, debilitated patients). **Inform patients about early signs of blood disorders (eg, sore throat, fever, pallor), and instruct them to notify the prescriber if these occur.** Complete blood counts should be performed. If a significant reduction in counts is observed, discontinue trimethoprim. Normal hematopoiesis can be restored with folic acid (leucovorin).

Hyperkalemia. Trimethoprim can cause hyperkalemia, especially in patients taking high doses, patients with renal impairment, and patients taking ACE inhibitors, ARBs, potassium-sparing diuretics, aldosterone antagonists, and potassium supplements. Risk can be reduced by checking serum potassium 4 days after starting treatment, and by exercising caution in patients taking other drugs that can elevate potassium.

Use in Pregnancy and Lactation. Trimethoprim should be avoided during pregnancy and lactation. The drug can exacerbate folate deficiency in pregnant women and cause folate deficiency in the nursing infant. In addition, trimethoprim may promote birth defects, especially during the first trimester.

TRIMETHOPRIM/SULFAMETHOXAZOLE

Preadministration Assessment

Therapeutic Goal

Indications include urinary tract infections caused by *E. coli* and other susceptible organisms, shigellosis, and *Pneumocystis pneumonia* (PCP).

Identifying High-Risk Patients

TMP/SMZ is *contraindicated* for nursing mothers, pregnant women near term, infants under 2 months old, patients with folate deficiency (manifested as megaloblastic anemia), and patients with a history of hypersensitivity to sulfonamides and chemically related drugs, including thiazide diuretics, loop diuretics, and sulfonylurea-type oral hypoglycemics.

Implementation: Administration

Routes

Oral; IV (for severe infections).

Dosage Adjustment

In patients with renal impairment (creatinine clearance of 15 to 30 mL/min), decrease dosage by 50%. If creatinine clearance falls below 15 mL/min, discontinue drug use.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Administration

Instruct patients to complete the prescribed course of treatment, even though symptoms may abate before the full course is over.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Although serious adverse reactions are rare, TMP/SMZ can nonetheless cause all of the toxicities associated with sulfonamides and trimethoprim used alone. Hence, the nursing

implications summarized above regarding adverse effects of the sulfonamides alone and trimethoprim alone also apply to the combination of TMP/SMZ.

Minimizing Adverse Interactions

TMP/SMZ has the same drug interactions as sulfonamides and trimethoprim used alone. Hence, the nursing implications summarized above regarding drug interactions of the sulfonamides alone and trimethoprim alone also apply to the combination of TMP/SMZ.

*Patient education information is highlighted as blue text.

Drug Therapy of Urinary Tract Infections

Organisms That Cause Urinary Tract Infections Specific Urinary Tract Infections and Their Treatment

Acute Cystitis

Acute Uncomplicated Pyelonephritis

Complicated Urinary Tract Infections

Recurrent Urinary Tract Infection

Acute Bacterial Prostatitis

Urinary Tract Antiseptics

Nitrofurantoin

Methenamine

Urinary tract infections (UTIs) are the most common infections encountered today. In the United States, UTIs account for over 7 million visits to healthcare providers each year. Among sexually active young women, 25% to 35% develop at least one UTI a year. Among elderly women in nursing homes, between 30% and 50% have bacteriuria at any given time. UTIs occur much less frequently in males, but are more likely to be associated with complications (eg, septicemia, pyelonephritis).

Infections may be limited to bacterial colonization of the urine, or bacteria may invade tissues of the urinary tract. When bacteria invade tissues, characteristic inflammatory syndromes result: *urethritis* (inflammation of the urethra), *cystitis* (inflammation of the urinary bladder), *pyelonephritis* (inflammation of the kidney and its pelvis), and *prostatitis* (inflammation of the prostate).

UTIs may be classified according to their location, in either the lower urinary tract (bladder and urethra) or upper urinary tract (kidney). Within this classification scheme, *cystitis* and *urethritis* are considered *lower tract infections*, whereas *pyelonephritis* is considered an *upper tract infection*.

UTIs are referred to as being *complicated* or *uncomplicated*. *Complicated* UTIs occur in both males and females and, by definition, are associated with some predisposing factor, such as calculi (stones), prostatic hypertrophy, an indwelling catheter, or an impediment to the flow of urine (eg, physiological obstruction). *Uncomplicated* UTIs occur primarily in women of child-bearing age and are not associated with any particular predisposing factor.

Several classes of antibiotics are used to treat UTIs. Among these are sulfonamides, trimethoprim, penicillins, aminoglycosides, cephalosporins, fluoroquinolones, and two urinary tract antiseptics: nitrofurantoin and methenamine. With the exception of the urinary tract antiseptics, all of these drugs are discussed at length in other chapters. The

basic pharmacology of the urinary tract antiseptics is introduced here.

ORGANISMS THAT CAUSE URINARY TRACT INFECTIONS

The bacteria that cause UTIs differ between community-acquired infections and hospital-acquired (nosocomial) infections. The majority (more than 80%) of uncomplicated, community-acquired UTIs are caused by *Escherichia coli*. Rarely, other gram-negative bacilli—*Klebsiella pneumoniae*, *Enterobacter*, *Proteus*, *Providencia*, and *Pseudomonas*—are the cause. Gram-positive cocci, especially *Staphylococcus saprophyticus*, account for 10% to 15% of community-acquired infections. Hospital-acquired UTIs are frequently caused by *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*, staphylococci, and enterococci; *E. coli* is responsible for less than 50% of these infections. Although most UTIs involve only one organism, infection with multiple organisms may occur, especially in patients with an indwelling catheter, renal stones, or chronic renal abscesses.

SPECIFIC URINARY TRACT INFECTIONS AND THEIR TREATMENT

In this section, we consider the characteristics and treatment of the major UTIs: acute cystitis, acute urethral syndrome, acute pyelonephritis, acute bacterial prostatitis, and recurrent UTIs. Most of these can be treated with oral therapy at home. The principal exception is severe pyelonephritis, which requires IV therapy in a hospital. Drugs and dosages for outpatient therapy in nonpregnant women are summarized in Table 89-1.

Acute Cystitis

Acute cystitis is a lower urinary tract infection that occurs most often in women of child-bearing age. Clinical manifestations are dysuria, urinary urgency, urinary frequency, suprapubic discomfort, pyuria, and bacteriuria (more than 100,000 bacteria per milliliter of urine). It is important to note that many women (30% or more) with symptoms of acute cystitis also have asymptomatic upper urinary tract infection (subclinical pyelonephritis). In uncomplicated, community-acquired cystitis, the principal causative organisms are *E. coli* (80%), *Staph. saprophyticus* (11%), and *Enterococcus faecalis*.

For community-acquired infections, three types of oral therapy can be employed: (1) single-dose therapy, (2) short-

TABLE 89-1 ■ Regimens for Oral Therapy of Urinary Tract Infections in Nonpregnant Women

Drug	Dose	Duration
ACUTE CYSTITIS		
First-Line Drugs		
Trimethoprim/sulfamethoxazole	160/800 mg 2 times/day	3 days
Trimethoprim	100 mg 2 times/day	3 days
Nitrofurantoin	100 mg 2 times/day	7 days
Ciprofloxacin	250 mg 2 times/day	3 days
Norfloxacin	400 mg 2 times/day	3 days
Levofloxacin	250 mg once daily	3 days
Second-Line Drugs		
Nitrofurantoin (macrocrystals)	50–100 mg 4 times/day	7 days
Nitrofurantoin (monohydrate/ macrocrystals)	100 mg 2 times/day	7 days
Fosfomycin	3 gm once	1 day
ACUTE UNCOMPLICATED PYELONEPHRITIS		
First-Line Drugs		
Trimethoprim/sulfamethoxazole	160/800 mg 2 times/day	14 days
Trimethoprim	100 mg 2 times/day	14 days
Ciprofloxacin	250–500 mg 2 times/day	14 days
Levofloxacin	250 mg once daily*	10 days
Second-Line Drugs		
Amoxicillin (with clavulanic acid)	500 mg 3 times/day	14 days
Cephalexin	500 mg 4 times/day	14 days
Cefotaxime	1 gm 3 times/day	14 days
Ceftriaxone	1–2 gm once daily	14 days
COMPLICATED URINARY TRACT INFECTIONS		
Trimethoprim/sulfamethoxazole	160/800 mg 2 times/day	7–14 days
Norfloxacin	400 mg 2 times/day	7–14 days
Ciprofloxacin	250–500 mg 2 times/day	7–14 days
Levofloxacin	500 mg once daily	7–14 days
Amoxicillin (with clavulanic acid)	500 mg 3 times/day	7–14 days
Cephalexin	500 mg 3 times/day	7–14 days
PROPHYLAXIS OF RECURRENT INFECTIONS		
Trimethoprim/sulfamethoxazole	40/200 mg [†] at bedtime 3 times/wk	6 months
Trimethoprim	100 mg at bedtime	6 months
Nitrofurantoin	50–100 mg at bedtime	6 months
Norfloxacin	200 mg at bedtime	6 months

*For infection due to *E. coli* without concurrent bacteremia.

[†]One-half of a single-strength tablet.

course therapy (3 days), and (3) conventional therapy (7 days). *Single-dose* therapy and *short-course* therapy are recommended only for uncomplicated, community-acquired infections in women who are not pregnant and whose symptoms began less than 7 days before starting treatment. As a rule, short-course therapy is more effective than single-dose therapy and hence is generally preferred. Advantages of short-course therapy over conventional therapy are lower cost, greater adherence, fewer side effects, and less potential for promoting emergence of bacterial resistance. *Conventional* therapy is indicated for all patients who do not meet the criteria for short-course therapy. Among these are males, children, pregnant women, and women with suspected upper tract involvement.

As indicated in Table 89-1, several drugs can be used for treatment. For uncomplicated cystitis, trimethoprim/sulfamethoxazole and nitrofurantoin are drugs of first choice. In

communities where resistance to these drugs exceeds 20%, the fluoroquinolones (eg, ciprofloxacin, norfloxacin) are good alternatives. When adherence is a concern, fosfomycin, which requires just one dose, is an attractive choice. As a rule, beta-lactam antibiotics (eg, amoxicillin; cephalexin and other cephalosporins) should be avoided. Why? Because they are less effective than the alternatives, and less well tolerated.

Acute Uncomplicated Pyelonephritis

Acute uncomplicated pyelonephritis is an infection of the kidneys. The disorder is common in young children, the elderly, and women of child-bearing age. Clinical manifestations include fever, chills, severe flank pain, dysuria, urinary frequency, urinary urgency, pyuria, and, usually, bacteriuria

(more than 100,000 bacteria per milliliter of urine). *Escherichia coli* is the causative organism in 90% of initial community-acquired infections.

Mild to moderate infection can be treated at home with oral antibiotics. Preferred options are trimethoprim/sulfamethoxazole, trimethoprim alone, ciprofloxacin, and levofloxacin. Treatment should last 14 days. Some regimens for oral therapy are shown in Table 89-1.

Severe pyelonephritis requires hospitalization and IV antibiotics. Options include ciprofloxacin, ceftriaxone, ceftazidime, ampicillin plus gentamicin, and ampicillin/sulbactam. Once the infection has been controlled with IV antibiotics, a switch to oral antibiotics should be made, usually within 24 to 48 hours.

Complicated Urinary Tract Infections

Complicated UTIs occur in males and females who have a structural or functional abnormality of the urinary tract that predisposes them to developing infection. Such predisposing factors include prostatic hypertrophy, renal calculi (stones), nephrocalcinosis, renal or bladder tumors, ureteric stricture, or an indwelling urethral catheter. Symptoms of complicated UTIs can range from mild to severe. Some patients even develop systemic illness, manifesting as fever, bacteremia, and septic shock.

The microbiology of complicated UTIs is less predictable than that of uncomplicated UTIs. Although *E. coli* is a common pathogen, it is by no means the only one. Other possibilities include *Klebsiella*, *Proteus*, *Pseudomonas*, *Staphylococcus aureus*, *Enterobacter* species, *Serratia* species, and even *Candida* species. Accordingly, if treatment is to succeed, we must determine the identity and drug sensitivity of the causative organism. To do so, urine for microbiologic testing should be obtained *before* giving any antibiotics. If symptoms are relatively mild, treatment should wait until test results are available. However, if symptoms are severe, immediate treatment with a broad-spectrum antibiotic can be instituted. Some options are presented in Table 89-1. Once test results are known, a drug specific to the pathogen can be substituted. Duration of treatment ranges from 7 days (for cystitis) to 14 days (for pyelonephritis or when there is systemic involvement).

Recurrent Urinary Tract Infection

Recurrent UTIs result from *relapse* or from *reinfection*. *Relapse* is caused by recolonization with the same organism responsible for the initial infection. In contrast, *reinfection* is caused by colonization with a new organism.

Reinfection. More than 80% of recurrent UTIs in females are due to reinfection. These usually involve the lower urinary tract and may be related to sexual intercourse or use of a contraceptive diaphragm. If reinfections are *infrequent* (only one or two a year), each episode should be treated as a separate infection. Single-dose or short-course therapy can be used.

When reinfections are *frequent* (three or more a year), long-term prophylaxis may be indicated. Prophylaxis can be achieved with low daily doses of several agents, including trimethoprim (100 mg), nitrofurantoin (50 or 100 mg), or trimethoprim/sulfamethoxazole (160 mg/800 mg). Prophylaxis

should continue for at least 6 months. During this time, periodic urine cultures should be obtained. If a symptomatic episode occurs, standard therapy for acute cystitis should be given. If reinfection is associated with sexual intercourse, the risk can be decreased by voiding after intercourse and by single-dose prophylaxis (eg, trimethoprim/sulfamethoxazole [160 mg/800 mg] taken after intercourse).

Relapse. Recolonization with the original infecting organism accounts for 20% of recurrent UTIs. Symptoms that reappear shortly after completion of a course of therapy suggest either a structural abnormality of the urinary tract, involvement of the kidneys, or chronic bacterial prostatitis, the most common cause of recurrent UTI in males. If obstruction of the urinary tract is present, it should be corrected surgically. If renal calculi are the cause, they should be removed.

Drug therapy is progressive. When relapse occurs in women after short-course therapy, a 2-week course of therapy should be tried. If this fails, an additional 4 to 6 weeks of therapy should be tried. If this too is unsuccessful, long-term therapy (6 months) may be indicated. Drugs employed for long-term therapy of relapse include trimethoprim/sulfamethoxazole, norfloxacin, and cephalexin.

Acute Bacterial Prostatitis

Acute bacterial prostatitis is defined as inflammation of the prostate caused by local bacterial infection. Clinical manifestations include high fever, chills, malaise, myalgia, localized pain, and various urinary tract symptoms (dysuria, nocturia, urinary urgency, urinary frequency, urinary retention). In most cases (80%), *E. coli* is the causative organism. Infection is frequently associated with an indwelling urethral catheter, urethral instrumentation, or transurethral prostatic resection. However, in many patients, the infection has no obvious cause.

Bacterial prostatitis responds well to antimicrobial therapy. Because of local inflammation, antibiotics can readily penetrate to the site of infection. (In the absence of inflammation, penetration of the prostate is difficult.) Drug selection and route depend on the causative organism and infection severity. For severe infection with *E. coli*, treatment starts with an IV agent (either aztreonam or a fluoroquinolone [eg, ciprofloxacin]), followed by 4 weeks with an oral agent (either doxycycline or a fluoroquinolone). For severe infection with vancomycin-sensitive *Enterococcus faecalis*, treatment starts with IV ampicillin/sulbactam, followed by 4 weeks with PO amoxicillin, levofloxacin, or doxycycline.

URINARY TRACT ANTISEPTICS

Two urinary tract antiseptics are currently available: nitrofurantoin and methenamine. Both are used only for UTIs. These drugs become concentrated in the urine, and are active against the common urinary tract pathogens. Neither drug achieves effective antibacterial concentrations in blood or tissues. According to recent guidelines, nitrofurantoin is a first-choice drug for uncomplicated cystitis. Two other urinary tract antiseptics—nalidixic acid [NegGram] and cinoxacin [Cinobac]—have been withdrawn. For information on these drugs, refer to the seventh edition of this text.

Nitrofurantoin

Mechanism of Action

Nitrofurantoin [Furadantin, Macrochantin, Macrobid] is a broad-spectrum antibacterial drug, producing bacteriostatic effects at low concentrations and bactericidal effects at high concentrations. Therapeutic levels are achieved only in urine. Nitrofurantoin can cause serious adverse effects.

Nitrofurantoin injures bacteria by damaging DNA. However, in order to damage DNA, the drug must first undergo enzymatic conversion to a reactive form. Nitrofurantoin is selectively toxic to bacteria because, unlike mammalian cells, bacteria possess relatively high levels of the enzyme needed for drug activation.

Antimicrobial Spectrum

Nitrofurantoin is active against a large number of gram-positive and gram-negative bacteria. Susceptible organisms include staphylococci, streptococci, *Neisseria*, *Bacteroides*, and most strains of *E. coli*. These sensitive bacteria rarely acquire resistance. Organisms that are frequently insensitive include *Proteus*, *Pseudomonas*, *Enterobacter*, and *Klebsiella*.

Therapeutic Use

Nitrofurantoin is indicated for acute infections of the lower urinary tract caused by susceptible organisms. In addition, the drug can be used for prophylaxis of recurrent lower UTI. Nitrofurantoin is not recommended for infections of the upper urinary tract.

Pharmacokinetics

Absorption and Distribution. Nitrofurantoin is available in three crystalline forms: *microcrystals*, *macrocrystals*, and *monohydrate/macrocrystals*. The two macrocrystalline forms are absorbed relatively slowly and produce less GI distress than the microcrystalline form. All formulations produce equivalent therapeutic effects. Nitrofurantoin is distributed to tissues, but only in small amounts. Therapeutic concentrations are achieved only in urine.

Metabolism and Excretion. About two-thirds of each dose undergoes metabolic degradation, primarily in the liver; the remaining one-third is excreted intact in the urine. Nitrofurantoin achieves a urinary concentration of about 200 mcg/mL (compared with less than 2 mcg/mL in plasma). The drug imparts a harmless brown color to the urine; patients should be informed of this effect.

For two reasons, nitrofurantoin should not be administered to individuals with renal impairment (creatinine clearance less than 40 mL/min). First, in the absence of good renal function, levels of nitrofurantoin in the urine are too low to be effective. Second, renal impairment reduces nitrofurantoin excretion, causing plasma levels of the drug to rise, thereby posing a risk of systemic toxicity.

Adverse Effects

Gastrointestinal Effects. The most frequent adverse reactions are GI disturbances (eg, anorexia, nausea, vomiting, diarrhea). These can be minimized by administering nitrofurantoin with milk or with meals, by reducing the dosage, and by using the macrocrystalline formulations.

Pulmonary Reactions. Nitrofurantoin can induce two kinds of pulmonary reactions: acute and subacute. Acute reactions, which are most common, manifest as dyspnea, chest pain, chills, fever, cough, and alveolar infiltrates. These symptoms resolve 2 to 4 days after discontinuing the drug. Acute pulmonary responses are thought to be hypersensitivity reactions. Patients with a history of these responses should not receive nitrofurantoin again. Subacute reactions are rare and

occur during prolonged treatment. Symptoms (eg, dyspnea, cough, malaise) usually regress over weeks to months following nitrofurantoin withdrawal. However, in some patients, permanent lung damage may occur.

Hematologic Effects. Nitrofurantoin can cause a variety of hematologic reactions, including agranulocytosis, leukopenia, thrombocytopenia, and megaloblastic anemia. In addition, hemolytic anemia may occur in infants and in patients whose red blood cells have an inherited deficiency in glucose-6-phosphate dehydrogenase. Because of the potential for hemolytic anemia in newborns, nitrofurantoin is contraindicated for pregnant women near term and for infants under the age of 1 month.

Peripheral Neuropathy. Damage to sensory and motor nerves is a serious concern. Demyelination and nerve degeneration can occur and may be irreversible. Early symptoms include muscle weakness, tingling sensations, and numbness. Patients should be informed about these symptoms and instructed to report them immediately. Neuropathy is most likely in patients with renal impairment and in those taking nitrofurantoin chronically.

Hepatotoxicity. Rarely, nitrofurantoin has caused severe liver injury, manifesting as hepatitis, cholestatic jaundice, and hepatic necrosis. Deaths have occurred. To reduce risk, patients should undergo periodic tests of liver function. Those who develop liver injury should discontinue nitrofurantoin immediately and never use it again.

Birth Defects. Results of the *National Birth Defects Prevention Study*, published in 2009, showed an association between nitrofurantoin and four types of birth defects: anophthalmia (the absence of one or both eyes), hypoplastic left heart syndrome (marked hypoplasia of the left ventricle and ascending aorta), atrial septal defects, and cleft lip with cleft palate. However, owing to limitations of the study, a causal relationship has not been established. Nonetheless, until more is known, it would seem prudent to avoid nitrofurantoin during pregnancy.

CNS Effects. Nitrofurantoin can cause multiple CNS effects (eg, headache, vertigo, drowsiness, nystagmus). All are readily reversible.

Preparations, Dosage, and Administration

Preparations. Nitrofurantoin is available in three crystalline forms: *microcrystals*, *macrocrystals*, and *monohydrate/macrocrystals*. *Nitrofurantoin microcrystals* [Furadantin] are supplied as an oral suspension (5 mg/mL). *Nitrofurantoin macrocrystals* [Macrochantin] are supplied in capsules (25, 50, and 100 mg). *Nitrofurantoin monohydrate/macrocrystals* [Macrobid] are supplied in 100-mg capsules.

Administration. Dosing is oral. GI distress can be reduced by (1) using Macrochantin or Macrobid, rather than Furadantin, and (2) giving the drug with meals or with milk.

Dosage. For acute cystitis, dosage depends on which formulation is used. With the macrocrystals [Macrochantin], the adult dosage is 50 mg 4 times a day for 7 days. With the monohydrate/macrocrystals [Macrobid], the adult dosage is 100 mg twice a day for 7 days.

For prophylaxis of recurrent cystitis, low doses are employed (eg, 50 to 100 mg at bedtime for adults and 1 mg/kg/day in one or two doses for children).

Methenamine

Mechanism of Action

Methenamine [Hiprex, Urex, Mandelamine] is a prodrug that, under acidic conditions, breaks down into ammonia and formaldehyde. The formaldehyde denatures bacterial proteins, causing cell death. For formaldehyde to be released, the urine must be acidic (pH 5.5 or less). Since formaldehyde is not formed at physiologic systemic pH, methenamine is devoid of systemic toxicity.

Antimicrobial Spectrum

Virtually all bacteria are susceptible to formaldehyde; there is no resistance. Certain bacteria (eg, *Proteus* species) can elevate urinary pH (by der alkaline conditions, infections with urea-splitting organisms are often unresponsive).

Therapeutic Uses

Methenamine is used for *chronic infection of the lower urinary tract*. However, trimethoprim/sulfamethoxazole is preferred. Methenamine is not active against upper tract infections. Why? Because, there is insufficient time for formaldehyde to form as the drug passes through. Methenamine does not prevent UTIs associated with catheters.

Pharmacokinetics

Absorption and Distribution. Methenamine is rapidly absorbed after oral administration. However, approximately 30% of each dose may be converted to ammonia and formaldehyde in the acidic environment of the stomach. This can be minimized by using an enteric-coated formulation. The drug is distributed throughout total body water.

Excretion. Methenamine is eliminated by the kidneys. Within the urinary tract, about 20% of the drug decomposes to form formaldehyde. Levels of formaldehyde are highest in the bladder. Since formaldehyde generation takes place slowly, and since transit time through the kidney is brief, formaldehyde levels in the kidney remain subtherapeutic. Ingestion of large volumes of fluid reduces antibacterial effects by diluting methenamine and raising urinary pH. Poorly metabolized acids (eg, hippuric acid, mandelic acid, ascorbic acid) have been administered with methenamine in attempts to acidify the urine, and thereby increase formaldehyde formation. However, there is no evidence that these acids enhance therapeutic effects.

Adverse Effects and Precautions

Methenamine is relatively safe and generally well tolerated. Gastric distress occurs occasionally, probably from formaldehyde in the stomach. Use of enteric-coated preparations may reduce this effect. Chronic high-dose therapy can cause bladder irritation, manifested as dysuria, frequent voiding, urinary urgency, proteinuria, and hematuria. Since decomposition of methenamine generates ammonia (in addition to formaldehyde), the drug is contraindicated for patients with liver dysfunction. Methenamine salts (methenamine mandelate, methenamine hippurate) should not be used by patients with renal impairment. Why? Because crystalluria may be caused by precipitating the mandelate or hippurate moiety.

Drug Interactions

Urinary Alkalinizers. Drugs that elevate urinary pH (eg, acetazolamide, sodium bicarbonate) inhibit formaldehyde production, and can thereby reduce the antibacterial effects. Patients taking methenamine should not receive alkalinizing agents.

Sulfonamides. Methenamine should not be combined with sulfonamides. Why? Because formaldehyde forms an insoluble complex with sulfonamides, thereby posing a risk of urinary tract injury from crystalluria.

Preparations, Dosage, and Administration

Methenamine, in the form of *methenamine hippurate* [Hiprex, Urex], is available in 1-gm tablets for oral dosing. The dosage for children ages 6 to 12 years is 500 mg to 1 gm twice a day. The dosage for adults and children age 12 years and older is 1 gm twice a day.

KEY POINTS

- *Escherichia coli* is the most common cause of uncomplicated, community-acquired UTIs.
- Except for pyelonephritis, most UTIs can be treated with oral therapy at home.
- Trimethoprim/sulfamethoxazole is frequently the treatment of choice for oral therapy of UTIs.
- Many drugs, including penicillins, cephalosporins, and fluoroquinolones, may be used for parenteral therapy of UTIs.
- Prophylaxis of recurrent UTI can be achieved with daily low doses of oral antibiotics (eg, trimethoprim/sulfamethoxazole).
- Nitrofurantoin, a urinary tract antiseptic, is a drug of choice for uncomplicated cystitis.

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Antimycobacterial Agents: Drugs for Tuberculosis, Leprosy, and *Mycobacterium avium* Complex Infection

DRUGS FOR TUBERCULOSIS

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Isoniazid

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DRUGS FOR LEPROSY (HANSEN'S DISEASE)

Overview of Treatment

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DRUGS FOR MYCOBACTERIUM AVIUM COMPLEX INFECTION

Our topic for this chapter is infections caused by three species of mycobacteria: *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and *Mycobacterium avium*. The mycobacteria are slow-growing microbes, and the infections they cause require prolonged treatment. Because therapy is prolonged, drug toxicity and poor patient adherence are significant obstacles to success. In addition, prolonged treatment promotes the emergence of drug-resistant mycobacteria. Because mycobacteria resist decolorizing by the dilute acid used in some staining protocols, these microorganisms are often referred to as *acid-fast bacteria*.

DRUGS FOR TUBERCULOSIS

Tuberculosis (TB) is a global epidemic. Worldwide, over 2 billion people harbor latent infection—nearly one-third of the Earth's population. In 2009, TB killed 1.7 million people—more than any other infectious disease. Although new cases in

the United States continue to decline (down from 20,673 in 1992 to 11,181 in 2010), in the rest of the world new cases are on the rise. The current estimate is 9 million new cases a year. Of these, the vast majority (95%) occur in developing countries. There are two reasons for this resurgence: HIV/AIDS and the emergence of multidrug-resistant mycobacteria.

CLINICAL CONSIDERATIONS

Pathogenesis

Tuberculosis is caused by *Mycobacterium tuberculosis*, an organism also known as the tubercle bacillus. Infections may be limited to the lungs or may become disseminated. In most cases, the bacteria are quiescent, and the infected individual has no symptoms. However, when the disease is active, morbidity can be significant. In the United States, approximately 10 million people harbor tubercle bacilli. However, only a small fraction have symptomatic disease.

Primary Infection

Infection with *M. tuberculosis* is transmitted from person to person by inhaling infected sputum that has been aerosolized, usually by coughing or sneezing. As a result, initial infection is in the lung. Once in the lung, tubercle bacilli are taken up by phagocytic cells (macrophages and neutrophils). At first, the bacilli are resistant to the destructive activity of phagocytes and multiply freely within them. Infection can spread from the lungs to other organs via the lymphatic and circulatory systems.

In most cases, immunity to *M. tuberculosis* develops within a few weeks, and the infection is brought under complete control. The immune system facilitates control by increasing the ability of phagocytes to suppress multiplication of tubercle bacilli. Because of this rapid response by the immune system, most individuals (90%) with primary infection never develop clinical or radiologic evidence of disease. However, even though symptoms are absent and the progression of infection is halted, the infected individual is likely to harbor tubercle bacilli lifelong, unless drugs are given to eliminate quiescent bacilli. Hence, in the absence of treatment, there is always some risk that latent infection may become active.

If the immune system fails to control the primary infection, clinical disease (tuberculosis) develops. The result is

necrosis and cavitation of lung tissue. Lung tissue may also become caseous (cheese-like in appearance). In the absence of treatment, tissue destruction progresses, and death may result.

Reactivation

The term *reactivation* refers to renewed multiplication of tubercle bacilli that had been dormant following control of a primary infection. Until recently, it was assumed that most new cases of symptomatic TB resulted from reactivation of an old (latent) infection. However, we now know that, among some groups, reactivation may be responsible for only 60% of new infections—the remaining 40% result from recent person-to-person transmission.

Diagnosis and Treatment of Active Tuberculosis

Modern chemotherapeutic agents have dramatically altered the treatment of TB. In the past, most patients required lengthy hospitalization. Today, hospitalization is generally unnecessary. Prolonged bed rest is neither required nor recommended. To reduce emergence of resistance, treatment is *always* done with two or more drugs. In addition, direct observation of dosing is now considered standard care.

The goal of treatment is to eliminate symptoms and prevent relapse. To accomplish this, treatment must kill tubercle bacilli that are actively dividing as well as those that are “resting.” Success is indicated by an absence of observable mycobacteria in sputum and by the failure of sputum cultures to yield colonies of *M. tuberculosis*.

Diagnosis

Diagnostic testing is indicated for (1) individuals with clinical manifestations that suggest TB and (2) individuals with a positive skin test or blood test (see below under *Diagnosis and Treatment of Latent Tuberculosis*), who are at high risk of developing active disease. A definitive diagnosis is made with a chest radiograph and microbiologic evaluation of sputum. A chest radiograph should be ordered for all persons suspected of active infection.

In traditional tests, the presence of *M. tuberculosis* in sputum is evaluated in two ways: by (1) microscopic examination of sputum smears and (2) culturing of sputum samples followed by laboratory evaluation. Microscopic examination cannot provide a definitive diagnosis. Why? Because direct observation cannot distinguish between *M. tuberculosis* and other mycobacteria. Furthermore, microscopic examination is much less sensitive than evaluation of cultured samples. Accordingly, sputum cultures are performed to permit a definitive diagnosis. Unfortunately, culturing *M. tuberculosis* is a slow process, taking 2 to 6 weeks to yield results.

With newer technology, known as *nucleic acid amplification (NAA) tests*, we can identify *M. tuberculosis* in sputum rapidly, typically within 24 to 48 hours. Note that this is 1 to 5 weeks sooner than when samples are cultured. Unfortunately, NAA tests have not been used widely in the United States, but this may soon change. Why? Because in 2009, the Centers for Disease Control and Prevention (CDC) issued new guidelines recommending that NAA tests be performed for each patient with signs and symptoms of pulmonary TB, providing a definitive diagnosis has not yet been established.

Drug Resistance

Drug resistance is a major impediment to successful therapy. Some infecting bacilli are inherently resistant; others develop resistance over the course of treatment. Some bacilli are resistant to just one drug; others are resistant to multiple drugs. Infection with a resistant organism may be acquired in two ways: (1) through contact with someone who harbors resistant bacteria, and (2) through repeated ineffectual courses of therapy (see below).

The emergence of *multidrug-resistant TB* (MDR-TB) and *extensively drug-resistant TB* (XDR-TB) are recent and ominous developments. MDR-TB is defined as TB that is resistant to both isoniazid and rifampin, our two most effective antituberculosis (anti-TB) drugs. XDR-TB, a severe form of MDR-TB, is defined as TB that is resistant not only to isoniazid and rifampin, but also to all fluoroquinolones (eg, moxifloxacin), and at least one of the injectable second-line anti-TB drugs (amikacin, kanamycin, or capreomycin). Infection with multidrug-resistant organisms greatly increases the risk of death, especially among patients with AIDS. In addition, multidrug resistance is expensive: The cost of treating one case of resistant TB is about \$180,000, compared with \$12,000 per case of nonresistant TB. Fortunately, multidrug resistance is rare in the United States: In 2009, there were 94 reported cases of MDR-TB (down from 134 in 2006) and no reported cases of XDR-TB (down from 4 in 2006).

The principal cause underlying the emergence of resistance is inadequate drug therapy. Treatment may be too short; dosage may be too low; patient adherence may be erratic; and, perhaps most importantly, the regimen may contain too few drugs.

The Prime Directive: Always Treat Tuberculosis with Two or More Drugs

Antituberculosis regimens must always contain two or more drugs to which the infecting organism is sensitive. To understand why this is so, we need to begin with five facts:

- Resistance in *M. tuberculosis* occurs because of spontaneous mutations.
- Each mutational event confers resistance to only one drug.
- Mutations conferring resistance to a single drug occur in about 1 of every 100 million (10^8) bacteria.
- The bacterial burden in active TB is well above 10^8 organisms but far below 10^{16} .
- *M. tuberculosis* grows slowly, hence treatment is prolonged.

Now, let's assume we initiate therapy with a single drug, and that all bacteria present are sensitive when we start. What will happen? Over time, at least one of the more than 10^8 bacteria in our patient will mutate to a resistant form. Hence, as we proceed with treatment, we will kill all sensitive bacteria, but the descendants of the newly resistant bacterium will continue to flourish, thereby causing treatment failure. In contrast, if we initiate therapy with *two* drugs, treatment will succeed. Why? Because failure would require that at least one bacterium undergo *two* resistance-conferring mutations, one for each drug. Since two such mutations occur in only 1 of every 10^{16} bacteria (10^{16} is the product of the probabilities for each mutation), and since the total bacterial load is much less than 10^{16} , the chances of the two events occurring in one of the bacteria in our patient are nil.

Not only do drug combinations decrease the risk of resistance, they can reduce the incidence of relapse. Because some

drugs (eg, isoniazid, rifampin) are especially effective against actively dividing bacilli, whereas other drugs (eg, pyrazinamide) are most active against intracellular (quiescent) bacilli, by using proper combinations of anti-TB agents, we can increase the chances of killing all tubercle bacilli present, whether they are actively multiplying or dormant. Hence, the risk of relapse is lowered.

In Chapter 83 (Basic Principles of Antimicrobial Therapy), we noted that treatment with multiple antibiotics broadens the spectrum of antimicrobial coverage, thereby increasing the risk of suprainfection. This is not the case with multidrug therapy of TB. The major drugs used against *M. tuberculosis* are selective for this organism. As a result, these drugs, even when used in combination, do not kill off other microorganisms, and therefore do not create the conditions that lead to suprainfection.

In summary, because treatment is prolonged, there is a high risk that drug-resistant bacilli will emerge if only one anti-TB agent is employed. Because the chances of a bacterium developing resistance to two drugs are very low, treatment with two or more drugs minimizes the risk of drug resistance. Therefore, when treating TB, we must always use two or more drugs to which the organism is sensitive.

Determining Drug Sensitivity

Because resistance to one or more anti-TB drugs is common, and because many patterns of resistance are possible, it is essential that we determine drug sensitivity in isolates from each patient at treatment onset. How do we test drug sensitivity? The traditional method is to culture sputum samples in the presence of antimycobacterial drugs. Unfortunately, the process is slow, usually taking 6 to 16 weeks to complete. Until test results are available, drug selection must be empiric, based on (1) patterns of drug resistance in the community and (2) the immunocompetence of the patient. However, once test

results are available, the regimen should be adjusted accordingly. In the event of treatment failure, sensitivity tests should be repeated.

A new, automated tuberculosis assay, known as *Xpert MTB/RIF*, can identify sensitivity to one key drug—rifampin—in less than 2 hours, while simultaneously confirming the presence of *M. tuberculosis*. This assay uses the NAA technology noted above. Unfortunately, the *Xpert MTB/RIF* device is expensive, and not yet approved for general use.

Treatment Regimens

Several regimens may be employed for active TB. Drug selection is based largely on the susceptibility of the infecting organism and the immunocompetence of the host. Therapy is usually initiated with a *four-drug* regimen; isoniazid and rifampin are almost always included. In the event of suspected or proved resistance, more drugs are added; the total may be as high as seven. Representative regimens are shown in Table 90-1 and discussed below.

Treatment can be divided into two phases. The goal of the initial phase (induction phase) is to eliminate actively dividing extracellular tubercle bacilli, and thereby render the sputum noninfectious. The goal of the second phase (continuation phase) is to eliminate intracellular “persisters.”

Drug-Sensitive Tuberculosis. If the infecting organisms are not resistant to isoniazid or rifampin, treatment is relatively simple. As indicated in Table 90-1, the induction phase, which lasts 2 months, consists of four drugs: *isoniazid, rifampin, pyrazinamide, and ethambutol*. Dosing may be done daily, twice weekly, or thrice weekly. The continuation phase, which lasts 4 months, consists of two drugs—*isoniazid and rifampin*—administered daily, twice weekly, or thrice weekly. Note that the entire course of treatment is prolonged, making adherence a significant problem.

TABLE 90-1 ■ Representative Antituberculosis Regimens

Drug Resistance	HIV-Negative Patients*	HIV-Positive Patients*	Interaction with Drugs for HIV Infection†
None	<p><i>Induction Phase:</i> IRPE for 2 months</p> <p><i>Continuation Phase:</i> IR for 4 months</p>	<p><i>Induction Phase:</i> IRPE for 2 months</p> <p><i>Continuation Phase:</i> IR for 4–7 months</p> <p>OR</p> <p><i>Induction Phase:</i> IPE + rifabutin for 2 months</p> <p><i>Continuation Phase:</i> I + rifabutin for 4–7 months</p>	<p>PIs: Rifampin can be used with ritonavir, but not with other PIs.</p> <p>NNRTIs: Rifampin can be used with high-dose nevirapine or efavirenz, but not with delavirdine.</p> <p>PIs: Rifabutin can be used with all PIs.</p> <p>NNRTIs: Rifabutin can be used with normal-dose nevirapine or efavirenz, but not with delavirdine.</p>
Isoniazid resistance	RPE for 6 months	<p>RPE for 6–9 months</p> <p>OR</p> <p>PE + rifabutin for 6–9 months</p>	<p>PIs and NNRTIs: Same as for rifampin above.</p> <p>PIs and NNRTIs: Same as for rifabutin above.</p>
Rifampin resistance	IPE for 18–24 months	<p>IPE for 18–24 months</p> <p>OR</p> <p><i>Induction Phase:</i> IPSE for 2 months</p> <p><i>Continuation Phase:</i> IPS for 7–10 months</p>	<p>All drugs for HIV infection can be used.</p> <p>All drugs for HIV infection can be used.</p>

*Drugs used in these regimens: E = ethambutol, I = isoniazid, P = pyrazinamide, R = rifampin, S = streptomycin.
†PI = HIV-protease inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor.

Isoniazid- or Rifampin-Resistant Tuberculosis. Infections that are resistant to a single drug—isoniazid or rifampin—usually respond well. Isoniazid-resistant TB can be treated for 6 months with three drugs: rifampin, ethambutol, and pyrazinamide. Rifampin-resistant TB can also be treated with three drugs—isoniazid, ethambutol, and pyrazinamide—but the duration is longer: 18 to 24 months, rather than 6 months.

Multidrug-Resistant TB and Extensively Drug-Resistant TB. MDR-TB and XDR-TB are much harder to manage than drug-sensitive TB. Treatment is prolonged (at least 24 months) and must use second- and third-line drugs, which are less effective than the first-line drugs (eg, isoniazid and rifampin) and are generally more toxic. Initial therapy may consist of five, six, or even seven drugs. Hence, an initial regimen might include (1) isoniazid; (2) rifampin; (3) pyrazinamide; (4) ethambutol; (5) kanamycin, amikacin, or capreomycin; (6) ciprofloxacin or ofloxacin; and (7) cycloserine, ethionamide, or *para*-aminosalicylic acid. As a last resort, infected tissue may be removed by surgery. Even with all of these measures, the prognosis is often poor: Among patients with XDR-TB, between 40% and 60% die. Factors that determine outcome include the extent of drug resistance, infection severity, and the immunocompetence of the host.

Patients with TB plus HIV Infection. Between 2% and 20% of patients with HIV infection develop active TB. Because of their reduced ability to fight infection, these patients require therapy that is more aggressive than in immunocompetent patients, and should last several months longer.

Drug interactions are a big problem, especially for patients taking *rifampin*. Why? Because rifampin, a cornerstone of TB therapy, can accelerate the metabolism of antiretroviral drugs (ie, drugs used to fight HIV), and can thereby decrease their effects. Specifically, rifampin can decrease the effects of most protease inhibitors and most non-nucleoside reverse transcriptase inhibitors (NNRTIs). Accordingly, it is best to avoid combining rifampin with these agents. Unfortunately, this means that patients will be denied optimal treatment for one of their infections. That is, if they take rifampin to treat TB, they will be unable to take most protease inhibitors or NNRTIs for HIV. Conversely, if they take protease inhibitors and NNRTIs to treat HIV, they will be unable to take rifampin for TB. This dilemma does not have an easy solution.

Like rifampin, *rifabutin* can accelerate metabolism of antiretroviral drugs. However, the degree of acceleration is much less. As a result, many of the antiretroviral drugs that must be avoided in patients taking rifampin can still be used in patients taking rifabutin.

Duration of Treatment

The ideal duration of treatment has not been established. For patients with drug-sensitive TB, the minimum duration is 6 months. For patients with multidrug-resistant infection, and for patients with HIV/AIDS, treatment may last as long as 24 months after sputum cultures have become negative.

Promoting Adherence: Directly Observed Therapy Combined with Intermittent Dosing

Patient nonadherence is the most common cause of treatment failure, relapse, and increased drug resistance. Recall that patients with TB must take multiple drugs for 6 months or more, making adherence a very real problem. Directly observed therapy (DOT), combined with intermittent dosing,

helps ensure adherence and thereby increases the chances of success.

In DOT, administration of each dose is done in the presence of an observer, usually a representative of the health department. DOT is now considered the standard of care for TB. In addition to promoting bacterial kill, DOT permits ongoing evaluation of the clinical response and adverse drug effects.

Intermittent dosing is defined as dosing 2 or 3 times a week, rather than every day. Of course, each dose is larger than with daily dosing. Studies have shown that intermittent dosing is just as effective as daily dosing, and no more toxic. The great advantage of intermittent dosing is that it makes DOT more convenient, and hence improves adherence.

Evaluating Treatment

Three modes are employed to evaluate therapy: bacteriologic evaluation of sputum, clinical evaluation, and chest radiographs.

In patients with positive pretreatment sputum tests, sputum should be evaluated every 2 to 4 weeks initially, and then monthly after sputum cultures become negative. With proper drug selection and good adherence, sputum cultures become negative in over 90% of patients after 3 months of treatment.

Treatment failures should be evaluated for drug resistance and patient adherence. In the absence of demonstrated drug resistance, treatment with the same regimen should continue, using DOT to ensure that medication is being taken as prescribed. In patients with drug-resistant TB, *two* effective drugs should be added to the regimen.

In patients with negative pretreatment sputum tests, treatment is monitored by chest radiographs and clinical evaluation. In most patients, clinical manifestations (eg, fever, malaise, anorexia, cough) should decrease markedly within 2 weeks. The radiograph should show improvement within 3 months.

After completing therapy, patients should be examined every 3 to 6 months for signs and symptoms of relapse.

Diagnosis and Treatment of Latent Tuberculosis

In the United States, an estimated 9 to 14 million people have latent TB. In the absence of treatment, 5% to 10% of these people will develop active TB. Because latent TB can become active, the condition poses a threat to the infected individual and to the community as well. Accordingly, testing and treatment are clearly desirable—but not for everyone: Because treatment of latent TB is often prolonged and carries a risk of drug toxicity, testing and treatment should be limited to people who really need it. In 2000, the American Thoracic Society and the CDC issued revised clinical guidelines—*Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection*—that specify who should be tested, who should be treated, and what drugs should be used. Recommendations specific to drug therapy were revised again in 2003. The discussion below reflects the 2003 recommendations.

Who Should Be Tested for Latent Tuberculosis?

Testing should be limited to people who are at high risk of either (1) having acquired the infection recently or (2) progressing from latent TB to active TB. Included in this group are people with HIV infection, people receiving immunosup-

pressive drugs, recent contacts of TB patients, and people with high-risk medical conditions, such as diabetes, silicosis, or chronic renal failure. A complete list of candidates for testing is given in Table 90–2. Routine testing of low-risk individuals is not recommended.

TABLE 90–2 ■ Candidates for Targeted Tuberculosis Testing

Individuals at High Risk of Recent Tuberculosis Infection

Contacts of TB patients

Residents and staff of high-risk congregate settings:

- Prisons and jails
- Nursing homes
- Hospitals and other healthcare facilities
- Homeless shelters
- Residential facilities for patients with AIDS

Persons who, in the last 5 years, immigrated from a country where TB is prevalent

Staff of mycobacteriology laboratories

Children and adolescents exposed to high-risk adults

Children under the age of 4 years

Individuals at High Risk of Progression from Latent to Active Tuberculosis

HIV-infected persons

Intravenous drug abusers

Patients taking immunosuppressive drugs for 1 month or more

Patients with a chest radiograph indicating fibrotic changes consistent with prior TB

Patients with other high-risk medical conditions, including

- Diabetes mellitus
- Chronic renal failure
- Silicosis
- Leukemia or lymphoma
- Clinical conditions associated with substantial weight loss, including gastrectomy state, intestinal bypass surgery, chronic peptic ulcer disease, chronic malabsorption syndromes, and carcinomas of the oropharynx and upper GI tract that inhibit adequate nutritional intake

How Do We Test for Latent Tuberculosis?

There are two types of tests for latent TB: (1) the *tuberculin skin test* (TST), which has been used for over 100 years; and (2) *interferon gamma release assays* (IGRAs), first approved for American use in 2001.

Tuberculin Skin Test. The TST is performed by giving an intradermal injection of a preparation known as *purified protein derivative* (PPD), an antigen derived from *M. tuberculosis*. If the individual has an intact immune system and has been exposed to *M. tuberculosis* in the past, the PPD will elicit a local immune response. The test is read 48 to 72 hours after the injection. A positive reaction is indicated by a region of induration (hardness) around the injection site.

The decision to treat latent TB is based on two factors: (1) the risk category of the individual and (2) the size of the region of induration produced by the TST (Table 90–3). For individuals at high risk, treatment is recommended if the region of induration is relatively small (5 mm). For individuals at moderate risk, treatment is indicated when the region of induration is larger (10 mm). And for individuals at low risk (who should not be routinely tested), the region must be larger still (15 mm) to justify treatment.

Interferon Gamma Release Assays. The IGRAs are *blood* tests for TB, rather than skin tests. These new tests are based on the observation that immune white blood cells (WBCs), following exposure to *M. tuberculosis*, will release interferon gamma when exposed to *M. tuberculosis* again. In the IGRAs, a patient's blood (or WBCs isolated from that blood) is exposed to antigens that represent *M. tuberculosis*. If the antigens trigger sufficient release of interferon gamma, the test is considered positive for TB.

In the United States, three IGRAs are now in use:

- QuantiFERON-TB Gold
- QuantiFERON-TB Gold in-Tube
- T-SPOT

These IGRAs are as sensitive as the TST, and more specific. Moreover, results with the IGRAs are available faster than with

TABLE 90–3 ■ Tuberculin Skin Test Results That Are Considered Positive—and Hence Justify Treatment—in Patients at Low, Moderate, and High Risk of Latent Tuberculosis

Risk Category	Who Is In the Risk Category?	Test Result Considered Positive
High	HIV-positive people Recent contacts of patients with TB People with fibrotic changes on their chest radiograph consistent with prior TB People taking immunosuppressive drugs for more than 1 month	5 mm of induration
Moderate	Recent immigrants from countries with a high prevalence of TB Intravenous drug abusers Residents and staff of high-risk congregate settings (eg, prisons, nursing homes, hospitals, homeless shelters) Mycobacteriology laboratory personnel Persons with high-risk medical conditions (eg, diabetes mellitus, chronic renal failure, silicosis, leukemia, lymphoma) Children and adolescents exposed to high-risk adults Children under 4 years old	10 mm of induration
Low	Persons with no risk factors for TB	15 mm of induration

the TST (24 hours vs. 48 to 72 hours), and only one office visit is required. Current CDC guidelines, issued in 2010, permit using IGRAs for all situations in which the TST has been used.

How Do We Treat Latent Tuberculosis?

In the United States, there are two preferred treatments for latent TB: (1) *isoniazid alone* taken daily for 9 months and (2) *isoniazid plus rifapentine* taken weekly for 3 months. Both treatments are equally effective. Isoniazid alone has been used for decades; isoniazid plus rifapentine is a new option. Because dosing with isoniazid plus rifapentine is so simple—just 12 doses instead of 270—completing the full course is more likely than with isoniazid alone.

Before starting treatment for latent TB, active TB must be ruled out. Why? Because latent TB is treated with just one or two drugs, and hence, if active TB were present, treatment would promote emergence of resistant bacilli. To exclude active disease, the patient should receive a physical examination and chest radiograph; if indicated, bacteriologic studies may also be ordered.

Isoniazid. For over 30 years, isoniazid has been the standard treatment for latent TB. The drug is effective, relatively safe, and inexpensive. However, isoniazid does have two drawbacks. First, to be effective, isoniazid must be taken for a long time—at least 6 months and preferably 9 months. Second, isoniazid poses a risk of liver damage.

How long should treatment last? Ideally, treatment should continue for 9 months. Treatment for 6 months is an option, but is not as reliable.

How often is isoniazid given? Dosing may be done once daily or twice a week. When twice-weekly dosing is used, each dose should be administered by DOT to ensure adherence.

What's the preferred isoniazid regimen? Of all the options, the preferred regimen is dosing once daily for 9 months. For adults, the daily dose is 5 mg/kg (max 300 mg). For children, the daily dose is 10–20 mg/kg (max 300 mg). When dosing is done twice weekly, higher doses are used.

Isoniazid plus Rifapentine. The combination of isoniazid plus rifapentine—taken just *once a week for only 3 months*—is just as effective as isoniazid alone taken once a day for 9 months, as shown in the PREVENT TB trial. Accordingly, in 2011, the CDC recommended isoniazid plus rifapentine as an equal alternative to 9 months of daily isoniazid. Because dosing is done just once a week, isoniazid plus rifapentine *must be administered by DOT*. In contrast, daily isoniazid is self-administered, without oversight by a healthcare provider.

Who can use the new regimen? Isoniazid plus rifapentine is recommended for people age 12 years and older, including those with HIV infection who are *not* taking antiretroviral drugs. As a rule, children age 2 to 11 years should use 9 months of daily isoniazid, and not isoniazid plus rifapentine. Because of its simplicity, the new regimen may be especially useful in correctional institutions, clinics for recent immigrants, and homeless shelters.

Who should *not* use the new regimen? The regimen should not be used by (1) children under 2 years old, because the safety and kinetics of rifapentine are unknown in this group, (2) HIV-infected patients taking antiretroviral drugs, because drug interactions have not been studied, (3) women who are pregnant or expecting to become pregnant during treatment, because safety in pregnancy is unknown, and (4) patients with latent TB with presumed resistance to isoniazid or rifapentine.

What's the dosage for isoniazid and rifapentine? For adults and children, the dosage for *isoniazid* is 15 mg/kg (900 mg max). The dosage for *rifapentine* is based on body weight as follows:

- 10–14 kg, 300 mg
- 14.1–25 kg, 450 mg
- 25.1–31 kg, 600 mg
- 32.1–49.9 kg, 750 mg
- 50 kg or greater, 900 mg

Vaccination Against Tuberculosis

Protection against TB can be conferred by inoculation with BCG vaccine, a freeze-dried preparation of attenuated *Mycobacterium bovis* (bacillus of Calmette and Guérin). In countries where TB is endemic, the World Health Organization recommends BCG vaccination in infancy, to protect children against severe, life-threatening TB infection (ie, miliary TB and tuberculous meningitis). In the United States, routine vaccination is not done. Why? Because there is a low risk of infection with *M. tuberculosis* and protection against pulmonary TB in adulthood is variable. Furthermore, vaccination with BCG can produce a false-positive result in the tuberculin skin test, which can't distinguish between antigens from *M. bovis* and antigens from *M. tuberculosis*. (Since the IGRAs are highly specific for antigens from *M. tuberculosis*, vaccination with BCG does not affect the results of these tests.) As discussed in Chapter 103, BCG vaccine is also used to treat carcinoma of the bladder.

PHARMACOLOGY OF INDIVIDUAL ANTITUBERCULOSIS DRUGS

Based on their clinical utility, the anti-TB drugs can be divided into two groups: first-line drugs and second-line drugs. The first-line drugs are *isoniazid*, *rifampin*, *rifapentine*, *rifabutin*, *pyrazinamide*, and *ethambutol*. Of these, isoniazid and rifampin are the most important. The second-line drugs—*levofloxacin*, *moxifloxacin*, *kanamycin*, *amikacin*, *capreomycin*, *streptomycin*, *para-aminosalicylic acid*, *ethionamide*, and *cycloserine*—are generally less effective, more toxic, and more expensive than the primary drugs. Second-line agents are used in combination with the primary drugs to treat disseminated TB and TB caused by organisms resistant to first-line drugs. Adverse effects and routes of administration of the anti-TB drugs are summarized in Table 90–4.

Isoniazid

Isoniazid [Nydrazid, Isotamine ♦] is the primary agent for treatment and prophylaxis of TB. This drug is superior to alternative drugs with regard to efficacy, toxicity, ease of use, patient acceptance, and affordability. With the exception of patients who cannot tolerate the drug, isoniazid should be taken by all individuals infected with isoniazid-sensitive strains of *M. tuberculosis*.

Antimicrobial Spectrum and Mechanism of Action

Isoniazid is highly selective for *M. tuberculosis*. The drug can kill tubercle bacilli at concentrations 10,000 times lower than those needed to affect gram-positive and gram-negative bacteria. Isoniazid is bactericidal to mycobacteria that are actively dividing, but is only bacteriostatic to “resting” organisms.

Although the mechanism by which isoniazid acts is not known with certainty, available data suggest the drug suppresses bacterial growth by inhibiting synthesis of mycolic acid, a component of the mycobacterial cell wall. Since my-

TABLE 90-4 ■ Antituberculosis Drugs: Routes and Major Adverse Effects

Drug	Route	Major Adverse Effects
First-Line Drugs		
Isoniazid	PO, IM	Hepatotoxicity, peripheral neuritis
Rifampin	PO, IV	Hepatotoxicity
Rifapentine	PO	Hepatotoxicity
Rifabutin	PO	Hepatotoxicity
Pyrazinamide	PO	Hepatotoxicity, polyarthritits
Ethambutol	PO	Optic neuritis
Second-Line Drugs		
Fluoroquinolones		
Levofloxacin	PO, IV	GI intolerance
Moxifloxacin	PO, IV	GI intolerance
Injectable Drugs		
Capreomycin	IM	Eighth nerve damage, nephrotoxicity
Kanamycin	IM, IV	Eighth nerve damage, nephrotoxicity
Amikacin	IM, IV	Eighth nerve damage, nephrotoxicity
Streptomycin	IM	Eighth nerve damage, nephrotoxicity
Others		
<i>p</i> -Aminosalicylic acid	PO	GI intolerance
Ethionamide	PO	GI intolerance, hepatotoxicity
Cycloserine	PO	Psychoses, seizure, rash

colic acid is not produced by other bacteria or by cells of the host, this mechanism would explain why isoniazid is so selective for tubercle bacilli.

Resistance

Tubercle bacilli can develop resistance to isoniazid during treatment. Acquired resistance results from spontaneous mutation—not from transfer of R factors. The precise mechanism underlying resistance has not been established. Emergence of resistance can be decreased through multidrug therapy. Organisms resistant to isoniazid are cross-resistant to ethionamide, but not to other drugs used for TB.

Pharmacokinetics

Absorption and Distribution. Isoniazid is administered orally and IM. Absorption is good with both routes. Once in the blood, isoniazid is widely distributed to tissues and body fluids. Concentrations in cerebrospinal fluid (CSF) are about 20% of those in plasma.

Metabolism. Isoniazid is inactivated in the liver, primarily by *acetylation*. The ability to acetylate isoniazid is genetically determined: about 50% of people in the United States are *rapid* acetylators and the other 50% are *slow* acetylators. The drug's half-life is about 1 hour in rapid acetylators and 3 hours in slow acetylators. It is important to note that differences in rates of acetylation generally have little impact on the *efficacy* of isoniazid, provided patients are taking the drug daily. However, *nonhepatic toxicities* may be more likely in slow acetylators, because drug accumulation is greater in these patients.

Excretion. Isoniazid is excreted in the urine, primarily as inactive metabolites. In patients who are slow acetylators and who also have renal insufficiency, the drug may accumulate to toxic levels.

Therapeutic Use

Isoniazid is indicated only for treating active and latent TB. When used for latent TB, the drug is administered alone or combined with rifapentine. When used for active TB, it must be taken in combination with at least one other agent (eg, rifampin).

Adverse Effects

Hepatotoxicity. Isoniazid can cause hepatocellular injury and multilobular necrosis. Deaths have occurred. Liver injury is thought to result from production of a toxic isoniazid metabolite. The greatest risk factor for liver damage is advancing age: The incidence is extremely low in patients younger than 20 years, 1.2% in those ages 35 to 49, 2.3% in those ages 50 to 64, and 8% in those older than 65 years. Patients should be informed about signs of hepatitis (anorexia, malaise, fatigue, nausea, yellowing of the skin or eyes) and instructed to notify the prescriber immediately if these develop. Patients should also undergo monthly evaluation for these signs. Some clinicians perform monthly determinations of serum aspartate aminotransferase (AST) activity, because elevation of AST activity is indicative of liver injury. However, because AST levels may rise and then return to normal, despite continued isoniazid use, increases in AST may not be predictive of clinical hepatitis. It is recommended that isoniazid be withdrawn if signs of hepatitis develop or if AST activity exceeds 3 to 5 times the pretreatment baseline. Caution should be exercised when giving isoniazid to alcoholics and individuals with pre-existing disorders of the liver.

Peripheral Neuropathy. Dose-related peripheral neuropathy is the most common adverse event. Principal symptoms are symmetric paresthesias (tingling, numbness, burning, pain) of the hands and feet. Clumsiness, unsteadiness, and muscle ache may develop. Peripheral neuropathy results from isoniazid-induced deficiency in pyridoxine (vitamin B₆). If peripheral neuropathy develops, it can be reversed by administering pyridoxine (50 to 200 mg daily). In patients predisposed to neuropathy (eg, alcohol abusers and diabetics), small doses of pyridoxine (10 to 25 mg/day) can be administered with isoniazid as prophylaxis against peripheral neuritis.

Other Adverse Effects. A variety of *central nervous system (CNS)* effects can occur, including optic neuritis, seizures, dizziness, ataxia, and psychologic disturbances (depression, agitation, impairment of memory, hallucinations, toxic psychosis). *Anemia* may result from isoniazid-induced deficiency in pyridoxine. *GI distress, dry mouth,* and *urinary retention* occur on occasion. *Allergy* to isoniazid can produce fever, rashes, and a syndrome resembling lupus erythematosus.

Drug Interactions

Interactions from Inhibiting Drug Metabolism. Isoniazid is a strong inhibitor of three cytochrome P450 isozymes, namely CYP2C9, CYP2C19, and CYP2E1. By inhibiting these isozymes, isoniazid can raise levels of other drugs, including phenytoin, carbamazepine, diazepam, and triazolam. Phenytoin is of particular concern. Signs of phenytoin excess include ataxia and incoordination. Plasma levels of phenytoin should be monitored, and phenytoin dosage should be reduced as appropriate. Dosage of isoniazid should not be changed.

Alcohol, Rifampin, Rifapentine, Rifabutin, and Pyrazinamide. Daily ingestion of alcohol or concurrent therapy with rifampin, rifapentine, rifabutin, or pyrazinamide increases the risk of hepatotoxicity. Patients should be encouraged to reduce or eliminate alcohol intake.

Preparations, Dosage, and Administration

Preparations. Isoniazid is supplied in tablets (100 and 300 mg) and a syrup (10 mg/mL) for oral use, and in solution (100 mg/mL in 10-mL vials), sold as *Nydrazid*, for IM injection. Isoniazid is also available in two fixed-dose combinations: (1) capsules, sold as *Rifamate*, contain 150 mg of isoniazid and 300 mg of rifampin, and (2) tablets, sold as *Rifater*, contain 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide.

Oral Dosage. For treatment of *active TB*, the adult dosage is 5 mg/kg/day or 15 mg/kg 2 or 3 times a week; the pediatric dosage is 10 to 20 mg/kg/day or 20 to 40 mg/kg 2 or 3 times a week. For treatment of *latent TB*, the preferred adult dosage is 5 mg/kg/day and the preferred pediatric dosage is 10 mg/kg/day.

Intramuscular Dosage. Parenteral therapy is administered in critical situations when oral treatment is not possible. The dosage is 300 mg/day.

Rifampin

Rifampin [Rifadin, Rimactane] equals isoniazid in importance as an anti-TB drug. Prior to the appearance of resistant tubercle bacilli, the combination of rifampin plus isoniazid was the most frequently prescribed regimen for uncomplicated pulmonary TB. Rifampin is a powerful inducer of cytochrome P450 enzymes, and hence can decrease the levels of many other drugs.

Antimicrobial Spectrum

Rifampin is a broad-spectrum antibiotic. The drug is active against most gram-positive bacteria as well as many gram-negative bacteria. The drug is bactericidal to *M. tuberculosis* and *M. leprae*. Other bacteria that are highly sensitive include *Neisseria meningitidis*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Legionella* species.

Mechanism of Action and Bacterial Resistance

Rifampin inhibits bacterial DNA-dependent RNA polymerase, and thereby suppresses RNA synthesis and, consequently, protein synthesis. The results are bactericidal. Because mammalian RNA polymerases are not affected, rifampin is selectively toxic to microbes. Bacterial resistance to rifampin results from production of an altered form of RNA polymerase.

Pharmacokinetics

Absorption and Distribution. Rifampin is well absorbed if taken on an empty stomach. However, if dosing is done with or shortly after a meal, both the rate and extent of absorption can be significantly lowered. Rifampin is distributed widely to tissues and body fluids, including the CSF. The drug is lipid soluble, and hence has ready access to intracellular bacteria.

Elimination. Rifampin is eliminated primarily by hepatic metabolism. Only about 20% of the drug leaves in the urine. Rifampin induces hepatic drug-metabolizing enzymes, including those responsible for its own inactivation. As a result, the rate at which rifampin is metabolized increases over the first weeks of therapy, causing the half-life of the drug to decrease—from an initial value of about 4 hours down to 2 hours at the end of 2 weeks.

Therapeutic Use

Tuberculosis. Rifampin is one of our most effective anti-TB drugs. This agent is bactericidal to tubercle bacilli at extracellular and intracellular sites. Rifampin is a drug of choice for treating pulmonary TB and disseminated disease. Because resistance can develop rapidly when rifampin is employed alone, the drug is always given in combination with at least one other anti-TB agent. Despite the capacity of rifampin to produce a variety of adverse effects, toxicity rarely requires discontinuing treatment.

Leprosy. Rifampin is bactericidal to *M. leprae* and has become an important agent for treating leprosy (see below under *Drugs for Leprosy [Hansen's Disease]*).

Meningococcus Carriers. Rifampin is highly active against *Neisseria meningitidis* and is indicated for short-term therapy to eliminate this bacterium from the nasopharynx of asymptomatic carriers. Because resistant organisms emerge rapidly, rifampin should not be used against active meningococcal disease.

Adverse Effects

Rifampin is generally well tolerated. When employed at recommended dosages, the drug rarely causes significant toxicity. The most common adverse effect of concern is hepatitis.

Hepatotoxicity. Rifampin is toxic to the liver, posing a risk of jaundice and even hepatitis. Asymptomatic elevation of liver enzymes occurs in about 14% of patients. However, the incidence of overt hepatitis is less than 1%. Hepatotoxicity is most likely in alcohol abusers and patients with pre-existing liver disease. These individuals should be monitored closely for signs of liver dysfunction. Tests of liver function (serum aminotransferase levels) should be made prior to treatment and every 2 to 4 weeks thereafter. Patients should be informed about signs of hepatitis (jaundice, anorexia, malaise, fatigue, nausea) and instructed to notify the prescriber if they develop.

Discoloration of Body Fluids. Rifampin frequently imparts a red-orange color to urine, sweat, saliva, and tears. Patients should be informed of this harmless effect. Permanent staining of soft contact lenses has occurred on occasion, and hence the patient should consult an ophthalmologist regarding the contact lens use.

Other Adverse Effects. Gastrointestinal disturbances (anorexia, nausea, abdominal discomfort) and *cutaneous reactions* (flushing, itching, rash) occur occasionally. Rarely, intermittent high-dose therapy has produced a *flu-like syndrome*, characterized by fever, chills, muscle aches, headache, and dizziness. This reaction appears to have an immunologic basis. In some pa-

tients, high-dose therapy has been associated with *shortness of breath, hemolytic anemia, shock, and acute renal failure.*

Drug Interactions

Accelerated Metabolism of Other Drugs. Because rifampin induces cytochrome P450 enzymes, it can hasten the metabolism of many drugs, thereby reducing their effects. This interaction is of special concern with *oral contraceptives, warfarin* (an anticoagulant), and certain *protease inhibitors* and *NNRTIs* used for HIV infection. Women taking oral contraceptives should consider a nonhormonal form of birth control. The dosage of warfarin may need to be increased.

Isoniazid and Pyrazinamide. Rifampin, isoniazid, and pyrazinamide are all hepatotoxic. Hence, when these drugs are used in combination, as they often are, the risk of liver injury is greater than when they are used alone.

Preparations, Dosage, and Administration

Preparations. *Oral.* Rifampin [Rifadin, Rimactane], by itself, is available in 150- and 300-mg capsules. In addition, rifampin is available in two fixed-dose combinations: (1) capsules, sold as *Rifamate*, containing 300 mg of rifampin and 150 mg of isoniazid, and (2) tablets, sold as *Rifater*, containing 120 mg of rifampin, 50 mg of isoniazid, and 300 mg of pyrazinamide.

Intravenous. Rifampin [Rifadin] is available in powdered form (600 mg) to be reconstituted for IV infusion.

Oral Dosage and Administration. For treatment of TB, the usual adult dosage is 600 mg, taken once a day, twice a week, or 3 times a week. The pediatric dosage is 10 to 20 mg/kg taken once a day, twice a week, or 3 times a week. Rifampin is administered 1 hour before meals or 2 hours after. Because rifampin is eliminated by hepatic metabolism, patients with liver impairment require a reduction in dosage. No change in dosage is needed in patients with kidney disease.

Intravenous Administration. Dissolve 600 mg of powdered rifampin in 10 mL of sterile water for injection to make a concentrated solution (60 mg/mL). Dilute an appropriate dose of the concentrate in 500 mL of 5% dextrose and infuse over 3 hours.

Rifapentine

Rifapentine [Priftin] is a long-acting analog of rifampin. Both drugs have the same mechanism of action, adverse effects, and drug interactions. When rifapentine was approved in 1998, it was the first new drug for TB in over 25 years.

Actions and Uses. Rifapentine is indicated only for pulmonary TB. At therapeutic doses, the drug is lethal to *M. tuberculosis*. The mechanism underlying cell kill is inhibition of DNA-dependent RNA polymerase. To minimize emergence of resistance, rifapentine must always be combined with at least one other anti-TB drug.

Pharmacokinetics. Rifapentine is well absorbed from the GI tract, especially in the presence of food. Plasma levels peak 5 to 6 hours after dosing. In the liver, rifapentine undergoes conversion to 25-desacetyl rifapentine, an active metabolite. Excretion is primarily (70%) fecal. Rifapentine and its metabolite have the same half-life—about 13 hours.

Adverse Effects. Rifapentine is well tolerated at recommended doses. Like rifampin, the drug imparts a red-orange color to urine, sweat, saliva, and tears. Permanent staining of contact lenses can occur.

Hepatotoxicity is the principal concern. In clinical trials, serum transaminase levels increased in 5% of patients. However, overt hepatitis occurred in only one patient. Because of the risk of hepatotoxicity, liver function tests (bilirubin, serum transaminases) should be performed at baseline and monthly thereafter. Patients should be informed about signs of hepatitis (jaundice, anorexia, malaise, fatigue, nausea) and instructed to notify the prescriber if these develop.

Drug Interactions. Like rifampin, rifapentine is a powerful inducer of cytochrome P450 drug-metabolizing enzymes. As a result, it can decrease the levels of other drugs. Important among these are *protease inhibitors* and *NNRTIs* (used for HIV infection), *oral contraceptives*, and *warfarin*.

Preparation, Dosage, and Administration. Rifapentine [Priftin] is available in 150-mg tablets. In patients with active TB, the dosage is 600 mg twice a week (with at least 3 days between doses) for 2 months, followed by 600 mg once a week for 4 months. Dosage for latent TB is presented above. Like all other drugs for TB, rifapentine must always be combined with at least one other anti-TB agent.

Rifabutin

Actions and Uses. Rifabutin [Mycobutin] is a close chemical relative of rifampin. Like rifampin, rifabutin inhibits mycobacterial DNA-dependent RNA polymerase, and thereby suppresses protein synthesis. The drug is approved for prevention of disseminated *M. avium* complex (MAC) disease in patients with advanced HIV infection (CD4 lymphocyte counts below 200 cells/mm³). In addition to this approved application, rifabutin is used off-label as an alternative to rifampin to treat TB in patients with HIV infection. Rifabutin is preferred to rifampin in HIV patients because it has less impact on the metabolism of protease inhibitors and NNRTIs.

Pharmacokinetics. Rifabutin is administered orally. Absorption is unaffected by food. Plasma levels peak in 2 to 3 hours. The drug is widely distributed and achieves high concentrations in the lungs. Rifabutin is metabolized in the liver and excreted in the urine, bile, and feces. Its half-life is 45 hours.

Adverse Effects. Rifabutin is generally well tolerated. The most common side effects are rash (4%), GI disturbances (3%), and neutropenia (2%). Like rifampin, rifabutin can impart a harmless red-orange color to urine, sweat, saliva, and tears; soft contact lenses may be permanently stained. Rifabutin poses a risk of uveitis, and hence should be discontinued if ocular pain or blurred vision develops. Other adverse effects include myositis, hepatitis, arthralgia, chest pain with dyspnea, and a flu-like syndrome.

Drug Interactions. Like rifampin, rifabutin induces cytochrome P450 enzymes, although less strongly than rifampin does. By increasing enzyme activity, rifabutin can decrease blood levels of other drugs, especially *oral contraceptives* and *delavirdine*, an NNRTI. Women using oral contraceptives should be advised to use a nonhormonal method of birth control.

Preparations, Dosage, and Administration. Rifabutin [Mycobutin] is supplied in 150-mg capsules. For treatment of TB, the adult dosage is 300 mg taken once a day, twice a week, or 3 times a week. The pediatric dosage is 10 to 20 mg/kg taken once a day or twice a week.

Pyrazinamide

Antimicrobial Activity and Therapeutic Use

Pyrazinamide is bactericidal to *M. tuberculosis*. How it kills bacteria is unknown. Currently, the combination of pyrazinamide with rifampin, isoniazid, and ethambutol is a preferred regimen for initial therapy of active disease caused by drug-sensitive *M. tuberculosis*. In addition, pyrazinamide, in combination with rifampin, may be used for short-course therapy of latent TB, although other regimens are preferred.

Pharmacokinetics

Pyrazinamide is well absorbed following oral administration and undergoes wide distribution to tissues and body fluids. In the liver, the drug is converted to pyrazinoic acid, an active metabolite, and then to 5-hydroxypyrazinoic acid, which is inactive. Excretion is renal, primarily as inactive metabolites.

Adverse Effects and Interactions

Hepatotoxicity. Liver injury is the principal adverse effect. High-dose therapy has caused hepatitis, and, rarely, fatal hepatic necrosis. The earliest manifestations of liver damage are elevations in serum levels of transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]). Levels of these enzymes should be measured prior to treatment and every 2 weeks thereafter. Patients should be informed about signs of hepatitis (eg, malaise, anorexia, nausea, vomiting, yellowish discoloration of the skin and eyes) and instructed to notify the prescriber if they develop. Pyrazinamide should be discontinued if significant injury to the liver occurs. The drug should not be used by patients with pre-existing liver disease.

The risk of liver injury is increased by concurrent therapy with isoniazid or rifampin, both of which are hepatotoxic. Pyrazinamide plus rifampin is contraindicated for patients

with active liver disease or a history of isoniazid-induced liver injury, and should be used with caution in patients who are taking hepatotoxic drugs or who drink alcohol in excess.

Nongouty Polyarthralgias. Polyarthralgias (pain in multiple joints) develop in 40% of patients, but only occasionally during the initial phase of treatment. Pain can usually be managed with a nonsteroidal anti-inflammatory drug (NSAID), such as aspirin or ibuprofen. A few patients may need to reduce the dosage of pyrazinamide or discontinue treatment.

Other Adverse Effects. Pyrazinamide and its metabolites can inhibit renal excretion of uric acid, thereby causing *hyperuricemia*. Although usually asymptomatic, pyrazinamide-induced hyperuricemia has (rarely) resulted in *gouty arthritis*. Additional adverse effects include *GI disturbances* (nausea, vomiting, diarrhea), *rash*, and *photosensitivity*.

Preparations, Dosage, and Administration

Pyrazinamide is supplied in 500-mg tablets. The dosage for adults is 15 to 30 mg/kg taken once a day or 50 to 70 mg/kg taken 2 or 3 times a week. The dosage for children is 15 to 20 mg/kg taken once a day or 50 to 70 mg/kg taken 2 or 3 times a week. For all patients, the maximum daily dosage is 2 gm. Pyrazinamide is also available in a fixed-dose combination with isoniazid and rifampin, sold as *Rifater*.

Ethambutol

Antimicrobial Action

Ethambutol [Myambutol, Etibi[®]] is active only against mycobacteria; nearly all strains of *M. tuberculosis* are sensitive. The drug is bacteriostatic, not bactericidal. In most cases, ethambutol is active against tubercle bacilli that are resistant to isoniazid and rifampin. Although we know that ethambutol can suppress incorporation of mycolic acid in the cell wall, the precise mechanism by which it suppresses bacterial growth has not been established.

Therapeutic Use

Ethambutol is an important anti-TB drug. This agent is employed for initial treatment of TB and for treating patients who have received therapy previously. Like other drugs for TB, ethambutol is always employed as part of a multidrug regimen.

Pharmacokinetics

Ethambutol is readily absorbed following oral administration. The drug is widely distributed to most tissues and body fluids. Levels in CSF, however, remain low. Ethambutol undergoes little hepatic metabolism and is excreted primarily in the urine. The half-life is 3 to 4 hours in patients with healthy kidneys, and increases to 8 hours in those with significant renal impairment.

Adverse Effects

Ethambutol is generally well tolerated. The only significant adverse effect is optic neuritis.

Optic Neuritis. Ethambutol can produce dose-related optic neuritis, resulting in blurred vision, constriction of the visual field, and disturbance of color discrimination. The mechanism underlying these effects is unknown. Symptoms usually resolve upon discontinuation of treatment. However, for some patients, visual disturbance may persist. Color discrimination and visual acuity should be assessed prior to treatment and monthly thereafter. Patients should be advised to report any alteration in vision. If ocular toxicity develops, ethambutol should be withdrawn immediately. Because visual changes can be difficult to monitor in pediatric patients, ethambutol is not recommended for children younger than 8 years.

Other Adverse Effects. Ethambutol can produce *allergic reactions* (dermatitis, pruritus), *GI upset*, and *confusion*. The drug inhibits renal excretion of uric acid, causing *asymptomatic hyperuricemia* in about 50% of patients; occasionally, elevation of uric acid levels results in *acute gouty arthritis*. Rare adverse effects include *peripheral neuropathy*, *renal damage*, and *thrombocytopenia*.

Preparations, Dosage, and Administration

Ethambutol [Myambutol] is supplied in 100- and 400-mg tablets. For initial therapy of TB, the dosage for adults and children is 15 to 25 mg/kg once a day, 50 mg/kg twice a week, or 25 to 30 mg/kg 3 times a week. For re-treatment therapy, the usual dosage is 25 mg/kg/day for the first 60 days and 15 mg/kg/day thereafter. Ethambutol may be taken with food if GI upset occurs.

Second-Line Antituberculosis Drugs

The group of second-line anti-TB drugs consists of two fluoroquinolones (levofloxacin and moxifloxacin), four injectable drugs (kanamycin, capreomycin, amikacin, streptomycin), and three other drugs (*para*-aminosalicylic acid [PAS], ethionamide, and cycloserine). In general, these drugs are less effective, more toxic, and more expensive than the first-line drugs. As a result, their principal indication is TB caused by organisms that have proved resistant to first-line agents. In addition, second-line drugs are used to treat severe pulmonary TB as well as disseminated (extrapulmonary) infection. The second-line drugs are always employed in conjunction with a major anti-TB drug. Principal toxicities are summarized in Table 90-4.

Fluoroquinolones

Levofloxacin [Levaquin] and moxifloxacin [Avelox] are fluoroquinolone antibiotics indicated for a wide variety of bacterial infections (see Chapter 91). Both drugs have good activity against *M. tuberculosis*. As therapy for TB, these drugs are reserved for infection caused by multidrug-resistant organisms. Both drugs are generally well tolerated, although GI disturbances are relatively common. Tendon rupture occurs rarely. Oral dosages for adults are as follows: levofloxacin, 500 to 750 mg/day, and moxifloxacin, 400 mg/day. These drugs are not recommended for children.

Injectable Drugs

Capreomycin. Capreomycin [Capastat Sulfate] is an antibiotic derived from a species of *Streptomyces*. Antibacterial effects probably result from inhibiting protein synthesis. The drug is bacteriostatic to *M. tuberculosis*. Capreomycin is used only for TB resistant to primary agents. The principal toxicity is renal damage, and hence the drug should not be taken by patients with kidney disease. Capreomycin may also cause eighth cranial nerve damage, resulting in hearing loss, tinnitus, and disturbed balance. Administration is by deep IM injection (the drug is not absorbed from the GI tract, and therefore cannot be administered PO). The usual adult dosage is 1 gm/day for 60 to 120 days, followed by 1-gm doses 2 to 3 times a week. The pediatric dosage is 15 mg/kg/day (up to a maximum of 1 gm).

Amikacin, Kanamycin, and Streptomycin. Amikacin [Amikin], kanamycin [Kantrex], and streptomycin are aminoglycoside antibiotics with good activity against *M. tuberculosis*. Like other aminoglycosides, these drugs are nephrotoxic and may also damage the eighth cranial nerve. These drugs are not absorbed from the GI tract, and hence administration is parenteral (IM or IV). For amikacin and kanamycin, the adult dosage for both routes is 15 mg/kg/day, and the pediatric dosage is 15 to 30 mg/kg/day. Streptomycin is usually given IM. The adult dosage is 20 to 40 mg/kg given daily or 25 to 30 mg/kg given twice or thrice weekly. The pediatric dosage is nearly the same: 15 mg/kg given daily or 25 to 30 mg/kg given twice or thrice weekly. The pharmacology of these and other aminoglycosides is discussed in Chapter 87.

Other Second-Line Drugs

Para-Aminosalicylic Acid. Actions and Uses. PAS [Paser Granules] is similar in structure and actions to the sulfonamides. Like the sulfonamides, PAS exerts its antibacterial effects by inhibiting synthesis of folic acid. However, in contrast to the sulfonamides, which are broad-spectrum antibiotics, PAS is active only against mycobacteria. In the United States, PAS has been employed primarily as a substitute for ethambutol in pediatric patients. The drug is always used in combination with other anti-TB agents.

Pharmacokinetics. PAS is administered orally, and absorption is good. The drug is distributed widely to most tissues and body fluids, although levels in CSF remain low. PAS undergoes extensive hepatic metabolism. Metabolites and parent drug are excreted in the urine.

Adverse Effects. PAS is poorly tolerated by adults; children accept the drug somewhat better. The most frequent adverse effects are GI disturbances (nausea, vomiting, diarrhea). Because PAS is administered in large doses as

a sodium salt, substantial sodium loading may occur. Additional adverse effects are allergic reactions, hepatotoxicity, and goiter.

Preparations, Dosage, and Administration. *Para*-aminosalicylate [Paser Granules] is supplied in 4-gm packets containing delayed-release granules. Administration is oral. If stomach upset occurs, PAS may be administered with food. The daily dosage for adults is 4 gm 3 times a day. The daily dosage for children is 275 to 420 mg/kg in three to four divided doses. The drug loses its effectiveness if exposed to heat, and hence should be stored cool (below 59°F).

Ethionamide. Actions and Uses. Ethionamide [Trecator], a relative of isoniazid, is active against mycobacteria, but less so than isoniazid itself. Ethionamide is administered with other anti-TB drugs to treat TB that is resistant to first-line agents. Gastrointestinal disturbances limit patient acceptance. Ethionamide is the least well tolerated of all anti-TB agents, and hence should be used only when there is no alternative.

Pharmacokinetics. Ethionamide is readily absorbed following oral administration. The drug is widely distributed to tissues and body fluids, including the CSF. Ethionamide undergoes extensive metabolism and is excreted in the urine, primarily as metabolites.

Adverse Effects. Gastrointestinal effects (anorexia, nausea, vomiting, diarrhea, metallic taste) occur often; intolerance of these effects frequently leads to discontinuation. Ethionamide is toxic to the liver. Hepatotoxicity is assessed by measuring serum transaminases (AST, ALT) prior to treatment and periodically thereafter. Additional adverse effects include peripheral neuropathy, CNS effects (convulsions, mental disturbance), and allergic reactions.

Preparations, Dosage, and Administration. Ethionamide [Trecator] is supplied in 250-mg tablets. The usual adult dosage is 15 to 20 mg/kg taken once daily or in two or three divided doses (to reduce GI upset). The recommended pediatric dosage is 15 to 20 mg/kg/day taken in two or three divided doses.

Cycloserine. Actions and Uses. Cycloserine [Seromycin Pulvules] is an antibiotic produced by a species of *Streptomyces*. The drug is bacteriostatic and acts by inhibiting cell wall synthesis. Cycloserine is used against TB resistant to first-line drugs.

Pharmacokinetics. Cycloserine is rapidly absorbed following oral administration. The drug is widely distributed to tissues and body fluids, including the CSF. Elimination is by hepatic metabolism and renal excretion; about 50% of the drug leaves unchanged in the urine. Cycloserine may accumulate to toxic levels in patients with renal impairment.

Adverse Effects. CNS effects occur frequently and can be severe. Possible reactions include anxiety, depression, confusion, hallucinations, paranoia, hyperreflexia, and seizures. Psychotic episodes occur in approximately 10% of patients; symptoms usually subside within 2 weeks following drug withdrawal. Pyridoxine may prevent neurotoxic effects. Other adverse effects include peripheral neuropathy, hepatotoxicity, and folate deficiency. To minimize the risk of adverse effects, serum concentrations of cycloserine should be measured periodically; peak concentrations, measured 2 hours after dosing, should be 25 to 35 mcg/mL.

Preparations, Dosage, and Administration. Cycloserine [Seromycin Pulvules] is supplied in 250-mg capsules. The initial dosage for adults is 250 mg twice daily for 2 weeks; the maintenance dosage is 500 mg to 1 gm daily in divided doses. The dosage for children is 10 to 20 mg/kg/day.

TMC207, a Promising Investigational Drug

TMC207 (also known as R207910) is the working name for a first-in-class *diarylquinoline*. The drug works faster and better than all other anti-TB drugs, and may also prove safer. In addition, TMC207 does not accelerate the metabolism of other drugs, and hence can be used safely in patients taking drugs for HIV. Because of these attributes, TMC207 is considered the most promising agent for TB to emerge in decades.

TMC207 is highly effective. In a mouse model of TB, a three-drug regimen consisting of TMC207 plus rifampin and pyrazinamide was compared with a conventional three-drug regimen consisting of isoniazid plus rifampin and pyrazinamide. The result? After 1 month with the TMC207 regimen, bacterial load was as low as seen after 2 months with the conventional regimen, indicating accelerated bacterial kill. And after 2 months with the TMC207 regimen, mycobacteria were cleared entirely from the lungs, an unprecedented outcome. In laboratory tests, TMC207 was bactericidal to all isolates of *M. tuberculosis* resistant to conventional therapy, including multidrug-resistant strains.

TMC207 has a unique mechanism of action: Bacterial kill results from inhibiting ATP synthase, an enzyme required by *M. tuberculosis* to make ATP. No other drug shares this mechanism, which explains why there's no cross-

resistance between TMC207 and conventional drugs. Since humans (and most other bacteria too) make ATP by a different pathway, TMC207 should be highly specific for mycobacteria, and should also prove very safe.

TMC207 has desirable kinetics. The drug undergoes rapid absorption after oral dosing, and distributes to all tissues. Of particular importance, it concentrates in cells of the lungs, reaching levels 10 times those in blood. Furthermore, TMC207 remains in the body for days, permitting continued bactericidal effects with just once-a-week dosing.

Interaction with rifampin may be a concern. Why? Because rifampin induces the activity of CYP3A4, the isozyme of cytochrome P450 that metabolizes TMC207. In a clinical trial, rifampin significantly reduced blood levels of TMC207. However, the clinical significance of this interaction is unclear.

Although resistance to TMC207 is uncommon, it does occur: About 1 in 200 million tubercle bacilli make a form of ATP synthase that is not inhibited by the drug. Accordingly, to prevent overgrowth with these resistant microbes, the regimen should always contain other anti-TB drugs.

Is TMC207 safe and effective in humans? Early studies suggest it is. In a 2-month, Phase II trial involving 50 patients, TMC207 showed significant activity against *M. tuberculosis*, with minimal side effects. Studies to evaluate safety and efficacy in a larger group for a longer time are in progress.

DRUGS FOR LEPROSY (HANSEN'S DISEASE)

Leprosy is a chronic infectious disease caused by *M. leprae*, an acid-fast bacillus. The infection is also known as Hansen's disease, in recognition of Gerhard Armauer Hansen, who demonstrated the involvement of *M. leprae* in 1873. Left untreated, leprosy can cause grotesque disfigurement. Fortunately, with the drugs available today, most patients can be cured. As a result, the worldwide incidence of leprosy has declined dramatically—from an estimated 12 million cases in the mid-1980s to about 249,000 new cases in 2008. In the United States, only 80 new cases were reported in 2008, and these occurred primarily among immigrants from endemic areas (eg, India, Brazil, Indonesia).

Infection with *M. leprae* affects the skin, eyes, peripheral nerves, and mucous membranes of the upper respiratory tract. Characteristic features are (1) skin lesions with local loss of sensation, (2) thickening of peripheral nerves, and (3) acid-fast bacilli in smears from skin lesions.

Leprosy is divided into two main classes: (1) paucibacillary (PB) leprosy and (2) multibacillary (MB) leprosy. Classification is based on clinical manifestations and the presence of *M. leprae* in skin smears. If skin smears are negative, the diagnosis is PB leprosy. Conversely, if any smear is positive, the diagnosis is MB leprosy. In many places, microbiologic analysis of skin smears is either unavailable or unreliable. Hence, in these places, classification must be based on clinical findings alone. In this case, if the patient has one to five skin lesions, the diagnosis is PB leprosy; if the patient has six or more skin lesions, the diagnosis is MB leprosy. The distinction between PB leprosy and MB leprosy is important because treatment differs for the two forms.

Overview of Treatment

As with TB, the cornerstone of treatment is multidrug therapy. If just one drug is used, resistance will occur. Most regimens include rifampin, the most effective drug for killing *M. leprae*. For patients with MB leprosy, the World Health Organization (WHO) recommends 12 months of treatment with three drugs: rifampin, dapsone, and clofazimine. For patients with PB leprosy, the WHO recommends 6 months of treatment with two drugs: rifampin and dapsone. For patients with *single-lesion PB leprosy* (ie, PB leprosy with just one skin lesion), the WHO recommends a single dose of the "ROM" regimen: rifampin, ofloxacin, and minocycline. With all three regimens, the relapse rate is very low (about 0.1%). Accordingly, all three are considered curative. Specific dosages for these regimens are summarized in Table 90-5.

Pharmacology of Individual Antileprosy Drugs

Rifampin

The basic pharmacology of rifampin [Rifadin, Rimaactane] is discussed above under *Pharmacology of Individual Antituberculosis Drugs*. Discussion here is limited to its use in leprosy.

Rifampin is by far our most effective agent for treating leprosy. In fact, the drug is more effective than any combination of other agents. A single dose kills more than 99.9% of viable *M. leprae*. After three monthly doses, less than 0.001% of the initial *M. leprae* population remains. Because of its pow-

TABLE 90-5 ■ Adult Regimens for Leprosy, as Recommended by the World Health Organization

Multibacillary Leprosy (Treat 12 Months with All 3 Drugs)	
Rifampin	600 mg once a month, supervised
Dapsone	100 mg daily, self-administered
Clofazimine	300 mg once a month, supervised
	or
	50 mg daily, self-administered
Paucibacillary Leprosy (Treat 6 Months with Both Drugs)	
Rifampin	600 mg once a month, supervised
Dapsone	100 mg daily, self-administered
Single-Lesion Paucibacillary Leprosy (Take All 3 Drugs Once)	
Rifampin	600 mg
Ofloxacin	400 mg
Minocycline	100 mg
Rifampin-Resistant Leprosy (Treat 12 Months)	
First 6 Months (Take All 3 Drugs Daily)	
Clofazimine	50 mg
Ofloxacin	400 mg
Minocycline	100 mg
Next 6 Months (Take Either Pair of Drugs Daily)	
Clofazimine	50 mg
Ofloxacin	400 mg
	or
Clofazimine	50 mg
Minocycline	100 mg

erful bactericidal actions, rifampin is a key component of standard antileprosy regimens.

The dosage currently recommended by the WHO is 600 mg *once a month*. In the past, rifampin was administered daily. However, we now know that monthly dosing is just as effective. Moreover, monthly dosing is much less expensive and minimizes hepatotoxicity and other adverse effects. Resistance can occur if rifampin is used alone. Accordingly, the drug is always combined with other antileprosy agents (eg, dapsone plus clofazimine).

Dapsone

Actions and Uses. Dapsone, taken orally, is weakly bactericidal to *M. leprae*. The drug is safe, inexpensive, and moderately effective. Dapsone is chemically related to the sulfonamides and shares their mechanism of action: inhibition of folic acid synthesis. Although once employed alone to treat leprosy, dapsone is now employed in combination with other antileprosy drugs, usually rifampin and clofazimine. In 2008, a topical formulation, sold as Aczone, was approved for treating acne (see Chapter 105).

Pharmacokinetics. Dapsone is absorbed rapidly and nearly completely from the GI tract. Once in the blood, the drug is widely distributed to tissues and body fluids. Dapsone undergoes hepatic metabolism followed by excretion in the urine. The average half-life is 28 hours.

Adverse Effects. Dapsone is generally well tolerated. The drug has been taken for years without significant untoward effects. The most common effects are GI disturbances, headache, rash, and a syndrome that resembles mononucleosis. Hemolytic anemia occurs occasionally; severe reactions are usually limited to patients with profound glucose-6-phosphate dehydrogenase deficiency. Rare reactions include agranulocytosis, exfoliative dermatitis, and hepatitis.

Preparations, Dosage, and Administration. Dapsone is formulated in 25- and 100-mg tablets. The usual dosage for adults is 100 mg/day. The dosage for children is 1 mg/kg/day. To prevent emergence of resistance, dapsone is always combined with another antileprosy drug (eg, rifampin, clofazimine).

Clofazimine

Actions and Uses. Clofazimine [Lamprene] is slowly bactericidal to *M. leprae*. Its mechanism of action is unknown. To prevent emergence of resistance, clofazimine is always combined with another antileprosy drug (eg,

TABLE 90-6 ■ Regimens for MAC Infection in Immunocompetent Adults

Pulmonary MAC

Daily Regimen

Clarithromycin (500 mg twice daily) *or* azithromycin (250 mg) *plus*
Ethambutol (25 mg/kg for 2 months, then 15 mg/kg thereafter) *plus*
Rifampin (600 mg) *or* rifabutin (300 mg) *may also add*
Streptomycin (15 mg/kg 3 times a week for 2–6 months)

Duration

Treat until cultures remain negative for 12 months

Disseminated MAC

Daily Regimen

Clarithromycin (500 mg twice daily) *or* azithromycin (250–500 mg) *plus*
Ethambutol (15 mg/kg) *plus*
Rifampin (600 mg) *or* rifabutin (300 mg) *may also add*
Streptomycin (15 mg/kg 3 times a week for 2–6 months)

Duration

Treat until cultures remain negative for 12 months

MAC = *Mycobacterium avium* complex.

rifampin, dapsone). In addition to its antibacterial action, clofazimine has anti-inflammatory actions.

Pharmacokinetics. Clofazimine is administered orally and undergoes partial absorption. Absorbed drug is retained in fatty tissue and the skin. Because of tissue retention, the half-life of clofazimine is extremely long—about 70 days.

Adverse Effects. Clofazimine is very safe. Dangerous reactions are rare. GI symptoms (nausea, vomiting, cramping, diarrhea) are common but mild. The drug frequently imparts a harmless red color to feces, urine, sweat, tears, and saliva. Deposition of clofazimine in the small intestine produces the most serious effects; intestinal obstruction, pain, and bleeding.

Clofazimine causes reversible reddish-black discoloration of the skin in most patients. Pigmentation begins 4 to 8 weeks after the onset of treatment, and generally clears within 12 months of drug cessation. Because it can darken the skin, patients with light-colored skin often find clofazimine unacceptable.

Preparations, Dosage, and Administration. Clofazimine is formulated in 50- and 100-mg capsules. The usual adult dosage is 50 mg daily. Clofazimine is not available in the United States or Canada.

The ROM Regimen

The ROM regimen (rifampin, ofloxacin, minocycline) is indicated for patients with single-lesion PB leprosy. Treatment consists of one-time dosing with rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg). Ofloxacin [Floxin], a fluoroquinolone antibiotic, is discussed in Chapter 91. Minocycline [Minocin], a member of the tetracycline family, is discussed in Chapter 86.

DRUGS FOR MYCOBACTERIUM AVIUM COMPLEX INFECTION

Mycobacterium avium complex (MAC) consists of two nearly indistinguishable organisms: *M. avium* and *M. intracellulare*. Colonization with MAC begins in the lungs or GI tract, but then may spread to the blood, bone marrow, liver, spleen, lymph nodes, brain, kidneys, and skin. Disseminated infection is common in patients infected with HIV; the incidence at autopsy is 50%. Among immunocompetent patients, symptomatic MAC infection is usually limited to the lungs. Signs and symptoms of disseminated MAC

infection include fever, night sweats, weight loss, lethargy, anemia, and abnormal liver function tests.

Drugs are used for prophylaxis and to treat active infection. Preferred agents for *prophylaxis* of disseminated infection are *azithromycin* and *clarithromycin*. Regimens for *treating active infection* in immunocompetent hosts should include (1) *azithromycin* or *clarithromycin* plus (2) *ethambutol*

plus (3) *rifampin* or *rifabutin*. Additional drugs may be added as needed; options include streptomycin, ciprofloxacin, clofazimine, and amikacin. Treatment of active infection in immunocompetent patients should continue for 12 months after cultures become negative. Representative regimens for immunocompetent patients are presented in Table 90-6. Regimens for patients with HIV infection are presented in Chapter 94.

KEY POINTS

- Most people infected with *M. tuberculosis* remain asymptomatic, although they will harbor dormant bacteria for life (in the absence of drug therapy).
- Symptomatic TB can result from reactivation of an old infection or from recent person-to-person transmission of a new infection.
- Drug resistance, and especially multidrug resistance, is a serious impediment to successful therapy of TB.
- The principal cause of drug resistance in TB is inadequate drug therapy, which kills sensitive bacteria while allowing resistant mutants to flourish.
- To prevent emergence of resistance, initial therapy of TB should consist of at least two drugs to which the infection is sensitive, and preferably four. Accordingly, isolates from all patients must undergo testing of drug sensitivity, a process that typically takes several weeks.
- Therapy of TB is prolonged, lasting from a minimum of 6 months to 2 years and even longer. As a result, patient adherence is a serious issue.
- Adherence can be greatly increased by using directly observed therapy (DOT) combined with intermittent dosing (rather than daily dosing).
- Three methods are employed to evaluate TB therapy: bacteriologic evaluation of sputum, clinical evaluation, and chest radiographs.
- The principal first-line drugs for TB are isoniazid, rifampin, pyrazinamide, and ethambutol. For initial therapy of active TB, patients may be given all four drugs.
- Initial therapy of MDR-TB and XDR-TB may require up to seven drugs.
- Tuberculosis in HIV-positive patients often can be treated with the same regimens used for HIV-negative patients, although the duration of treatment may be longer.
- Isoniazid can injure the liver. The greatest risk factor is advancing age. Patients who develop liver injury should discontinue isoniazid immediately.
- Isoniazid can cause peripheral neuropathy by depleting pyridoxine (vitamin B₆). Peripheral neuropathy can be reversed or prevented with pyridoxine supplements.
- Rifampin induces drug-metabolizing enzymes, and can thereby increase the metabolism of other drugs; important among these are oral contraceptives, warfarin, and certain protease inhibitors and NNRTIs used for HIV infection.
- Like isoniazid, rifampin and pyrazinamide are hepatotoxic. Accordingly, when these three drugs are combined, as they often are, the risk of liver injury can be substantial.
- Ethambutol can cause optic neuritis.
- The *tuberculin skin test* (TST)—used to identify people with latent TB—is performed by giving an intradermal injection of PPD (purified protein derivative) and then measuring the zone of induration (hardness) at the site 48 to 72 hours later.
- New blood tests, known as interferon gamma release assays (IGRAs), are as sensitive as the TST and more specific. Moreover, results with the IGRAs are available faster (within 24 hours) and don't require a return visit to the office.
- For years, isoniazid, taken daily for 9 months, has been the preferred treatment for latent TB. However, a much simpler regimen—isoniazid plus rifapentine taken once a week for just 3 months—is just as effective, and hence is likely to replace isoniazid alone as standard treatment.

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Summary of Major Nursing Implications*

The nursing implications summarized below are limited to the drug therapy of TB.

IMPLICATIONS THAT APPLY TO ALL ANTITUBERCULOSIS DRUGS

Promoting Adherence

Treatment of active TB is prolonged and demands concurrent use of two or more drugs; as a result, adherence can be a significant problem. **To promote adherence, educate the patient about the rationale for multidrug therapy and the need for long-term treatment. Encourage patients to take their medication exactly as prescribed, and to continue treatment until the infection has resolved.** Adherence can be greatly increased by using directly observed therapy (DOT) combined with intermittent dosing (rather than daily dosing).

Evaluating Treatment

Success is indicated by (1) reductions in fever, malaise, anorexia, cough, and other clinical manifestations of TB (usually within weeks); (2) radiographic evidence of improvement (usually in 3 months); and (3) an absence of *M. tuberculosis* in sputum (usually after 3 to 6 months).

ISONIAZID

In addition to the implications summarized below, see above for implications on *Promoting Adherence* and *Evaluating Treatment* that apply to all anti-TB drugs.

Preadministration Assessment

Therapeutic Goal

Treatment of active or latent infection with *M. tuberculosis*.

Baseline Data

Obtain a chest radiograph, microbiologic tests of sputum, and baseline tests of liver function.

Identifying High-Risk Patients

Isoniazid is *contraindicated* for patients with acute liver disease or a history of isoniazid-induced hepatotoxicity.

Use with *caution* in alcohol abusers, diabetic patients, patients with vitamin B₆ deficiency, patients over the age of 50, and patients who are taking phenytoin, rifampin, rifabutin, rifapentine, or pyrazinamide.

Implementation: Administration

Routes

Oral, IM.

Administration

Advise patients to take isoniazid on an empty stomach, either 1 hour before meals or 2 hours after. Advise patients to take the drug with meals if GI upset occurs.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hepatotoxicity. Isoniazid can cause hepatocellular damage and multilobular hepatic necrosis. **Inform patients about signs of hepatitis (jaundice, anorexia, malaise, fatigue, nausea), and instruct them to notify the prescriber immediately if these develop.** Evaluate patients monthly for signs of hepatitis. Monthly determinations of AST activity may be ordered. If clinical signs of hepatitis appear, or if AST activity exceeds 3 to 5 times the pretreatment baseline, isoniazid should be withdrawn. Daily ingestion of alcohol increases the risk of liver injury; **urge the patient to minimize or eliminate alcohol consumption.**

Peripheral Neuropathy. Inform patients about symptoms of peripheral neuropathy (tingling, numbness, burning, or pain in the hands or feet), and instruct them to notify the prescriber if these occur. Peripheral neuritis can be reversed with small daily doses of pyridoxine (vitamin B₆). In patients at high risk of neuropathy (eg, alcohol abusers, diabetic patients), give pyridoxine prophylactically.

Minimizing Adverse Interactions

Phenytoin. Isoniazid can suppress the metabolism of phenytoin, thereby causing phenytoin levels to rise. Plasma phenytoin should be monitored. If necessary, phenytoin dosage should be reduced.

RIFAMPIN

In addition to the implications summarized below, see above for implications on *Promoting Adherence* and *Evaluating Treatment* that apply to all anti-TB drugs.

Preadministration Assessment

Therapeutic Goal

Treatment of active TB or leprosy.

Baseline Data

Obtain a chest radiograph, microbiologic tests of sputum, and baseline tests of liver function.

Identifying High-Risk Patients

Rifampin is *contraindicated* for patients taking delavirdine (an NNRTI) and most protease inhibitors.

Use with *caution* in alcohol abusers, patients with liver disease, and patients taking warfarin.

Implementation: Administration

Routes

Oral, IV.

Dosage

Reduce the dosage in patients with liver disease.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Administration

Instruct the patient to take oral rifampin once a day, either 1 hour before a meal or 2 hours after.

Administer IV rifampin by slow infusion (over 3 hours).

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hepatotoxicity. Rifampin may cause jaundice or hepatitis. Inform patients about signs of liver dysfunction (anorexia, darkened urine, pale stools, yellow discoloration of eyes or skin), and instruct them to notify the prescriber if these develop. Monitor patients for signs of liver dysfunction. Tests of liver function should be made prior to treatment and every 2 to 4 weeks thereafter.

Discoloration of Body Fluids. Inform patients that rifampin may impart a harmless red-orange color to urine, sweat, saliva, and tears. Warn patients that soft contact lenses may undergo permanent staining; advise them to consult an ophthalmologist about continued use of these lenses.

Minimizing Adverse Interactions

Accelerated Metabolism of Other Drugs. Rifampin can accelerate the metabolism of many drugs, thereby reducing their effects. This action is of particular concern with oral contraceptives, warfarin, most protease inhibitors, and delavirdine (an NNRTI). Advise women taking oral contraceptives to use a nonhormonal form of birth control. Monitor warfarin effects and increase dosage as needed. Do not combine protease inhibitors or NNRTIs with rifampin.

Pyrazinamide and Isoniazid. These hepatotoxic anti-TB drugs can increase the risk of liver injury when used with rifampin.

PYRAZINAMIDE

In addition to the implications summarized below, see above for implications on *Promoting Adherence* and *Evaluating Treatment* that apply to all anti-TB drugs.

Preadministration Assessment

Therapeutic Goal

Treatment of active and latent TB.

Baseline Data

Obtain a chest radiograph, microbiologic tests of sputum, and baseline tests of liver function.

Identifying High-Risk Patients

Pyrazinamide is *contraindicated* for patients with severe liver dysfunction or acute gout.

Use with *caution* in alcohol abusers.

Implementation: Administration

Route

Oral.

Administration

Usually administered once a day.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hepatotoxicity. Inform patients about symptoms of hepatitis (malaise, anorexia, nausea, vomiting, yellowish discoloration of the skin and eyes), and instruct them to notify the prescriber if these develop. Levels of AST and ALT should be measured prior to treatment and every 2 weeks thereafter. If severe liver injury occurs, pyrazinamide should be withdrawn. The risk of liver injury is increased by concurrent therapy with isoniazid, rifampin, rifabutin, or rifapentine, all of which are hepatotoxic.

Nongouty Polyarthralgias. Polyarthralgias develop in 40% of patients. Advise patients to take an NSAID (eg, aspirin, ibuprofen) to relieve pain. Some patients may need to stop pyrazinamide, or at least reduce the dosage.

ETHAMBUTOL

In addition to the implications summarized below, see above for implications on *Promoting Adherence* and *Evaluating Treatment* that apply to all anti-TB drugs.

Preadministration Assessment

Therapeutic Goal

Treatment of active TB.

Baseline Data

Obtain a chest radiograph, microbiologic tests of sputum, and baseline vision tests.

Identifying High-Risk Patients

Ethambutol is *contraindicated* for patients with optic neuritis.

Implementation: Administration

Route

Oral.

Administration

Usually administered once a day. Advise patients to take ethambutol with food if GI upset occurs.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Optic Neuritis. Ethambutol can cause dose-related optic neuritis. Symptoms include blurred vision, altered color discrimination, and constriction of visual fields. Baseline vision tests are required. Instruct patients to report any alteration in vision (eg, blurring of vision, reduced color discrimination). If ocular toxicity develops, ethambutol should be withdrawn at once.

*Patient education information is highlighted as blue text.

Miscellaneous Antibacterial Drugs: Fluoroquinolones, Metronidazole, Daptomycin, Rifampin, Rifaximin, Bacitracin, and Polymyxins

Fluoroquinolones

Ciprofloxacin

Other Systemic Fluoroquinolones

Additional Antibacterial Drugs

Metronidazole

Daptomycin

Rifampin

Rifaximin

Fidaxomicin

Bacitracin

Polymyxin B

FLUOROQUINOLONES

The fluoroquinolones are fluorinated analogs of nalidixic acid, a narrow-spectrum quinolone antibiotic used only for urinary tract infections (UTIs). However, unlike nalidixic acid, the fluoroquinolones are broad-spectrum agents that have multiple applications. Benefits derive from disrupting DNA replication and cell division. Fluoroquinolones do not disrupt synthesis of proteins or the cell wall. All of the systemic fluoroquinolones can be administered orally. As a result, these drugs are attractive alternatives for people who might otherwise require intravenous antibacterial therapy. Although side effects are generally mild, all fluoroquinolones can cause tendinitis and tendon rupture, usually of the Achilles tendon. Fortunately, the risk is low. Bacterial resistance develops slowly, but has become common in *Neisseria gonorrhoeae*, and hence these drugs are no longer recommended for this infection. Six fluoroquinolones are currently available for systemic therapy. Six others—gatifloxacin, enoxacin, lomefloxacin, sparfloxacin, trovafloxacin, and alatrofloxacin—were withdrawn in recent years. Fluoroquinolones used solely for topical treatment of the eye are listed in Table 104–7, Chapter 104.

Ciprofloxacin

Ciprofloxacin [Cipro, Proquin XR] was among the first fluoroquinolones available and will serve as our prototype for the group. The drug is active against a broad spectrum of bacte-

rial pathogens, and may be administered PO or IV. Ciprofloxacin has been used as an alternative to parenteral antibiotics for treatment of several serious infections. Because it can be administered by mouth, patients receiving ciprofloxacin can be treated at home, rather than going to the hospital for IV antibacterial therapy.

Mechanism of Action

Ciprofloxacin inhibits two bacterial enzymes: *DNA gyrase* and *topoisomerase IV*. Both are needed for DNA replication and cell division. DNA gyrase converts closed circular DNA into a supercoiled configuration. In the absence of supercoiling, DNA replication cannot take place. Topoisomerase IV helps separate daughter DNA strands during cell division. Since the mammalian equivalents of DNA gyrase and topoisomerase IV are largely insensitive to fluoroquinolones, cells of the host are spared. Ciprofloxacin is rapidly bactericidal.

Antimicrobial Spectrum

Ciprofloxacin is active against a broad spectrum of bacteria, including most aerobic gram-negative bacteria and some gram-positive bacteria. Most urinary tract pathogens, including *Escherichia coli* and *Klebsiella*, are sensitive. The drug is also highly active against most bacteria that cause enteritis (eg, *Salmonella*, *Shigella*, *Campylobacter jejuni*, *E. coli*). Other sensitive organisms include *Bacillus anthracis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, meningococci, and many streptococci. Activity against anaerobes is fair to poor. *Clostridium difficile* is resistant.

Bacterial Resistance

Resistance to fluoroquinolones has developed during treatment of infections caused by *Staphylococcus aureus*, *Serratia marcescens*, *C. jejuni*, *P. aeruginosa*, and *N. gonorrhoeae*. Two mechanisms appear responsible: (1) alterations in DNA gyrase and topoisomerase IV and (2) increased drug export. Bacteria do not directly inactivate fluoroquinolones, and there have been no reports of resistance via transfer of R factors.

Pharmacokinetics

Ciprofloxacin may be given PO or IV. Following oral dosing, the drug is absorbed rapidly but incompletely. High concentrations are achieved in urine, stool, bile, saliva, bone, and prostate tissue. Drug levels in cerebrospinal fluid remain low. Ciprofloxacin has a plasma half-life of about 4 hours. Elimination is by hepatic metabolism and renal excretion.

Therapeutic Uses

Ciprofloxacin is approved for a wide variety of infections. Among these are infections of the respiratory tract, urinary tract, GI tract, bones, joints, skin, and soft tissues. Also, ciprofloxacin is a preferred drug for preventing anthrax in people

who have inhaled anthrax spores. Because ciprofloxacin is active against a variety of pathogens and can be given orally, the drug represents an alternative to parenteral treatment for many serious infections. Owing to high rates of resistance, ciprofloxacin is a poor choice for staphylococcal infections. The drug is not useful against infections caused by anaerobes.

Because of concerns about tendon injury (see below), systemic ciprofloxacin is generally avoided in children under 18 years old. Nonetheless, the drug does have two approved pediatric uses: (1) treatment of complicated urinary tract and kidney infections caused by *E. coli*, and (2) postexposure treatment of inhalational anthrax. Ciprofloxacin is the only systemic fluoroquinolone approved for pediatric use.

Adverse Effects

Ciprofloxacin can induce a variety of mild adverse effects, including GI reactions (nausea, vomiting, diarrhea, abdominal pain) and central nervous system (CNS) effects (dizziness, headache, restlessness, confusion). *Candida* infections of the pharynx and vagina may develop during treatment. Very rarely, seizures have occurred. In the elderly, ciprofloxacin poses a significant risk of confusion, somnolence, psychosis, and visual disturbances.

Rarely, ciprofloxacin and other fluoroquinolones have caused *tendon rupture*, usually of the Achilles tendon. The incidence is 1 in 10,000 or less. People at highest risk are those 60 and older, those taking glucocorticoids, and those who have undergone heart, lung, or kidney transplantation. How do fluoroquinolones damage tendons? When given to immature animals, fluoroquinolones disrupt the extracellular matrix of cartilage. A similar mechanism may underlie tendon rupture in humans. Since tendon injury is reversible if diagnosed early, fluoroquinolones should be discontinued at the first sign of tendon pain, swelling, or inflammation. In addition, patients should refrain from exercise until tendinitis has been ruled out. Although there are no controlled studies on the use of ciprofloxacin during pregnancy or lactation, available data indicate that such use poses little or no risk of tendon damage to either the fetus or nursing infant.

Ciprofloxacin and other fluoroquinolones pose a risk of *phototoxicity* (severe sunburn), characterized by burning, erythema, exudation, vesicles, blistering, and edema. These can occur following exposure to direct sunlight, indirect sunlight, and sunlamps—even if a sunscreen has been applied. Patients should be warned about phototoxicity and advised to avoid sunlight and sunlamps. People who must go outdoors should wear protective clothing and apply a sunscreen. Ciprofloxacin should be withdrawn at the first sign of a phototoxic reaction (eg, burning sensation, redness, rash).

Ciprofloxacin and other fluoroquinolones increase the risk of developing *Clostridium difficile* infection (CDI), a potentially severe infection of the bowel. CDI results from killing off intestinal bacteria that normally keep *C. difficile* in check.

Ciprofloxacin and other fluoroquinolones can exacerbate muscle weakness in patients with *myasthenia gravis*. Accordingly, patients with a history of *myasthenia gravis* should not receive these drugs.

Drug and Food Interactions

Cationic Compounds. Absorption of ciprofloxacin can be reduced by compounds that contain cations. Among these are (1) aluminum- or magnesium-containing antacids, (2) iron

salts, (3) zinc salts, (4) sucralfate, (5) calcium supplements, and (6) milk and other dairy products, all of which contain calcium ions. These cationic agents should be administered at least 6 hours before ciprofloxacin or 2 hours after.

Elevation of Drug Levels. Ciprofloxacin can increase plasma levels of several drugs, including *theophylline* (used for asthma), *warfarin* (an anticoagulant), and *tinidazole* (an antifungal drug). Toxicity could result. For patients taking theophylline, drug levels should be monitored and the dosage adjusted accordingly. For patients taking warfarin, prothrombin time should be monitored and the dosage of warfarin reduced as appropriate.

Preparations, Dosage, and Administration

Preparations. Ciprofloxacin is available for oral and IV administration. For oral therapy, ciprofloxacin is supplied in immediate-release tablets (100, 250, 500, and 750 mg) sold as *Cipro*, extended-release tablets (500 and 1000 mg) sold as *Cipro XR* and *Proquin XR*, and a suspension (250 and 500 mg/5 mL) sold as *Cipro*. For IV therapy, ciprofloxacin is supplied in solution (2 and 10 mg/mL) sold as *Cipro I.V.*

Dosage and Administration. *Oral.* Dosing may be done with or without food. The dosage for urinary tract infections is 250 or 500 mg 2 times a day, usually for 7 to 14 days. For other infections, dosages range from 500 to 750 mg 2 times a day. Dosage should be reduced for patients with renal impairment. Dosages for anthrax prevention are presented below.

Intravenous. Intravenous dosages range from 200 to 400 mg every 12 hours. Infusions should be done slowly (over 60 minutes). Dosages for anthrax prevention are presented below.

Inhalational Anthrax. Ciprofloxacin is used to reduce the incidence of anthrax or prevent anthrax progression in people who have inhaled *B. anthracis* spores. The dosage for adults is 500 mg PO (or 400 mg IV) every 12 hours for 60 days. The dosage for children is 15 mg/kg PO (or 10 mg/kg IV) every 12 hours for 60 days (with the proviso that individual oral doses not exceed 500 mg, and individual IV doses not exceed 400 mg). Management of inhalational anthrax is discussed at length in Chapter 110 (Potential Weapons of Biologic, Radiologic, and Chemical Terrorism).

Other Systemic Fluoroquinolones Ofloxacin

Basic Pharmacology. Ofloxacin [Floxin] is similar to ciprofloxacin in mechanism of action, antimicrobial spectrum, therapeutic applications, and adverse effects. Like ciprofloxacin, the drug may be administered PO or IV. Bioavailability is high (90%) in the absence of food, and greatly reduced in the presence of food. Ofloxacin is widely distributed to tissues and excreted in the urine. Like ciprofloxacin, ofloxacin can cause a variety of mild adverse effects, including nausea, vomiting, headache, and dizziness. In addition, ofloxacin may intensify sensitivity to sunlight, thereby increasing the risk of severe sunburn. Like other fluoroquinolones, ofloxacin can (1) exacerbate muscle weakness in patients with *myasthenia gravis*, (2) increase the risk of CDI, and (3) cause tendinitis and tendon rupture, especially among those over age 60, those taking glucocorticoids, and those who have undergone a heart, lung, or kidney transplantation. Ofloxacin elevates plasma levels of warfarin, but, in contrast to ciprofloxacin, has little effect on levels of theophylline. Absorption of oral ofloxacin is reduced by cationic substances: milk, milk products, sucralfate, iron and zinc salts, and magnesium- and aluminum-containing antacids.

Preparations, Dosage, and Administration. Ofloxacin [Floxin] is available in tablets (200, 300, and 400 mg) for dosing with or without food. The usual daily dosage is 200 to 400 mg every 12 hours. Treatment duration ranges from 1 day to 6 weeks. Dosage should be reduced in patients with renal impairment.

Moxifloxacin

Basic Pharmacology. Moxifloxacin [Avelox] is a broad-spectrum fluoroquinolone indicated for respiratory tract infections (community-acquired pneumonia [CAP], acute sinusitis, acute exacerbations of chronic bronchitis), intra-abdominal infections, and infections of the skin and skin structures. Administration is oral or IV. The drug is well absorbed from the GI tract, undergoes wide distribution, and is eliminated by hepatic metabolism and renal excretion. Side effects are generally mild, the most common being nausea, vomiting, diarrhea, stomach pain, dizziness, and altered sense of taste. Like other fluoroquinolones, moxifloxacin can promote development of CDI, exacerbate muscle weakness in patients with *myasthenia gravis*, and

cause tendinitis and tendon rupture. The drug may also pose a risk of phototoxicity. Moxifloxacin does not increase levels of warfarin or digoxin, but does prolong the QT interval, and hence may pose a risk of serious dysrhythmias. Accordingly, the drug should be used with great caution, if at all, in patients taking prodysrhythmic drugs or in those with hypokalemia or pre-existing QT prolongation.

Preparations, Dosage, and Administration. For systemic therapy, moxifloxacin [Avelox, Avelox I.V.] is available in 400-mg tablets and in solution (400 mg/250 mL) for slow IV infusion. Oral and IV dosages are the same, and should be reduced in patients with renal impairment. The usual dosage for sinusitis and pneumonia is 400 mg once a day for 10 days; the usual dosage for bronchitis is 400 mg once a day for 5 days; the drug may be done with or without food. However, because absorption can be reduced by cationic substances (eg, milk, sucralfate, iron and zinc salts, magnesium- or aluminum-containing antacids), moxifloxacin should be administered at least 4 hours before these agents or 8 hours after.

Norfloxacin

Norfloxacin [Noroxin] is a fluoroquinolone antibiotic with an antimicrobial spectrum like that of ciprofloxacin. The drug is used for oral therapy of UTIs and prostatitis.

Pharmacokinetics. Norfloxacin undergoes rapid but incomplete absorption from the GI tract. The drug is widely distributed to body tissues and fluids. Excretion is primarily renal, resulting in high concentrations in the urine. About 30% of the drug is eliminated in the bile and feces. In patients with normal kidney function, the half-life is approximately 4 hours; this value doubles in patients with renal impairment.

Therapeutic Uses. Norfloxacin is approved for prostatitis caused by *E. coli* and for UTIs caused by *P. aeruginosa* and other gram-negative bacteria that can display multidrug resistance. The drug is also approved for uncomplicated urethral and cervical gonorrhea, but is no longer recommended for this use.

Adverse Effects. Norfloxacin is generally well tolerated. Gastrointestinal effects (nausea, vomiting, anorexia) have been most frequent. The drug has produced a variety of CNS reactions, including headache, dizziness, drowsiness, lightheadedness, depression, and disturbance of vision. Skin rash develops occasionally. Like other fluoroquinolones, norfloxacin can promote development of CDI, exacerbate muscle weakness in patients with myasthenia gravis, and cause tendinitis and tendon rupture. The drug also increases the risk of severe sunburn.

Drug and Food Interactions. Norfloxacin shares the same interactions as ciprofloxacin. Absorption is suppressed by cationic agents, including milk products, aluminum- and magnesium-containing antacids, iron and zinc salts, and sucralfate. The drug can elevate levels of theophylline and intensify effects of warfarin.

Preparations, Dosage, and Administration. Norfloxacin [Noroxin] is supplied in 400-mg tablets, for dosing with a full glass of water, 1 hour before meals or 2 hours after. For uncomplicated UTIs, the usual dosage is 400 mg twice daily for 3 days. Prolonged treatment (10 days to 3 weeks) is employed for patients with complicated infections of the urinary tract. Dosage should be reduced in patients with renal impairment.

Levofloxacin

Levofloxacin [Levaquin] is active against *Strep. pneumoniae* (also known as pneumococcus), *H. influenzae*, *Staph. aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, and *Proteus mirabilis*. Approved indications include urinary tract infections, chronic bacterial prostatitis, inhalational anthrax, complicated skin and skin structure infections, and certain respiratory tract infections: acute maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis, and CAP, including CAP caused by penicillin-resistant pneumococci. Possible adverse effects include peripheral neuropathy, rhabdomyolysis, tendinitis, tendon rupture, phototoxicity, and CDI, as well as muscle weakness in patients with myasthenia gravis. To treat systemic infections, levofloxacin may be administered PO or IV. Absorption from the GI tract is reduced by cationic substances (eg, magnesium- and aluminum-containing antacids, zinc and iron salts, sucralfate, milk and milk products) but not by most foods. Levofloxacin is available in tablets (250, 500, and 750 mg), an oral solution (25 mg/mL), and a solution for slow IV infusion (5 and 25 mg/mL). The usual dosage is 500 mg once a day for 7 to 14 days. In patients with renal impairment, the dosage is 500 mg every 48 hours. Oral doses may be taken with or without food.

Gemifloxacin

Therapeutic Use. Gemifloxacin [Factive] is an oral fluoroquinolone approved for two respiratory tract infections in adults: (1) mild to moderate CAP and (2) acute bacterial exacerbations of chronic bronchitis (ABECB). The drug is active against *H. influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*,

Mycoplasma pneumoniae, *Legionella pneumophila*, and *Strep. pneumoniae*, including strains that are multidrug resistant. Gemifloxacin causes a high incidence of rash and, compared with older fluoroquinolones used for respiratory infections, has no significant advantages and costs more. Accordingly, the older agents—levofloxacin and moxifloxacin—are preferred.

Adverse Effects. Gemifloxacin is generally well tolerated. The most common reactions are diarrhea, rash, nausea, headache, abdominal pain, vomiting, dizziness, and altered sense of taste. In addition, the drug may cause tendinitis, tendon injury, phototoxicity, hypersensitivity reactions, liver damage, and CDI, as well as muscle weakness in patients with myasthenia gravis. Like some other fluoroquinolones, gemifloxacin can prolong the QT interval, thereby posing a risk of dysrhythmias. Accordingly, the drug should not be used by patients taking prodysrhythmic drugs or those with hypokalemia or pre-existing QT prolongation.

The incidence of rash with gemifloxacin is much higher than with other fluoroquinolones. Women under 40 years of age are at greatest risk. Symptoms are severe in about 10% of patients who develop a rash; in the rest, symptoms are mild to moderate. As a rule, gemifloxacin-induced rash resolves spontaneously in 1 to 2 weeks, although some patients require treatment with systemic glucocorticoids. If rash develops, gemifloxacin should be discontinued.

Drug Interactions. As with ciprofloxacin, absorption of gemifloxacin can be reduced by compounds that contain cations. Among these are iron salts, zinc salts, sucralfate, aluminum- or magnesium-containing antacids, and milk and other dairy products, which contain calcium ions. To ensure adequate absorption, these cationic agents should be administered at least 6 hours before gemifloxacin or 2 hours after.

Preparations, Dosage, and Administration. Gemifloxacin [Factive] is available in 320-mg tablets for oral dosing, with or without food. The dosage for CAP is 320 mg once a day for 7 days, and the dosage for ABECB is 320 mg once a day for 5 days. For patients with severe renal impairment, the dosage should be reduced to 160 mg once a day. To prevent high concentrations in the urine, all patients should consume liberal amounts of fluid.

ADDITIONAL ANTIBACTERIAL DRUGS

Metronidazole

Metronidazole [Flagyl, Protostat] is used for protozoal infections and infections caused by obligate anaerobic bacteria. The basic pharmacology of metronidazole is discussed in Chapter 99, as is the drug's use against protozoal infections. Consideration here is limited to antibacterial applications.

Mechanism of Antibacterial Action. Metronidazole is lethal to anaerobic organisms only. To exert bactericidal effects, metronidazole must first be taken up by cells and then converted into its active form; only anaerobes can perform the conversion. The active form interacts with DNA to cause strand breakage and loss of helical structure, effects that result in inhibition of nucleic acid synthesis and, ultimately, cell death. Since aerobic bacteria are unable to activate metronidazole, they are insensitive to the drug.

Antibacterial Spectrum. Metronidazole is active against obligate anaerobes only. Sensitive bacterial pathogens include *Bacteroides fragilis* (and other *Bacteroides* species), *C. difficile* (and other *Clostridium* species), *Fusobacterium* species, *Gardnerella vaginalis*, *Peptococcus* species, and *Peptostreptococcus* species.

Therapeutic Uses. Metronidazole is active against a variety of anaerobic bacterial infections, including infections of the CNS, abdominal organs, bones and joints, skin and soft tissues, and genitourinary tract. Frequently, these infections also involve aerobic bacteria, and hence therapy must include a drug active against them. Metronidazole is a drug of choice for *C. difficile* infection, as discussed in Box 85-1, Chapter 85. In addition, the drug is employed for prophylaxis in surgical procedures associated with a high risk of infection by anaerobes (eg, colorectal surgery, abdominal surgery, vaginal surgery). Metronidazole is also used in combination with a

tetracycline and bismuth subsalicylate to eradicate *Helicobacter pylori* in people with peptic ulcer disease. Development of resistance to metronidazole is rare.

Preparations, Dosage, and Administration. For initial treatment of serious bacterial infections, metronidazole is administered by IV infusion. Under appropriate conditions, the patient may switch to oral therapy.

Intravenous Formulations. Metronidazole is available in two formulations—powder and solution—for IV use. The powdered form [Flagyl IV] is supplied in 500-mg vials and must be reconstituted prior to use (see below). The solution (generic only) contains 5 mg of metronidazole per milliliter and is ready for IV use.

Preparation of Powdered Metronidazole for IV Infusion. The powder is readied for infusion in three steps: (1) reconstitution, (2) dilution in IV solution, and (3) neutralization. These steps must be performed in the order given. The powder is reconstituted using 4.4 mL of any of the following liquids: sterile water for injection, bacteriostatic water for injection, 0.9% sodium chloride injection, or bacteriostatic 0.9% sodium chloride injection. The resulting concentrated solution contains approximately 100 mg of metronidazole per milliliter. This solution is then diluted to a concentration of 8 mg/mL (or less) using any of the following IV solutions: 0.9% sodium chloride injection, 5% dextrose injection, or lactated Ringer's injection. Neutralization of the diluted solution is accomplished by adding 5 mEq of sodium bicarbonate injection for each 500 mg of metronidazole present; this procedure should elevate pH to a value between 6 and 7. Neutralized solutions should not be refrigerated, since cooling may cause metronidazole to precipitate.

Intravenous Dosage and Administration. Infusions must be done slowly (over a 1-hour span). Therapy of anaerobic infections in adults is initiated with a loading dose of 15 mg/kg. After this, maintenance doses of 7.5 mg/kg are given every 6 to 8 hours. Treatment duration is usually 1 to 2 weeks. Patients with renal impairment and those receiving prolonged treatment may need a reduced dosage to avoid toxicity from drug accumulation.

Oral Preparations and Dosage. Metronidazole [Flagyl, Flagyl ER, Flagyl 375, Protostat] is supplied in capsules (375 mg), immediate-release tablets (250 and 500 mg), and extended-release tablets (750 mg). The adult dosage for anaerobic infections is 7.5 mg/kg every 6 hours. For bacterial vaginosis in adults, a dosage of 750 mg (extended-release formulation) once daily for 7 days is effective. The dosage for *C. difficile* infection is 500 mg 3 times a day for 10 to 14 days.

Daptomycin

Daptomycin [Cubicin] is the first representative of a new class of antibiotics, the *cyclic lipopeptides*. The drug has a unique mechanism and can rapidly kill virtually all clinically relevant gram-positive bacteria, including methicillin-resistant *Staph. aureus*. Daptomycin is devoid of significant drug interactions, and the only notable side effect is possible muscle injury. The drug is given once daily by IV infusion, and there is no need to monitor its plasma level.

Mechanism of Action. Daptomycin has a novel mechanism of action. The drug inserts itself into the bacterial cell membrane, and thereby forms channels that permit efflux of intracellular potassium (and possibly other cytoplasmic ions). Loss of intracellular ions has two effects. First, it depolarizes the cell membrane. And second, it inhibits synthesis of DNA, RNA, and proteins, and thereby causes cell death.

Antibacterial Spectrum. Daptomycin is active only against gram-positive bacteria. The drug cannot penetrate the outer membrane of gram-negative bacteria, and hence cannot harm them. Daptomycin is rapidly bactericidal to staphylococci (including methicillin- and vancomycin-resistant *Staph. aureus* and methicillin-resistant *Staph. epidermidis*), enterococci (including vancomycin-resistant *E. faecium* and *E. faecalis*), streptococci (including penicillin-resistant *Strep. pneumoniae*), and most other aerobic and anaerobic gram-positive bacteria. As a rule, daptomycin is more rapidly bactericidal than either vancomycin, linezolid, or quinupristin/dalfopristin.

Therapeutic Use. Daptomycin has two approved indications: (1) bloodstream infection with *Staph. aureus*, and (2) complicated skin and skin structure infections caused by susceptible strains of the following gram-positive bacteria: *Staph. aureus* (including methicillin-resistant strains), *Strep. pyogenes*, *Strep. agalactiae*, *Strep. dysgalactiae* subspecies *equisimilis*, and *E. faecalis* (vancomycin-susceptible strains only). The drug is being

tested for other possible uses, including endocarditis and infections caused by vancomycin-resistant enterococci. Daptomycin should *not* be used for CAP. Why? Because clinical trials have shown that, in patients receiving daptomycin, the rate of death and serious cardiorespiratory events is higher than in patients receiving equally effective alternatives.

Resistance. Out of more than 1000 patients receiving daptomycin in clinical trials, only 2 had infections resistant to the drug. The mechanism of resistance has not been identified. There is no known mechanism by which resistance can be transferred from one bacterium to another. Also, there is no cross-resistance between daptomycin and any other class of antibiotics.

Pharmacokinetics. Daptomycin is administered by IV infusion, and a significant fraction (92%) becomes bound to plasma proteins. The drug undergoes minimal metabolism. Most of each dose is excreted unchanged in the urine. In patients with normal renal function, the half-life is 9 hours. However, in those with severe renal impairment (creatinine clearance less than 30 mL/min), and in those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), the half-life increases threefold. As a result, if the dosage is not reduced, plasma drug levels can rise dangerously high.

Adverse Effects. Daptomycin is generally well tolerated. The most common adverse effects are constipation (6.2%), nausea (5.8%), diarrhea (5.2%), injection-site reactions (5.8%), headache (5.4%), insomnia (4.5%) and rash (4.3%).

Daptomycin may pose a small risk of *myopathy* (muscle injury). In clinical trials with doses that were larger and more frequent than those used now, patients often experienced muscle pain and weakness in association with increased levels of creatine phosphokinase (CPK), a marker for muscle injury. However, with currently approved doses, elevation of CPK is rare. Nonetheless, patients should be warned about possible muscle injury, and told to report any muscle pain or weakness. In addition, CPK levels should be measured weekly. If the level rises markedly (to more than 10 times the upper limit of normal), daptomycin should be discontinued. Daptomycin should also be discontinued in patients who report muscle pain or weakness in conjunction with a more moderate rise in CPK.

Daptomycin may cause *eosinophilic pneumonia*, a rare but serious condition in which eosinophils (white blood cells) accumulate in the lungs, and thereby impair lung function. Symptoms include fever, cough, and shortness of breath. Left untreated, the condition can rapidly progress to respiratory failure and death.

Drug Interactions. Daptomycin appears devoid of significant drug interactions. It does not induce or inhibit cytochrome P450, and hence should not affect drugs that are metabolized by this enzyme system. In clinical studies, daptomycin did not affect the kinetics of warfarin, simvastatin, or aztreonam. Concurrent use of daptomycin plus tobramycin caused a moderate increase in daptomycin levels and a moderate decrease in tobramycin levels. Accordingly, caution is needed when these drugs are combined.

Like daptomycin, the HMG-CoA reductase inhibitors (eg, simvastatin [Zocor]) can cause myopathy. However, in clinical trials, no patient receiving simvastatin plus daptomycin developed signs of muscle injury. Nonetheless, given our limited experience with daptomycin, it may be prudent to suspend HMG-CoA reductase inhibitors while daptomycin is used.

Preparations, Dosage, and Administration. Daptomycin [Cubicin] is available as a powder in 500-mg single-use vials. Following reconstitution in 0.9% sodium chloride, the drug is given by a slow (30-minute) IV infusion. For patients with normal renal function, the dosage is 4 to 6 mg/kg once every 24 hours. For patients with severe renal impairment, and for those on hemodialysis or CAPD, the dosage is 4 to 6 mg/kg once every 48 to 72 hours. Daptomycin powder should be stored refrigerated at 2°C to 8°C (36°F to 46°F). After reconstitution, the solution may be stored at room temperature for 12 hours or refrigerated for 48 hours. Daptomycin is compatible with 0.9% sodium chloride solution and lactated Ringer's solution, but not with solutions that contain dextrose.

Rifampin

Rifampin [Rifadin, Rimactane] is a broad-spectrum antibacterial agent employed primarily for tuberculosis (see Chapter 90). However, the drug is also used against several nontuberculous infections. Rifampin is useful for treating *asymptomatic carriers* of *Neisseria meningitidis*, but is not given to treat active meningococcal infection. Unlabeled uses include treatment of leprosy, gram-negative bacteremia in infancy, and infections caused by *Staph. epidermidis* and *Staph. aureus* (eg, endocarditis, osteomyelitis, prostatitis). Rifampin has also been employed for prophylaxis of meningitis due to *H. influenzae*. Because resistance can develop rapidly, established bacterial infections should not be treated with rifampin alone. The basic pharmacology of rifampin and its use in tuberculosis are presented in Chapter 90.

Rifaximin

Rifaximin [Xifaxan] is an oral, nonabsorbable analog of rifampin used to kill bacteria in the gut. Like rifampin, rifaximin inhibits bacterial DNA-dependent RNA polymerase, and thereby inhibits RNA synthesis, resulting in inhibition of protein synthesis and subsequent bacterial death.

Rifaximin has two approved uses. The drug was approved initially for *traveler's diarrhea* caused by *E. coli* in patients at least 12 years old. Rifaximin is not effective against severe diarrhea associated with fever or bloody stools, and should not be used if these are present. More recently, rifaximin was approved for *prevention of hepatic encephalopathy* (brain injury) in patients with chronic liver disease. Why does liver disease cause brain injury, and how does rifaximin help? In all of us, intestinal bacteria produce ammonia, a toxic substance that is normally cleared by the liver. However, in patients with liver disease, the liver can't remove much ammonia, and hence it can accumulate to levels that can harm the brain. Rifaximin helps prevent encephalopathy by killing the intestinal bacteria that produce ammonia. Off-label uses for rifaximin include *irritable bowel syndrome* and *recurrent C. difficile infection*.

Rifaximin is administered by mouth, and very little (less than 0.4%) is absorbed. As a result, the drug achieves high concentrations in the intestinal tract, and then is excreted unchanged in the stool.

Rifaximin is well tolerated. Gastrointestinal effects—nausea, flatulence, defecation urgency—occur in some patients. Because so little drug is absorbed, systemic effects are minimal. However, studies in rats and rabbits indicate that rifaximin is teratogenic, and hence should not be used by pregnant women. There have been postmarketing reports of hypersensitivity reactions (rash, allergic dermatitis, urticaria, pruritus, angioneurotic edema), but rifaximin has not been clearly identified as the cause.

Rifaximin is available in 200- and 550-mg tablets for oral dosing, with or without food. For *traveler's diarrhea*, the dosage is 200 mg 3 times a day for 3 days. To *prevent hepatic encephalopathy*, the dosage is 550 mg 2 times a day for as long as needed.

Fidaxomicin

Fidaxomicin [Dificid], approved in 2011, is a narrow-spectrum, bactericidal, macrocyclic antibiotic indicated only for diarrhea associated with *C. difficile* infection (CDI). In one trial, fidaxomicin was compared with vancomycin, a standard treatment for CDI. The result? The cure rate with fidaxomicin was higher than with vancomycin, and the recurrence rate was lower. Like rifaximin, fidaxomicin inhibits DNA-dependent RNA polymerase, and thereby inhibits RNA synthesis, causing inhibition of protein synthesis and subsequent bacterial death. Fidaxomicin is administered by mouth, and systemic absorption is low. As a result, the drug achieves high concentrations in the intestine, where it acts to kill *C. difficile*. The most common adverse effects are nausea (11%), vomiting (7%), abdominal pain (6%), GI hemorrhage (4%), anemia (2%), and neutropenia (2%). Fidaxomicin is supplied in 200-mg tablets for dosing with or without food. The dosage for CDI is 200 mg twice daily for 10 days. A course of treatment with fidaxomicin is more expensive than with vancomycin: \$2800 vs. \$1300. *Clostridium difficile* infection and its management are discussed at length in Box 85-1, Chapter 85.

Bacitracin

Bacitracin is a polypeptide antibiotic produced by a strain of *Bacillus subtilis*. Administration is topical. Because systemic administration can cause serious toxicity, and because superior systemic agents are available, bacitracin is no longer available for systemic infections.

Mechanism of Action and Antimicrobial Spectrum. Bacitracin inhibits synthesis of the bacterial cell wall, thereby promoting cell lysis and death. The drug is active against most gram-positive bacteria, including staphylococci, streptococci, and *C. difficile*. *Neisseria* species and *H. influenzae* are also susceptible, but most other gram-negative bacteria are resistant. Acquisition of resistance by sensitive organisms is uncommon.

Therapeutic Uses. Bacitracin is used for topical treatment of bacterial infections. The drug is very active against staphylococci and group A streptococci, the pathogens that cause most acute infections of the skin. Because of this activity, bacitracin has been marketed in a variety of topical preparations for treatment of skin infections. Many of these preparations contain additional antibiotics, usually polymyxin B, neomycin, or both.

Adverse Effects. Rarely, topical bacitracin causes local hypersensitivity reactions. Parenteral (IM) administration, which is no longer done, can produce severe nephrotoxicity.

Polymyxin B

Polymyxin B is a bactericidal drug employed primarily for local effects. Because of serious systemic toxicity, parenteral administration is rare.

Antibacterial Spectrum and Mechanism of Action. Polymyxin B is bactericidal to a broad spectrum of aerobic, gram-negative bacilli. Gram-positive bacteria and most anaerobes are resistant.

Bactericidal effects result from binding of polymyxin B to the bacterial cell membrane, an action that disrupts membrane structure and thereby increases membrane permeability. The increase in permeability leads to inhibition of cellular respiration and cell death. The resistance displayed by gram-positive bacteria has been attributed to the thick gram-positive cell wall, a structure that may block access of polymyxin B to the cell membrane.

Therapeutic Uses. Polymyxin B is used primarily for topical treatment of the eyes, ears, and skin. Preparations designed for application to the skin frequently contain other antibiotics, such as bacitracin and neomycin. In addition to its topical uses, polymyxin B (together with neomycin) has been employed as a bladder irrigant to prevent infection in patients with indwelling catheters.

Parenteral use is extremely limited; polymyxin B is not a drug of choice for any systemic infection. The primary indication for parenteral polymyxin B is serious infection caused by *P. aeruginosa*. Polymyxin B may be given when preferred drugs have been ineffective or intolerable.

Adverse Effects. The major adverse effects associated with parenteral therapy are neurotoxicity and nephrotoxicity. Both occur frequently and limit systemic use of the drug. Polymyxin B is not absorbed when applied topically, and hence topical use does not cause systemic effects. Rarely, topical polymyxin B produces hypersensitivity.

KEY POINTS

- Fluoroquinolones are broad-spectrum antibiotics with a wide variety of clinical applications.
- Patients who might otherwise require hospitalization for parenteral antibacterial therapy can often be treated at home with an oral fluoroquinolone.
- Fluoroquinolones act by inhibiting bacterial DNA gyrase and topoisomerase IV.
- Because fluoroquinolones can cause tendinitis and tendon rupture, they should be discontinued at the first sign of tendon pain or inflammation. Also, the patient should not exercise until tendinitis has been ruled out.
- Fluoroquinolones pose a risk of phototoxicity. Accordingly, patients should avoid sunlight and sunlamps, and should use protective clothing and a sunscreen if they must go outdoors.
- Fluoroquinolones can exacerbate muscle weakness in patients with myasthenia gravis, and hence should not be used in patients with a history of this disorder.
- Absorption of fluoroquinolones can be reduced by cationic substances, including milk products (calcium), aluminum- and magnesium-containing antacids, iron and zinc salts, and sucralfate.
- In addition to its use against protozoa (see Chapter 99), metronidazole is used against infections caused by obligate anaerobic bacteria, including *Bacteroides fragilis* and *C. difficile*.

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Summary of Major Nursing Implications*

FLUOROQUINOLONES

Ciprofloxacin
Gemifloxacin
Levofloxacin
Moxifloxacin
Norfloxacin
Ofloxacin

Except where noted, the implications summarized below apply to all fluoroquinolones.

Preadministration Assessment

Therapeutic Goal

Treatment of fluoroquinolone-sensitive infections. (See text for indications for specific agents.)

Identifying High-Risk Patients

Fluoroquinolones are *contraindicated* in patients with a history of myasthenia gravis.

Use all fluoroquinolones with *caution* in patients with renal impairment, and in patients age 60 and older, patients taking glucocorticoids, and patients who have undergone a heart, liver, or kidney transplantation.

Use *moxifloxacin* with *great caution* in patients with hypokalemia or pre-existing QT prolongation, and in those taking prodysrhythmic drugs.

Implementation: Administration

Routes

Oral. Ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin.

Intravenous. Ciprofloxacin, levofloxacin, and moxifloxacin.

Inhalation. Ciprofloxacin only.

Administration

Oral. Advise patients to take *norfloxacin* on an empty stomach (1 hour before meals or 2 hours after) and with a full glass of water.

Inform patients taking *ciprofloxacin*, *gemifloxacin*, *levofloxacin*, *moxifloxacin*, and *ofloxacin* that dosing can be done with or without food.

Advise patients to take their fluoroquinolone no sooner than 6 hours after ingesting cationic compounds, including iron salts, zinc salts, sucralfate, calcium supplements, dairy products, and aluminum- or magnesium-containing antacids.

Instruct patients to complete the prescribed course of treatment, even though symptoms may abate before the full course is over.

Intravenous. Administer IV fluoroquinolones by slow infusion (over 60 minutes or longer).

Dosage

Dosage for all fluoroquinolones, oral or IV, should be reduced in patients with significant renal impairment.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Tendinitis and Tendon Rupture. Fluoroquinolones can cause tendinitis and tendon rupture, usually in the Achilles tendon. Use with caution in patients at elevated risk (ie, patients age 60 and older, patients taking glucocorticoids, and patients who have undergone a heart, liver, or kidney transplantation). **Inform patients about the risk of tendon damage and instruct them to report early signs of tendon injury (pain, swelling, inflammation), and to refrain from exercise until tendinitis has been ruled out.** If tendinitis is diagnosed, the fluoroquinolone should be discontinued.

Phototoxicity. Fluoroquinolones increase the risk of severe sunburn, characterized by burning, erythema, exudation, vesicles, blistering, and edema. **Advise patients to avoid sunlamps, and to use a sunscreen and protective clothing when outdoors.** Discontinue fluoroquinolones at the first sign of phototoxicity (eg, burning sensation, redness, rash).

QT Prolongation. *Moxifloxacin* can prolong the QT interval, thereby posing a risk of severe cardiac dysrhythmias. Generally avoid this drug in patients with hypokalemia or pre-existing QT prolongation, and in those taking prodysrhythmic drugs.

Myasthenia Gravis. Fluoroquinolones can exacerbate muscle weakness in patients with myasthenia gravis, and hence should not be used in patients with a history of the disorder.

Minimizing Adverse Drug and Food Interactions

Cationic Compounds. Absorption of oral fluoroquinolones can be reduced by cationic compounds, including iron salts, zinc salts, sucralfate, aluminum- or magnesium-containing antacids, calcium supplements, and calcium-containing foods (ie, milk and milk products). **Instruct patients to take these cationic compounds at least 6 hours before or 2 hours after their fluoroquinolone.**

Warfarin. *Ciprofloxacin*, *norfloxacin*, and *ofloxacin* can increase warfarin levels, thereby posing a risk of bleeding. Monitor prothrombin time and reduce warfarin dosage as indicated.

Theophylline. *Ciprofloxacin* and *ofloxacin* can increase theophylline levels, thereby posing a risk of toxicity, including seizures. Monitor theophylline levels and reduce the dosage as indicated.

*Patient education information is highlighted as blue text.

Antifungal Agents

Drugs for Systemic Mycoses

Amphotericin B, a Polyene Antibiotic

Azoles

Echinocandins

Flucytosine, a Pyrimidine Analog

Drugs for Superficial Mycoses

Overview of Drug Therapy

Azoles

Griseofulvin

Polyene Antibiotics

Allylamines

Other Drugs for Superficial Mycoses

The antifungal agents fall into two major groups: drugs for *systemic mycoses* (ie, systemic fungal infections) and drugs for *superficial mycoses*. A few drugs are used for both. Systemic infections occur much less frequently than superficial infections, but are much more dangerous. Accordingly, therapy of systemic mycoses is our main focus.

DRUGS FOR SYSTEMIC MYCOSES

Systemic mycoses can be subdivided into two categories: opportunistic infections and nonopportunistic infections. The opportunistic mycoses—*candidiasis*, *aspergillosis*, *cryptococcosis*, and *mucormycosis*—are seen primarily in debilitated or immunocompromised hosts. In contrast, nonopportu-

nistic infections can occur in any host. These latter mycoses, which are relatively uncommon, include *sporotrichosis*, *blastomycosis*, *histoplasmosis*, and *coccidioidomycosis*. Treating systemic mycoses can be difficult: These infections often resist treatment and hence may require prolonged therapy with drugs that frequently prove toxic. Drugs of choice for systemic mycoses are summarized in Table 92-1.

The systemic antifungal drugs fall into four classes: polyene antibiotics, azoles, echinocandins, and pyrimidine analogs. Class members and mechanisms of action are summarized in Table 92-2.

Amphotericin B, a Polyene Antibiotic

Amphotericin B [Abelcet, Amphotec, AmBisome, Fungi-zone*] belongs to a drug class known as *polyene antibiotics*, so named because their structures contain a series of conjugated double bonds. Nystatin, another antifungal drug, is in the same family.

Amphotericin B—an important but dangerous drug—is active against a broad spectrum of pathogenic fungi and is a drug of choice for most systemic mycoses (see Table 92-1). Unfortunately, amphotericin B is highly toxic: To varying degrees, infusion reactions and renal damage occur in all patients. Because of its potential for harm, amphotericin B should be employed only against infections that are progressive and potentially fatal.

Amphotericin B is available in four formulations: a conventional formulation (amphotericin B deoxycholate) and three lipid-based formulations. The lipid-based formulations are as effective as the conventional formulation and cause less

TABLE 92-1 ■ Drugs of Choice for Systemic Mycoses

Infection	Causative Organism	Drugs of Choice	Alternative Drugs
Aspergillosis	<i>Aspergillus</i> species	Voriconazole	Amphotericin B, itraconazole, posaconazole, caspofungin, micafungin
Blastomycosis	<i>Blastomyces dermatitidis</i>	Amphotericin B or itraconazole	No alternative recommended
Candidiasis	<i>Candida</i> species	Amphotericin B or fluconazole, either one ± flucytosine	Itraconazole, voriconazole, caspofungin
Coccidioidomycosis	<i>Coccidioides immitis</i>	Amphotericin B or fluconazole	Itraconazole, ketoconazole
Cryptococcosis	<i>Cryptococcus neoformans</i>	Amphotericin B ± flucytosine	Itraconazole
Chronic suppression		Fluconazole	Amphotericin B
Histoplasmosis	<i>Histoplasma capsulatum</i>	Amphotericin B or itraconazole	Fluconazole, ketoconazole
Chronic suppression		Itraconazole	Amphotericin B
Mucormycosis	<i>Mucor</i>	Amphotericin B	No alternative recommended
Paracoccidioidomycosis	<i>Paracoccidioides brasiliensis</i>	Amphotericin B or itraconazole	Ketoconazole
Sporotrichosis	<i>Sporothrix schenckii</i>	Amphotericin B or itraconazole	Fluconazole

TABLE 92-2 • Classes of Systemic Antifungal Drugs

Drug Class	Mechanism of Action	Class Members
Polylene Antibiotics	Bind to ergosterol and thereby disrupt the fungal cell membrane	Amphotericin B
Azoles	Inhibit synthesis of ergosterol and thereby disrupt the fungal cell membrane	Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole
Echinocandins	Inhibit synthesis of beta-1,3-D-glucan and thereby disrupt the fungal cell wall	Anidulafungin Caspofungin Micafungin
Pyrimidine Analogs	Disrupt synthesis of RNA and DNA	Flucytosine

toxicity—but are much more expensive. For treatment of systemic mycoses, all formulations are administered by IV infusion. Infusions are given daily or every other day for several months.

Mechanism of Action

Amphotericin B binds to components of the fungal cell membrane, thereby increasing permeability. The resultant leakage of intracellular cations (especially potassium) reduces viability. Depending on the concentration of amphotericin B and the susceptibility of the fungus, the drug may be fungistatic or fungicidal.

The component of the fungal membrane to which amphotericin B binds is *ergosterol*, a member of the *sterol* family of compounds. Hence, for a cell to be susceptible, its cytoplasmic membrane must contain sterols. Since bacterial membranes lack sterols, bacteria are not affected.

Much of the toxicity of amphotericin is attributable to the presence of sterols (principally cholesterol) in mammalian cell membranes. When amphotericin binds with cholesterol in mammalian membranes, the effect is similar to that seen in fungi. However, there is some degree of selectivity: Amphotericin binds more strongly to ergosterol than it does to cholesterol, and hence fungi are hurt more than we are.

Microbial Susceptibility and Resistance

Amphotericin B is active against a broad spectrum of fungi. Some protozoa (eg, *Leishmania braziliensis*) are also susceptible. As noted, bacteria are resistant.

Emergence of resistant fungi is extremely rare, and occurs only with long-term amphotericin use. In all cases of resistance, the fungal membranes had reduced amounts of ergosterol or none at all.

Therapeutic Uses

Amphotericin B is a drug of choice for most systemic mycoses (see Table 92-1). Before this drug became available, systemic fungal infections usually proved fatal. Treatment is prolonged; 6 to 8 weeks is common. In some cases, treatment may last for 3 or 4 months. In addition to its antifungal applications, amphotericin B is a drug of choice for leishmaniasis (see Chapter 99).

Pharmacokinetics

Absorption and Distribution. Amphotericin is poorly absorbed from the GI tract, and hence oral therapy cannot be used for systemic infection. Rather, amphotericin must be administered IV. When the drug leaves the vascular system, it undergoes extensive binding to sterol-containing membranes of tissues. Levels about half those in plasma are achieved in aqueous humor and in peritoneal, pleural, and joint fluids. Amphotericin B does not readily penetrate to the cerebrospinal fluid (CSF).

Metabolism and Excretion. Little is known about the elimination of amphotericin B. We do not know if the drug is metabolized or if it is ultimately removed from the body. Renal excretion of unchanged amphotericin is minimal. Accordingly, there is no need to reduce the dosage in patients with pre-existing renal impairment. Complete elimination of amphotericin takes a long time; the drug has been detected in tissues more than a year after cessation of treatment.

Adverse Effects

Amphotericin can cause a variety of serious adverse effects. Patients should be under close supervision, preferably in a hospital.

Infusion Reactions. Intravenous amphotericin frequently produces fever, chills, rigors, nausea, and headache. These reactions are caused by release of proinflammatory cytokines (tumor necrosis factor, interleukin-1, interleukin-6) from monocytes and macrophages. Symptoms begin 1 to 3 hours after starting the infusion and persist about an hour. Mild reactions can be reduced by pretreatment with diphenhydramine plus acetaminophen. Aspirin can also help, but it may increase kidney damage (see below). Intravenous meperidine or dantrolene can be given if rigors occur. If other measures fail, hydrocortisone (a glucocorticoid) can be used to decrease fever and chills. However, since glucocorticoids can reduce the patient's ability to fight infection, routine use of hydrocortisone should be avoided. Infusion reactions are less intense with lipid-based amphotericin formulations than with the conventional formulation.

Amphotericin infusion produces a high incidence of phlebitis. This can be minimized by changing peripheral venous sites often, administering amphotericin through a large central vein, and pretreatment with heparin.

Nephrotoxicity. Amphotericin is toxic to cells of the kidney. Renal impairment occurs in practically all patients. The extent of kidney damage is related to the total dose administered over the full course of treatment. In most cases, renal function normalizes after amphotericin use stops. However, if the total dose exceeds 4 gm, residual impairment is likely. Kidney damage can be minimized by infusing 1 L of saline on the days amphotericin is given. Other nephrotoxic drugs (eg, aminoglycosides, cyclosporine, nonsteroidal anti-inflammatory drugs [NSAIDs]) should be avoided. To evaluate renal injury, tests of kidney function should be performed every 3 to 4 days, and intake and output should be monitored. If plasma creatinine content rises above 3.5 mg/dL, amphotericin dosage should be reduced. As noted, the degree of renal damage is less with lipid-based amphotericin than with the conventional formulation.

Hypokalemia. Damage to the kidneys often causes hypokalemia. Potassium supplements may be needed to correct the problem. Potassium levels and serum creatinine should be monitored often.

Hematologic Effects. Amphotericin can cause bone marrow suppression, resulting in normocytic, normochromic anemia. Hematocrit determinations should be conducted to monitor red blood cell status.

Effects Associated with Intrathecal Injection. Intrathecal administration may cause nausea, vomiting, headache, and pain in the back, legs, and abdomen. Rare reactions include visual disturbances, impairment of hearing, and paresthesias (tingling, numbness, or pain in the hands and feet).

Other Adverse Effects. Infusion of amphotericin may be associated with delirium, hypotension, hypertension, wheezing, and hypoxia. Rarely, amphotericin causes rash, convulsions, anaphylaxis, dysrhythmias, acute liver failure, and nephrogenic diabetes insipidus.

Drug Interactions

Nephrotoxic Drugs. Use of amphotericin with other nephrotoxic drugs (eg, aminoglycosides, cyclosporine, NSAIDs) increases the risk of kidney damage. Accordingly, these combinations should be avoided if possible.

Flucytosine. Amphotericin potentiates the antifungal actions of flucytosine, apparently by enhancing flucytosine entry into fungi. Thanks to this interaction, combining flucytosine with low-dose amphotericin can produce antifungal effects equivalent to those of high-dose amphotericin alone. By allowing a reduction in amphotericin dosage, the combination can reduce the risk of amphotericin-induced toxicity.

Preparations, Dosage, and Administration

Preparations. Amphotericin B is available in a conventional formulation—*amphotericin B deoxycholate* (generic only)—and three lipid-based formulations: *liposomal amphotericin B* [AmBisome], *amphotericin B cholesteryl sulfate complex* [Amphotec], and *amphotericin B lipid complex* [Abelcet]. The lipid-based formulations cause less nephrotoxicity and fewer infusion reactions than the conventional formulation. However, these formulations are considerably more expensive.

Routes. For treatment of systemic mycoses, amphotericin B is almost always administered IV. Infusions should be performed slowly (over 2 to 4 hours) to minimize phlebitis and cardiovascular reactions. Alternate-day dosing can reduce adverse effects. For most patients, several months of therapy are required. Because amphotericin B does not readily enter the CSF, intrathecal injection is used for fungal meningitis.

Intravenous Dosage and Administration. Fungal Infections. Dosage is individualized and based on disease severity and the patient's ability to tolerate treatment. Optimal dosage has not been established. A small test dose (1 mg) is often infused to assess patient reaction. After this, therapy is initiated with a dosage of 0.25 mg/kg/day. Maintenance dosages range from 1.5 to 6 mg/kg/day, depending on the severity of the infection and the form of amphotericin used. Dosage should be reduced in patients with renal impairment. The infusion solution should be checked periodically for a precipitate and, if one is seen, the infusion should be stopped immediately. Because the treatment period is prolonged, the administration site should be rotated—so as to reduce the risk of phlebitis and help ensure continued availability of a suitable vein.

Leishmaniasis. Leishmaniasis can be treated with *amphotericin B deoxycholate* or *liposomal amphotericin B* [AmBisome]. For conventional amphotericin B deoxycholate, the dosage is 0.5 to 1 mg/kg daily every other day for up to 8 weeks. For AmBisome, the traditional dosage is 3 mg/kg on days 1, 2, 3, 4, 5, 14, and 21. However, a single infusion of 10 mg/kg may be just as effective.

Azoles

Like amphotericin B, the azoles are broad-spectrum antifungal drugs. As a result, azoles represent an alternative to amphotericin B for most systemic fungal infections (see Table 92-1). In contrast to amphotericin, which is highly toxic and must be given IV, the azoles have lower toxicity and can be given by mouth. However, azoles do have one disadvantage: they inhibit hepatic cytochrome P450 drug-metabolizing enzymes, and can thereby increase the levels of many other

drugs. Of the 14 azoles in current use, only 5—itraconazole, ketoconazole, fluconazole, voriconazole, and posaconazole—are indicated for systemic mycoses. Azoles used for superficial mycoses are discussed separately below.

Itraconazole

Itraconazole [Sporanox] is an alternative to amphotericin B for several systemic mycoses (see Table 92-1), and will serve as our prototype for the azole family. The drug is safer than amphotericin B and has the added advantage of oral dosing. Principal adverse effects are cardiosuppression and liver injury. Like other azoles, itraconazole can inhibit drug-metabolizing enzymes, and can thereby raise levels of other drugs.

Mechanism of Action. Itraconazole inhibits the synthesis of *ergosterol*, an essential component of the fungal cytoplasmic membrane. The result is increased membrane permeability and leakage of cellular components. Accumulation of ergosterol precursors may also contribute to antifungal actions. Itraconazole suppresses ergosterol synthesis by inhibiting fungal cytochrome P450-dependent enzymes.

Therapeutic Use. Itraconazole is active against a broad spectrum of fungal pathogens. At this time, it is a drug of choice for *blastomycosis*, *histoplasmosis*, *paracoccidioidomycosis*, and *sporotrichosis*, and an alternative to amphotericin B for *aspergillosis*, *candidiasis*, and *coccidioidomycosis*. Itraconazole may also be used for superficial mycoses.

Pharmacokinetics. Itraconazole is administered PO (in capsules or suspension). Food increases absorption of itraconazole capsules, but decreases absorption of itraconazole oral suspension. Interestingly, administration with a cola beverage enhances absorption. Once absorbed, the drug is widely distributed to lipophilic tissues. Concentrations in aqueous fluids (eg, saliva, CSF) are negligible. The drug undergoes extensive hepatic metabolism. About 40% of each dose is excreted in the urine as inactive metabolites.

Adverse Effects. Itraconazole is well tolerated in usual doses. Gastrointestinal reactions (nausea, vomiting, diarrhea) are most common, occurring in about 10% of patients. Other common reactions include rash (8.6%), headache (3.8%), abdominal pain (3.3%), and edema (3.5%). In addition to these relatively benign effects, itraconazole may cause two potentially serious effects: cardiac suppression and liver injury.

Cardiac Suppression. Itraconazole has negative inotropic actions that can cause a transient decrease in ventricular ejection fraction. Cardiac function returns to normal by 12 hours after dosing. Because of its negative inotropic actions, itraconazole should not be used for *superficial* fungal infections (dermatomycoses, onychomycosis) in patients with heart failure, a history of heart failure, or other indications of ventricular dysfunction. The drug may still be used to treat *serious* fungal infections in patients with heart failure, but only with careful monitoring, and only if the benefits clearly outweigh the risks. If signs and symptoms of heart failure worsen, itraconazole should be stopped.

Liver Injury. Itraconazole has been associated with rare cases of liver failure, some of which were fatal. Although a causal link has not been established, caution is nonetheless advised. Patients should be informed about signs of liver impairment (persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain, jaundice, dark urine, pale stools) and, if they appear, should seek medical attention immediately.

Drug Interactions. Inhibition of Hepatic Drug-Metabolizing Enzymes. Itraconazole inhibits CYP3A4 (the 3A4 isozyme of cytochrome P450) and can thereby in-

TABLE 92-3 ■ Some Drugs Whose Levels Can Be Increased by Azole Antifungal Drugs

Target Drug	Class	Consequence of Excessive Level
Pimozide [Orap]	Antipsychotic	Fatal dysrhythmias
Dofetilide [Tikosyn]	Antidysrhythmic	Fatal dysrhythmias
Quinidine	Antidysrhythmic	Fatal dysrhythmias
Cisapride [Propulsid]*	Prokinetic agent	Bleeding
Warfarin [Coumadin]	Anticoagulant	Hypoglycemia
Sulfonylureas	Oral hypoglycemic	Central nervous system toxicity
Phenytoin [Dilantin]	Antiseizure drug	Increased nephrotoxicity
Cyclosporine [Sandimmune]	Immunosuppressant	Increased nephrotoxicity
Tacrolimus [Prograf]	Immunosuppressant	Rhabdomyolysis
Lovastatin [Mevacor]	Antihyperlipidemic	Rhabdomyolysis
Simvastatin [Zocor]	Antihyperlipidemic	Coronary vasospasm
Eletriptan [Relpax]	Antimigraine	Fatal respiratory depression
Fentanyl [Duragesic, others]	Opioid analgesic	Cardiosuppression
Calcium channel blockers	Antihypertensive, antianginal	

*In 2000, cisapride was voluntarily withdrawn from the U.S. market and is now available only through an investigational limited-access program.

crease levels of many other drugs (Table 92-3). The most important are cisapride, pimozide, dofetilide, and quinidine. Why? Because, when present at high levels, these drugs can cause potentially fatal ventricular dysrhythmias. Accordingly, concurrent use with itraconazole is contraindicated. Other drugs of concern include cyclosporine, digoxin, warfarin, and sulfonylurea-type oral hypoglycemics. In patients taking cyclosporine or digoxin, levels of these drugs should be monitored; in patients taking warfarin, prothrombin time should be monitored; and in patients taking sulfonylureas, levels of blood glucose should be monitored.

Drugs That Raise Gastric pH. Drugs that decrease gastric acidity—antacids, histamine₂ (H₂) antagonists, and proton pump inhibitors—can greatly reduce absorption of oral itraconazole. Accordingly, these agents should be administered at least 1 hour before itraconazole or 2 hours after. (Since proton pump inhibitors have a prolonged duration of action, patients using these drugs may have insufficient stomach acid for itraconazole absorption, regardless of when the proton pump inhibitor is given.)

Preparations, Dosage, and Administration. Itraconazole [Sporanox] is available in suspension (10 mg/mL) and capsules (100 mg) for oral use. The capsules should be taken with food and/or a cola beverage to increase absorption. The recommended dosage is 200 mg once a day. If needed, the dosage may be increased to 200 mg twice a day.

Fluconazole

Actions and Uses. Fluconazole [Diflucan], a member of the azole family, is an important antifungal drug. It has the same mechanism as itraconazole: inhibition of cytochrome P450-dependent synthesis of ergosterol, with resultant damage to the cytoplasmic membrane and accumulation of ergosterol precursors. The drug is primarily fungistatic. Fluconazole is used for blastomycosis; histoplasmosis; meningitis caused by *Cryptococcus neoformans* and *Coccidioides immitis*; and vaginal, oropharyngeal, esophageal, and disseminated *Candida* infections. In addition, fluconazole is used investigationally for leishmaniasis (see Chapter 99).

Pharmacokinetics. Fluconazole is well absorbed (90%) following oral dosing, and undergoes wide distribution to tissues and body fluids, including the CSF. Most of each dose is eliminated unchanged in the urine. Fluconazole has a half-life of 30 hours, making once-a-day dosing sufficient.

Adverse Effects. Fluconazole is generally well tolerated. The most common reactions are nausea (3.7%), headache (1.9%), rash (1.8%), vomiting (1.7%), abdominal pain (1.7%), and diarrhea (1.5%). Rarely, treatment has been associated with hepatic necrosis, Stevens-Johnson syndrome, and anaphylaxis.

Use in Pregnancy. When taken in high doses (400 to 800 mg/day) throughout all or most of the first trimester, fluconazole can cause serious birth defects, including cleft palate, femoral bowing, congenital heart disease, and facial abnormalities. By contrast, treatment of vaginal candidiasis with a single low dose (150 mg) appears to be safe. High-dose therapy is now classified in Food and Drug Administration (FDA) Pregnancy Risk Category D, whereas low-dose therapy remains in Category C.

Drug Interactions. Like other azole antifungal drugs, fluconazole can inhibit CYP3A4, and can thereby increase levels of other drugs, including warfarin, phenytoin, cyclosporine, zidovudine, rifabutin, and sulfonylurea oral hypoglycemics.

Preparations, Dosage, and Administration. Fluconazole [Diflucan] is available in solution (2 mg/mL) for IV infusion, and in tablets (50, 100, 150, and 200 mg) and suspension (10 and 40 mg/mL) for oral use. Because oral absorption is rapid and nearly complete, oral and IV dosages are the same. For treatment of *oropharyngeal* and *esophageal candidiasis*, the usual dosage is 200 mg on the first day, followed by 100 mg once daily thereafter. For treatment of *systemic candidiasis* and *cryptococcal meningitis*, the usual dosage is 400 mg on the first day, followed by 200 mg once daily thereafter. Duration of treatment ranges from 3 weeks to more than 3 months, depending on the infection.

Voriconazole

Actions and Uses. Voriconazole [Vfend], a member of the azole family, is an important drug for treating life-threatening fungal infections. Like other azoles, voriconazole inhibits cytochrome P450-dependent enzymes, and thereby suppresses synthesis of ergosterol, a critical component of the fungal cytoplasmic membrane. As a result, voriconazole is active against a broad spectrum of fungal pathogens, including *Aspergillus* species, *Candida* species, *Scedosporium* species, *Fusarium* species, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Cryptococcus neoformans*. At this time, voriconazole has four approved indications: (1) candidemia, (2) invasive aspergillosis, (3) esophageal candidiasis, and (4) serious infections caused by *Scedosporium apiospermum* or *Fusarium* species in patients unresponsive to or intolerant of other drugs.

According to guidelines from the Infectious Disease Society of America, voriconazole has replaced amphotericin B as the drug of choice for invasive aspergillosis. Voriconazole is just as effective as amphotericin B and poses a much lower risk of kidney damage. However, voriconazole does have its own set of adverse effects, including hepatotoxicity, visual disturbances,

hypersensitivity reactions, hallucinations, and fetal injury. In addition, like other azoles, voriconazole can interact with many drugs.

Pharmacokinetics. Voriconazole may be administered IV or PO. With oral dosing, bioavailability is high (96%), but can be reduced by food. Plasma levels peak 2 hours after ingestion. The drug's half-life is dose dependent, and can range from 6 hours up to 24 hours. Voriconazole undergoes extensive metabolism by hepatic cytochrome P450 enzymes.

Adverse Effects. The most common adverse effects are visual disturbances, fever, rash, nausea, vomiting, diarrhea, headache, sepsis, peripheral edema, abdominal pain, and respiratory disorders. During clinical trials, the effects that most often led to discontinuing treatment were liver damage, visual disturbances, and rash.

Hepatotoxicity. Voriconazole can cause hepatitis, cholestasis, and fulminant hepatic failure. Fortunately, these events are both uncommon and generally reversible. To monitor for injury, liver function tests should be obtained before treatment and periodically thereafter.

Visual Disturbances. Reversible, dose-related visual disturbances develop in 30% of patients. Symptoms include reduced visual acuity, increased brightness, altered color perception, and photophobia. As a rule, these begin within 30 minutes of dosing and then greatly diminish over the next 30 minutes. Owing to the risk of visual impairment, patients should be warned against driving, especially at night.

Hypersensitivity Reactions. Voriconazole may cause dermatologic reactions, ranging from rash to life-threatening Stevens-Johnson syndrome. During infusion, anaphylactoid reactions have occurred, manifesting with tachycardia, chest tightness, dyspnea, faintness, flushing, fever, and sweating. If these symptoms develop, the infusion should stop.

Teratogenicity. Voriconazole is teratogenic in rats and can cause fetal harm in humans. The drug is classified in FDA Pregnancy Risk Category D, and hence should not be used during pregnancy unless the potential benefits are deemed to outweigh the risk to the fetus. Women taking the drug should use effective contraception.

Drug Interactions. Voriconazole can interact with many other drugs. Several mechanisms are involved. Voriconazole is both a substrate for and inhibitor of hepatic cytochrome P450 enzymes. As a result, drugs that inhibit P450 can raise voriconazole levels, and drugs that induce P450 can lower voriconazole levels. On the other hand, because voriconazole itself can inhibit P450, voriconazole can raise levels of other drugs. Therefore

- To ensure that voriconazole levels are adequate, voriconazole should not be combined with powerful P450 inducers, including rifampin, rifabutin, carbamazepine, and phenobarbital.
- To avoid excessive voriconazole levels, voriconazole should not be combined with powerful P450 inhibitors.
- To avoid toxicity from accumulation of other drugs, voriconazole should not be combined with some agents that are P450 substrates, including cisapride, pimozide, and sirolimus.

Preparations, Dosage, and Administration. Voriconazole [Vfend] is available in 200-mg, single-use vials for IV infusion, and in two oral formulations: tablets (50 and 200 mg) and a powder for oral suspension (40 mg/mL after reconstitution). Treatment is initiated with IV voriconazole and later can be switched to oral voriconazole as appropriate.

Intravenous therapy consists of two loading doses (6 mg/kg each given 12 hours apart) followed by maintenance doses of 4 mg/kg every 12 hours. All IV doses should be infused slowly, over 1 to 2 hours (maximum rate 3 mg/kg/hr). If the response is inadequate, maintenance doses can be increased by 50%. Patients with *mild to moderate* hepatic cirrhosis should receive the standard two loading doses, but maintenance doses should be halved. (There are no data on dosing in patients with *severe* cirrhosis.) Patients with significant renal impairment (creatinine clearance less than 50 mL/min), should use oral voriconazole, not IV voriconazole. Why? Because, in the absence of adequate kidney function, the solubilizing agent (not voriconazole itself) in the IV formulation can accumulate to dangerous levels.

After receiving IV loading doses, patients who can tolerate oral therapy may be switched to voriconazole tablets. The usual dosage is 200 mg every 12 hours for patients over 40 kg and 100 mg every 12 hours for patients under 40 kg. If the response is inadequate, doses can be increased by 50%. Oral dosing should be done 1 hour before meals or 1 hour after.

Ketoconazole

Actions and Antifungal Spectrum. Ketoconazole belongs to the azole family of antifungal agents. Benefits derive from inhibiting synthesis of ergosterol, an essential component of the fungal cytoplasmic membrane. Ketoconazole is active against most fungi that cause systemic mycoses, as well as fungi that cause superficial infections (dermatophytes and *Candida* species).

Therapeutic Use. Ketoconazole is an alternative to amphotericin B for systemic mycoses. The drug is much less toxic than amphotericin and only somewhat less effective. Specific indications are listed in Table 92-1. Responses to ketoconazole are slow. Accordingly, the drug is less useful for severe, acute infections than for long-term suppression of chronic infections. Ketoconazole is also a valuable drug for superficial mycoses.

Pharmacokinetics. Absorption. Ketoconazole is a weak base and hence requires an acidic environment for dissolution and absorption. Oral ketoconazole is well absorbed from the GI tract, provided that gastric acid levels are normal. In patients with achlorhydria (absence of gastric acid), absorption is low. Drugs that reduce gastric acidity (eg, antacids, H₂ blocking agents, proton pump inhibitors) decrease absorption.

Distribution. Most ketoconazole in the blood is bound to plasma proteins. The drug crosses the blood-brain barrier poorly, and concentrations in the CSF remain low. In contrast, high levels of ketoconazole are achieved in the skin, making oral ketoconazole useful against superficial mycoses.

Elimination. Ketoconazole is eliminated by hepatic metabolism. Its half-life is approximately 3 hours. In patients with liver impairment, the half-life can be substantially prolonged. Because elimination is hepatic, renal impairment does not influence the intensity or duration of effects. Hence, no dosage adjustment is needed in patients with kidney disease.

Adverse Effects. Ketoconazole is generally well tolerated. The most common adverse reactions—nausea and vomiting—can be reduced by giving the drug with food. The most serious effects involve the liver.

Hepatotoxicity. Effects of ketoconazole on the liver are rare but potentially severe. Fatal hepatic necrosis has occurred. Liver function should be evaluated at baseline and at least monthly thereafter. Ketoconazole should be discontinued at the first sign of liver injury. The drug should be employed with caution in patients with a history of hepatic disease. Patients should be advised to notify the prescriber if they experience symptoms suggesting liver injury (eg, unusual fatigue, anorexia, nausea, vomiting, jaundice, dark urine, pale stools).

Effects on Sex Hormones. Just as ketoconazole inhibits steroid synthesis in fungi, the drug can inhibit steroid synthesis in humans. In males, inhibition of testosterone synthesis has caused gynecomastia, decreased libido, and reduced potency; reversible sterility has occurred with high doses. In females, reduction of estradiol synthesis has caused menstrual irregularities.

Other Adverse Effects. Ketoconazole can produce a variety of relatively mild adverse effects, including rash, itching, dizziness, fever, chills, constipation, diarrhea, photophobia, and headache. Rarely, ketoconazole has caused anaphylaxis, severe epigastric pain, and altered adrenal function.

Drug Interactions. Drugs that decrease gastric acidity—antacids, H₂ antagonists, proton pump inhibitors—can greatly reduce ketoconazole absorption. Accordingly, these agents should be administered no sooner than 2 hours after ingestion of ketoconazole.

Like other azoles, ketoconazole inhibits CYP3A4, and can thereby increase levels of other drugs.

Rifampin reduces plasma levels of ketoconazole, apparently by enhancing hepatic metabolism. If these drugs are used concurrently, ketoconazole dosage should be increased—and even then it may be impossible to achieve therapeutic levels.

Preparations, Dosage, and Administration. Ketoconazole is supplied in 200-mg oral tablets. The recommended adult dosage is 200 mg once a day. To treat severe infection, daily doses of 400 to 800 mg may be required. The dosage for children over 2 years old is 3.3 to 6.6 mg/kg/day in a single dose. Duration of treatment is 6 months or longer. Since an acidic environment is needed for ketoconazole absorption, patients with achlorhydria should dissolve the tablets in 4 mL of 0.2 N hydrochloric acid, and then sip the solution through a plastic or glass straw to avoid damaging the teeth.

Posaconazole

Actions and Uses. Posaconazole [Noxafil, Posanol[®]], approved in 2006, is the newest member of the azole family. Like other azoles, the drug binds with ergosterol in the fungal cell membrane, and thereby compromises membrane integrity. *In vitro*, posaconazole has strong activity against *Aspergillus* and *Candida*, and good activity against several other fungi. Currently, the drug has only two indications: (1) *treatment* of oropharyngeal candidiasis, including infections resistant to itraconazole and/or fluconazole; and (2) *prophylaxis* of invasive *Aspergillus* and *Candida* infection in immunocompromised patients.

Pharmacokinetics. Posaconazole is administered by mouth, and food greatly enhances absorption. For example, when dosing is done with a low-fat meal or liquid nutritional supplement, peak plasma levels are 3 times higher than when dosing is done on an empty stomach. In the blood, posaconazole is highly (over 98%) protein bound. In the liver, posaconazole undergoes a

process known as UDP glucuronidation, rather than metabolism by cytochrome P450 enzymes (although it can inhibit CYP3A4). Elimination is mainly fecal (71%) and partly urinary (13%). The mean elimination half-life is 35 hours.

Adverse Effects. Posaconazole can cause a variety of adverse effects, which are usually mild. In clinical trials, adverse effects were similar to those seen with itraconazole and fluconazole. The most common reactions were nausea (38%), vomiting (29%), and headache (28%). Like other azoles, posaconazole can cause liver injury. In addition, there have been reports of QT prolongation and dysrhythmias.

Drug Interactions. Like other azoles, posaconazole inhibits CYP3A4, and can thereby increase levels of many other drugs. Two immunosuppressants—cyclosporine and tacrolimus—are of particular concern. If posaconazole is combined with cyclosporine or tacrolimus, their dosages should be reduced by 25% and 66%, respectively. Combined use of posaconazole with pimozide, halofantrine, or quinidine is *contraindicated* (because raising levels of these drugs can lead to QT prolongation and dysrhythmias), as is combined use with ergot alkaloids (because raising their levels can lead to ergotism).

Two drugs—rifabutin and phenytoin—can induce UDP glucuronidase (the hepatic enzyme that metabolizes posaconazole) and can thereby reduce posaconazole levels by nearly 50%. Accordingly, an increase in posaconazole dosage may be needed.

Esomeprazole, a proton pump inhibitor (PPI) given to lower gastric acidity, can reduce levels of posaconazole by nearly 50%. Therapeutic failure could result. Whether other PPIs also reduce posaconazole levels has not been determined.

Preparations, Dosage, and Administration. Posaconazole [Noxafil, Posanol[®]] is supplied as a 40-mg/mL oral suspension. To promote absorption, each dose should be taken with a full meal or a liquid nutritional supplement. Dosages are as follows:

- *Prophylaxis of invasive fungal infections*—200 mg 3 times a day for as long as neutropenia or immunosuppression persists
- *Oropharyngeal candidiasis*—200 mg twice daily on day 1, followed by 100 mg once daily for 13 days
- *Oropharyngeal candidiasis refractory to itraconazole and/or fluconazole*—400 mg twice daily for as long as indicated

Echinocandins

The echinocandins are the newest class of antifungal drugs. In contrast to amphotericin B and the azoles, which disrupt the fungal *cell membrane*, the echinocandins disrupt the fungal *cell wall*. Echinocandins cannot be dosed orally, and their antifungal spectrum is narrow, being limited mainly to *Aspergillus* and *Candida* species. Three echinocandins are available: caspofungin, micafungin, and anidulafungin. When dosage is appropriate, all three appear therapeutically equivalent.

Caspofungin

Actions and Uses. Caspofungin [Cancidas], introduced in 2001, was the first echinocandin available. Antifungal effects result from inhibiting the biosynthesis of beta-1,3-D-glucan, an essential component of the cell wall of some fungi, including *Candida* and *Aspergillus*. Caspofungin is approved for IV therapy of (1) invasive aspergillosis in patients unresponsive to or intolerant of traditional agents (eg, amphotericin B, itraconazole), and (2) systemic *Candida* infections, including candidemia and *Candida*-related peritonitis, pleural space infections, and intra-abdominal abscesses. The drug is better tolerated than amphotericin B, and appears just as effective.

Pharmacokinetics. Caspofungin is not absorbed from the GI tract, and hence must be given parenterally (by IV infusion). In the blood, 97% of the drug is protein bound. Caspofungin is cleared from the blood with a half-life of 9 to 11 hours. The principal mechanism of plasma clearance is redistribution to tissues, not metabolism or excretion. Over time, the drug undergoes gradual metabolism followed by excretion in the urine and feces.

Adverse Effects. Caspofungin is generally well tolerated. The most common adverse effects are fever (3.6% to 26%) and phlebitis at the injection site (11.3% to 15.7%). Less common reactions include headache (6% to 11.3%), rash (4.6%), nausea (2.5% to 6%), and vomiting (1.2% to 3.1%). In addition, caspofungin can cause effects that appear to be mediated by histamine release. Among these are rash, facial flushing, pruritus, and a sense of warmth. One case of anaphylaxis has been reported.

Use in Pregnancy. Caspofungin is embryotoxic in rats and rabbits. To date, there are no adequate data on effects in pregnant women. Currently, the drug is classified in FDA Pregnancy Risk Category C, and hence should be avoided during pregnancy unless the potential benefits outweigh the potential risks to the fetus.

Drug Interactions. Drugs that induce cytochrome P450 may decrease levels of caspofungin. Powerful inducers include efavirenz [Sustiva], nelfinavir [Viracept], rifampin [Rifadin], carbamazepine [Tegretol], and phenytoin [Dilantin]. Patients taking these drugs may need to increase caspofungin dosage.

Caspofungin can decrease levels of tacrolimus [Prograf], an immunosuppressant. If these drugs are taken concurrently, levels of tacrolimus should be monitored and dosage increased as needed.

Combining caspofungin with cyclosporine [Sandimmune, others] increases the risk of liver injury, as evidenced by a transient elevation in plasma levels of liver enzyme. Accordingly, the combination should generally be avoided.

Preparations, Dosage, and Administration. Caspofungin [Cancidas] is supplied as a powder (50 and 70 mg) to be reconstituted in sterile saline for IV infusion. Treatment for adults consists of a 70-mg loading dose followed by daily maintenance doses of 50 mg each. All doses should be infused slowly (over 1 hour). Treatment duration depends on infection severity and the clinical response. For patients with *moderate* liver impairment, maintenance doses should be reduced to 35 mg. There are no data on dosage for patients with *severe* liver impairment.

Micafungin

Actions and Uses. Micafungin [Mycamine], approved in 2005, was the second echinocandin antifungal agent available for general use. Like caspofungin, micafungin inhibits synthesis of beta-1,3-D-glucan, an essential component of the cell wall of *Candida*. Micafungin, administered IV, is indicated for (1) *prevention of Candida* infection in patients undergoing a bone marrow transplantation; (2) *treatment of esophageal candidiasis*; (3) *treatment of candidemia*, the fourth most common bloodstream infection among hospitalized patients in the United States; and (4) *treatment of disseminated infection, peritonitis, or abscesses caused by Candida*. For all four indications, fluconazole and itraconazole are preferred.

Pharmacokinetics. Like caspofungin, micafungin is not absorbed from the GI tract, and hence is given IV. Protein binding in blood exceeds 99%. Micafungin undergoes hepatic metabolism—mainly by pathways that do not involve cytochrome P450—followed by excretion in the feces. The elimination half-life is 11 to 17 hours.

Adverse Effects. Micafungin is generally well tolerated. The most common side effects are headache, nausea, vomiting, diarrhea, fever, and phlebitis at the infusion site. Elevation of liver enzymes has occurred, suggesting injury to the liver. Patients may also experience histamine-mediated reactions, including rash, itching, facial swelling, and vasodilation. There have been isolated reports of severe allergic reactions, including life-threatening anaphylaxis.

Drug Interactions. Micafungin appears largely devoid of significant drug interactions. Of note, micafungin does not alter the kinetics of the following immunosuppressants: mycophenolate [CellCept], cyclosporine [Sandimmune, others], tacrolimus [Prograf], and prednisolone—nor do these drugs alter the kinetics of micafungin. Micafungin can intensify the effects of sirolimus [Rapamune] (an immunosuppressant) and nifedipine [Procardia, others] (a calcium channel blocker). Accordingly, patients treated with sirolimus or nifedipine should be monitored closely for signs of toxicity. Because micafungin does not interact very much with the cytochrome P450 system, it is unlikely to alter the effects of drugs that do.

Preparations, Dosage, and Administration. Micafungin [Mycamine] is supplied as a lyophilized powder (50 and 100 mg) in single-use, light-protected vials, and must be reconstituted prior to infusion. The recommended dosage is 50 mg once a day to prevent *Candida* infection, 100 mg once a day to treat candidemia, and 150 mg once a day to treat esophageal candidiasis. All doses are given by a 1-hour IV infusion. Faster infusion rates increase the risk of a histamine reaction.

Anidulafungin

Actions and Uses. Anidulafungin [Eraxis], approved in 2006, has good activity against *Candida* species, and poor activity against most other fungi. Indications are limited to IV therapy of esophageal candidiasis, candidemia, and other serious *Candida* infections. Like caspofungin and micafungin, anidulafungin inhibits synthesis of beta-1,3-D-glucan, and thereby disrupts the *Candida* cell wall.

Pharmacokinetics. Like other echinocandins, anidulafungin is not absorbed from the GI tract, and hence must be given IV. In the blood, 84% of the drug is protein bound. Clearance is the result of slow, spontaneous chemical degradation, followed by excretion in the feces. The plasma half-life is 40 to 50 hours.

Adverse Effects. Anidulafungin is generally well tolerated. The most common side effects are diarrhea (3.1%), hypokalemia (3.1%), and headache

(1.3%). Possible histamine-mediated reactions (rash, urticaria, pruritus, flushing, dyspnea, hypotension) have been reported, especially at higher infusion rates. Accordingly, the infusion rate should not exceed 1.1 mg/min. A few patients have developed signs of liver damage (hepatitis, elevation of circulating liver enzymes, worsening of hepatic failure).

Drug Interactions. No clinically relevant drug interactions have been reported. Anidulafungin is neither a substrate for, inducer of, nor inhibitor of hepatic cytochrome P450 drug-metabolizing enzymes, and hence will not interact with other drugs affected by this system.

Preparations, Dosage, and Administration. Anidulafungin [Eraxis] is available as a powder (50 and 100 mg) to be reconstituted in the supplied diluent, and then further diluted prior to IV infusion. To minimize histamine-related reactions, the infusion rate should not exceed 1.1 mg/min. Dosages are as follows:

- **Esophageal candidiasis**—Infuse a single 100-mg loading dose on day 1, followed by 50 mg once a day thereafter, continuing for at least 14 days and at least 7 days after the last positive culture.
- **Candidemia and other serious *Candida* infections**—Infuse a single 200-mg loading dose on day 1, followed by 100 mg once a day thereafter, continuing for at least 14 days after the last positive culture.

Flucytosine, a Pyrimidine Analog

Flucytosine [Ancobon], a pyrimidine analog, is employed for serious infections caused by susceptible strains of *Candida* and *Cryptococcus neoformans*. Because development of resistance is common, flucytosine is almost always used in combination with amphotericin B. Extreme caution is needed in patients with renal impairment and hematologic disorders.

Mechanism of Action. Flucytosine is taken up by fungal cells, which then convert it to 5-fluorouracil (5-FU), a powerful antimetabolite. The ultimate effect is disruption of fungal DNA and RNA synthesis. Flucytosine is relatively harmless to us because mammalian cells lack cytosine deaminase, the enzyme that converts flucytosine to 5-FU.

Fungal Resistance. Development of resistance during therapy is common and constitutes a serious clinical problem. Several mechanisms have been described, including (1) a reduction in cytosine permease (needed for fungal uptake of flucytosine) and (2) loss of cytosine deaminase (needed to convert flucytosine to its active form).

Antifungal Spectrum and Therapeutic Uses. Flucytosine has a narrow antifungal spectrum. Fungicidal activity is highest against *Candida* species and *Cryptococcus neoformans*. Most other fungi are resistant. Because of this narrow spectrum, flucytosine is indicated only for candidiasis and cryptococcosis. For treatment of serious infections (eg, cryptococcal meningitis, systemic candidiasis), flucytosine should be combined with amphotericin B. This combination offers two advantages over flucytosine alone: (1) antifungal activity is enhanced and (2) emergence of resistant fungi is reduced.

Pharmacokinetics. Flucytosine is readily absorbed from the GI tract and is well distributed throughout the body. The drug has good access to the central nervous system; levels in the CSF are about 80% of those in plasma. Flucytosine is eliminated by the kidneys, principally as unchanged drug. The half-life is about 4 hours in patients with normal renal function. However, in patients with renal insufficiency, the half-life is greatly prolonged, and hence dosage must be reduced.

Adverse Effects. Hematologic Effects. Bone marrow suppression is the most serious complication of treatment. Marrow suppression usually manifests as reversible neutropenia or thrombocytopenia. Rarely, fatal agranulocytosis develops. Platelet and leukocyte counts should be determined weekly. Adverse hematologic effects are most likely when plasma levels of flucytosine exceed 100 mcg/mL. Accordingly, the dosage should be adjusted to keep drug levels below

this value. Flucytosine should be used with caution in patients with pre-existing bone marrow suppression.

Hepatotoxicity. Mild and reversible liver dysfunction occurs frequently, but severe hepatic injury is rare. Liver function should be monitored (by making weekly determinations of serum transaminase and alkaline phosphatase levels).

Drug Interactions. Flucytosine is often combined with amphotericin B. As noted, this combination offers several advantages. However, the combination can also be detrimental. Since amphotericin B is nephrotoxic, and since flucytosine is eliminated by the kidneys, amphotericin B-induced kidney damage may suppress flucytosine excretion, and may thereby promote flucytosine toxicity. Therefore, it is important to monitor renal function and flucytosine levels when amphotericin B and flucytosine are combined.

Like itraconazole, flucytosine inhibits hepatic drug-metabolizing enzymes, and can thereby raise levels of several other drugs. With at least four drugs—*cisapride*, *pimozide*, *dofetilide*, and *quinidine*—elevated levels can lead to potentially fatal dysrhythmias. Accordingly, flucytosine must not be combined with these drugs.

Preparations, Dosage, and Administration. Flucytosine [Ancobon] is available in 250- and 500-mg oral capsules. The usual dosage for patients with normal kidney function is 50 to 150 mg/kg/day administered in 4 divided doses at 6-hour intervals. At this dosage, some patients must ingest 10 or more capsules 4 times a day. Dosages must be reduced for patients with renal insufficiency. Nausea and vomiting associated with drug administration can be decreased by swallowing the capsules over a 15-minute interval.

DRUGS FOR SUPERFICIAL MYCOSES

The superficial mycoses are caused by two groups of organisms: (1) *Candida* species and (2) dermatophytes (species of *Epidermophyton*, *Trichophyton*, and *Microsporum*). *Candida* infections usually occur in mucous membranes and moist skin; chronic infections may involve the scalp, skin, and nails. Dermatophytoses are generally confined to the skin, hair, and nails. Superficial infections with dermatophytes are more common than superficial infections with *Candida*.

Overview of Drug Therapy

Superficial mycoses can be treated with a variety of topical and oral drugs. For mild to moderate infections, topical agents are generally preferred. Specific indications for the drugs used against superficial mycoses are summarized in Tables 92-4 and 92-5. Some of these drugs are also used for systemic mycoses.

Dermatophytic Infections (Ringworm)

Dermatophytic infections are commonly referred to as *ringworm* (because of the characteristic ring-shaped lesions). There are four principal dermatophytic infections, defined by their location: *tinea pedis* (ringworm of the foot, or "athlete's foot"), *tinea corporis* (ringworm of the body), *tinea cruris* (ringworm of the groin, or "jock itch"), and *tinea capitis* (ringworm of the scalp).

Tinea Pedis. *Tinea pedis*, the most common fungal infection, generally responds well to topical therapy. Available agents are listed in Table 92-4. Patients should be advised to wear absorbent cotton socks, change their shoes often, and dry their feet after bathing.

Tinea Corporis. *Tinea corporis* usually responds to a topical azole or allylamine (see Table 92-4). Treatment should continue for at least 1 week after symptoms have cleared. Severe infection may require a systemic antifungal agent (eg, griseofulvin).

TABLE 92-4 ■ Drugs for Superficial Fungal Infections*

Drug	Route	Ringworm [†]	Candida Infection		Onychomycosis [‡]
			Skin	Mouth	
Azoles					
Clotrimazole	Topical	✓	✓	✓	
Econazole	Topical	✓	✓		✓
Fluconazole	Oral	✓		✓	✓
Itraconazole	Oral	✓			✓
Ketoconazole	Oral	✓	✓	✓	✓
	Topical	✓			
Miconazole	Topical	✓	✓		
Oxiconazole	Topical	✓			
Sertaconazole	Topical	✓			
Sulconazole	Topical	✓			
Allylamines					
Butenafine	Topical	✓			
Naftifine	Topical	✓			
Terbinafine	Oral	✓			✓
	Topical	✓			
Others					
Amphotericin B	Topical		✓		
Ciclopirox	Topical	✓	✓		✓
Griseofulvin	Oral	✓			✓
Nystatin	Topical		✓	✓	
Tolnaftate	Topical	✓			
Undecylenate	Topical	✓			

*Vulvovaginal candidiasis is addressed in Table 92-5.

[†]Ringworm is a popular term for dermatophytic infections, including tinea pedis (ringworm of the foot, "athlete's foot"), tinea cruris (ringworm of the groin, "jock itch"), tinea corporis (ringworm of the body), and tinea capitis (ringworm of the scalp).

[‡]Onychomycosis is a clinical term for fungal infection of the toenails and fingernails.

Tinea Cruris. Tinea cruris responds well to topical therapy. Treatment should continue for at least 1 week after symptoms have cleared. If the infection is severely inflamed, a systemic antifungal drug (eg, clotrimazole) may be needed; topical or systemic glucocorticoids may be needed as well.

Tinea Capitis. Tinea capitis is difficult to treat. Topical drugs are not likely to work. Oral griseofulvin, taken for 6 to 8 weeks, is considered standard therapy. However, oral terbinafine, taken for only 2 to 4 weeks, may be more effective.

Candidiasis

Vulvovaginal Candidiasis. Vulvovaginal candidiasis is very common, occurring in 75% of women at least once in their lives. Most cases are caused by *Candida albicans*, and many of the rest are caused by *Candida glabrata*, especially in patients with HIV/AIDS. Factors that predispose to *Candida* infection include pregnancy, obesity, diabetes, debilitation, HIV infection, and use of certain drugs, including oral contraceptives, systemic glucocorticoids, anticancer agents, immunosuppressants, and systemic antibiotics. In the past, most regimens required daily application of a topical drug for 1 to 2 weeks. However, with current drugs, just 1 or 3 days of

topical therapy can be curative. In addition, oral therapy may be used: A single 150-mg dose of fluconazole can be curative—but it causes more side effects (headache, rash, GI disturbance) than topical agents. For women with recurrent vulvovaginal candidiasis, weekly prophylaxis with oral fluconazole is highly effective—but relapse is common when treatment is stopped. Major drugs for uncomplicated vulvovaginal candidiasis are summarized in Table 92-5. All appear equally effective. Hence, drug selection is based largely on patient preference. The longer regimens have no demonstrated advantage over the shorter ones.

Oral Candidiasis. Oral candidiasis, also known as thrush, is seen often. Topical agents—nystatin, clotrimazole, miconazole, and amphotericin B—are generally effective. In the immunocompromised host, oral therapy with fluconazole or ketoconazole is usually required.

Onychomycosis (Fungal Infection of the Nails)

Fungal infection of the nails, known as onychomycosis, is difficult to eradicate and requires prolonged treatment. Infections may be caused by dermatophytes or *Candida* species. Because onychomycosis is largely a cosmetic concern, treatment is usually optional.

TABLE 92-5 ■ Some Preferred Products for Uncomplicated Vulvovaginal Candidiasis

Generic Name	Trade Name	Formulation	Dosage
Oral Preparation			
Fluconazole	Diffucan	150-mg oral tablet	1 tablet once
Topical Preparations			
Butoconazole	Gynazole-1	2% cream, SR	1 applicatorful vaginally once
	Mycelex-3	2% cream	1 applicatorful vaginally × 3 days
Clotrimazole	Mycelex-7	100-mg vaginal tablet	1 tablet vaginally × 7 days
	Gyne-Lotrimin	100-mg vaginal tablet	1 tablet vaginally × 7 days
	Gyne-Lotrimin 3	200-mg vaginal tablet	1 tablet vaginally × 3 days
	Gyne-Lotrimin 3	2% cream	1 applicatorful vaginally × 3 days
	Gyne-Lotrimin	1% cream	1 applicatorful vaginally × 7–14 days
	Mycelex-7	1% cream	1 applicatorful vaginally × 7–14 days
Miconazole	Miconazole 3	4% cream	1 applicatorful vaginally × 3 days
	Monistat 3	4% cream	1 applicatorful vaginally × 3 days
	Miconazole 7	2% cream	1 applicatorful vaginally × 7 days
	Monistat 7	2% cream	1 applicatorful vaginally × 7 days
	Monistat 1	1200-mg suppository	1 suppository vaginally once
	Monistat 3	200-mg suppository	1 suppository vaginally × 3 days
	Monistat 7	100-mg suppository	1 suppository vaginally × 7 days
Terconazole	Terazol 3	80-mg suppository	1 suppository vaginally × 3 days
	Terazol 3	0.8% cream	1 applicatorful vaginally × 3 days
	Terazol 7	0.4% cream	1 applicatorful vaginally × 7 days
Tioconazole	Monistat 1	6.5% ointment	1 applicatorful vaginally once
	Vagistat-1	6.5% ointment	1 applicatorful vaginally once

SR = sustained-release formulation.

Onychomycosis may be treated with oral antifungal drugs or with topical ciclopirox. Success rates with oral therapy are quite low, and rates with topical therapy are even lower.

Oral Therapy. The drugs used most often are *terbinafine* [Lamisil] and *itraconazole* [Sporanox]. Both are active against *Candida* species and dermatophytes. Once in the body, these drugs become incorporated into keratin as the nails grow. Drug may also diffuse into the nails from the tissue below. Side effects include headache, GI disturbances (eg, nausea, vomiting, abdominal pain), and skin reactions (eg, itching, rash). Treatment generally lasts 3 to 6 months. Unfortunately, even with this prolonged therapy, the cure rate is relatively low (about 50%).

Topical Therapy with Ciclopirox. *Ciclopirox* [Penlac Nail Lacquer] is the only topical agent for onychomycosis available in the United States.* In contrast to oral terbinafine or itraconazole, which are active against *Candida* species and several dermatophytes, topical ciclopirox is active against only one dermatophyte—*Trichophyton rubrum*—and has no activity against *Candida*. Ciclopirox is applied once a day to activity against *Candida*. Ciclopirox is applied once a day to the nails and immediately adjacent skin. New coats are applied over old ones. Once a week, all coats are removed with alcohol. Side effects are minimal and localized. Unfortunately, despite prolonged use (up to 48 weeks), ciclopirox confers only modest benefits: Complete cure occurs in less than 12% of patients and, even when complete cure *does* occur, the recurrence rate is high—about 40%. Compared with

oral therapy, topical ciclopirox is safer and cheaper, but much less effective.

Use of ciclopirox for superficial fungal infections of the skin is discussed below.

Azoles

Twelve members of the azole family are used for superficial mycoses (see Tables 92-4 and 92-5). The usual route is topical. Three of the twelve—itraconazole, fluconazole, and ketoconazole—are also used for systemic mycoses (see above).

The azoles are active against a broad spectrum of pathogenic fungi, including dermatophytes and *Candida* species. Antifungal effects result from inhibiting the biosynthesis of ergosterol, an essential component of the fungal cytoplasmic membrane.

Clotrimazole

Therapeutic Uses. Topical clotrimazole is a drug of choice for dermatophytic infections and candidiasis of the skin, mouth, and vagina.

Adverse Effects. When applied to the skin, clotrimazole can cause stinging, erythema, edema, urticaria, pruritus, and peeling. However, the incidence is low. Intravaginal administration occasionally causes a burning sensation and lower abdominal cramps. Oral clotrimazole can cause GI distress.

Preparations, Dosage, and Administration. Clotrimazole is available as an oral troche, as a cream or suppository for intravaginal use, and in three formulations for application to the skin: cream, lotion, and solution. For fungal infections of the skin, the drug is applied twice daily for 2 to 4 weeks. For vulvovaginal candidiasis, several dosing schedules have been

*Two other topical preparations for onychomycosis—amorolfine 5% lacquer [Loceryl, Curanail] and tioconazole 28% paint—are available outside the United States.

employed, including (1) insertion of one 100-mg vaginal tablet for 7 days, (2) insertion of one 200-mg vaginal tablet for 3 days, and (3) application of a 2% vaginal cream for 3 days. Trade names for dermatologic products are Desenex, Cruex, Lotrimin, and Canesten[®], and trade names for vaginal products are Gyne-Lotrimin and Mycelex.

Ketoconazole

Ketoconazole [Koric, Extina, Nizoral, Xolegel, Ketoderm[®]] is approved for oral and topical therapy of superficial mycoses. Oral ketoconazole provides effective treatment of dermatophytic infections as well as candidiasis of the skin, mouth, and vagina. However, because of the toxicity associated with oral use, this route should be reserved for infections that have failed to respond to topical agents. Ketoconazole for topical use is available in five formulations: 2% foam [Extina] and 2% gel [Xolegel] for seborrheic dermatitis, 1% shampoo [Nizoral-AD] for dandruff, 2% shampoo [Nizoral] for tinea versicolor, and 2% cream [Koric, Ketoderm[®]] for dermatophytic infections and candidiasis of the skin. The basic pharmacology of ketoconazole is discussed above under *Drugs for Systemic Mycoses*.

Miconazole

Therapeutic Uses. Miconazole [Micatin, Monistat 3, Monistat 7, Oravig, others] is an azole antifungal drug available for topical and systemic administration. Topical miconazole is a drug of choice for dermatophytic infections and for cutaneous and vulvovaginal candidiasis. A new buccal tablet is used for oropharyngeal candidiasis.

Adverse Effects. Adverse effects of topical miconazole are generally mild. Intravaginal administration causes burning, itching, and irritation in about 7% of users. When applied to the skin, miconazole occasionally causes irritation, burning, and maceration. Topical application is not associated with systemic toxicity.

Drug Interactions. Intravaginal miconazole can intensify the anticoagulant effects of warfarin. One woman using the combination reported bruising, bleeding gums, and a nosebleed. We have long known that systemic miconazole can inhibit metabolism of warfarin, thereby causing warfarin levels to rise. Apparently, intravaginal miconazole can be absorbed in amounts sufficient to do the same. Because of this interaction, women taking warfarin should not use intravaginal miconazole. If the drugs must be used concurrently, anticoagulation should be monitored closely and warfarin dosage reduced as indicated.

Preparations, Dosage, and Administration. Miconazole is available in cream, liquid, and powder formulations for application to the skin; in cream and suppository formulations for intravaginal application; and as a 50-mg buccal tablet [Oravig] for oropharyngeal candidiasis. Cutaneous mycoses are treated with twice-daily applications for 2 to 4 weeks. Oropharyngeal candidiasis is treated by placing a buccal tablet to the upper gum once daily for 14 days. Dosing options for vulvovaginal candidiasis are shown in Table 92-5.

Itraconazole

Itraconazole [Sporanox] can be used for oral therapy of onychomycosis of the toenails or fingernails. For infection of the toenails, the dosage is 200 mg once daily for 12 weeks. For infection of the fingernails, dosing is done in repeating cycles consisting of 1 week of treatment (200 mg twice daily) followed by 3 weeks off. The basic pharmacology of itraconazole is discussed above under *Drugs for Systemic Mycoses*.

Fluconazole

Fluconazole [Diflucan] can be used for oral therapy of vulvovaginal candidiasis, oropharyngeal candidiasis, and onychomycosis. For vulvovaginal candidiasis, the dosage for treating ongoing infection is 150 mg once; the dosage for preventing recurrent infection is 150 mg once a week for 6 months. The dosage for oropharyngeal candidiasis is 200 mg on day 1 followed by 100 mg daily for 2 weeks. The dosage for onychomycosis is 100 mg daily for 3 to 12 weeks. The basic pharmacology of fluconazole is discussed above under *Drugs for Systemic Mycoses*.

Newer Azole Drugs

Econazole. Econazole [Spectazole] is available for topical application only. The drug is indicated for ringworm infections and superficial candidiasis. Local adverse effects (burning, erythema, stinging, itching) occur in about 3% of patients. Less than 1% of topical econazole is absorbed, and systemic toxicity has not been reported. Econazole, supplied in a 1% cream, is applied twice daily for 2 to 4 weeks.

Oxiconazole and Sulconazole. Oxiconazole [Oxistat] and sulconazole [Exelderm] are broad-spectrum antifungal drugs. Both are approved for topical treatment of tinea infections. Local adverse effects (itching, burning,

irritation, erythema) occur in less than 3% of patients. Neither drug is absorbed to a significant degree. Systemic toxicity has not been reported. Oxiconazole is supplied as a cream and lotion. Sulconazole is supplied as a cream and solution. Both drugs are applied once daily for 2 to 4 weeks.

Butoconazole, Terconazole, and Tioconazole. These azole drugs are approved only for topical treatment of vulvovaginal candidiasis. All three are fungicidal. Local adverse effects (burning, itching) occur in 2% to 6% of users. Absorption following intravaginal administration is low, and systemic reactions are rare (except for headache with terconazole). Owing to a small risk of fetal injury, these drugs are not recommended for use during the first trimester of pregnancy. Trade names, formulations, and dosages are presented in Table 92-5.

Sertaconazole. Sertaconazole [Ertaczo], available by prescription, is indicated for topical therapy of tinea pedis. The 2% cream is applied twice daily for 4 weeks. Mild local reactions (itching, burning, irritation, erythema) occur in 2% of patients. Blood levels are undetectable following repeated applications, and systemic effects have not been reported. Cure rates are like those seen with generic clotrimazole and miconazole—older azoles that are much cheaper and can be purchased without a prescription.

Griseofulvin

Griseofulvin [Grifulvin V, Gris-PEG] is administered orally to treat superficial mycoses. The drug is inactive against organisms that cause systemic mycoses.

Mechanism of Action. Following absorption, griseofulvin is deposited in the keratin precursor cells of skin, hair, and nails. Because griseofulvin is present, newly formed keratin is resistant to fungal invasion. Hence, as infected keratin is shed, it is replaced by fungus-free tissue.

Griseofulvin kills fungi by inhibiting fungal mitosis. How? It binds to components of microtubules, the structures that form the mitotic spindle. Because griseofulvin acts by disrupting mitosis, the drug only affects fungi that are actively growing.

Pharmacokinetics. Administration is oral, and absorption can be enhanced by dosing with a fatty meal. As noted, griseofulvin is deposited in the keratin precursor cells of skin, hair, and nails. Elimination is by hepatic metabolism and renal excretion.

Therapeutic Uses. Griseofulvin is employed orally to treat dermatophytic infections of the skin, hair, and nails. The drug is not active against *Candida* species, nor is it useful against systemic mycoses. Dermatophytic infections of the skin respond relatively quickly (in 3 to 8 weeks). However, infections of the palms may require 2 to 3 months of treatment, and a year or more may be needed to eliminate infections of the toenails.

Adverse Effects. Most untoward effects are not serious. Transient headache is common, occurring in about 15% of patients. Other mild reactions include rash, insomnia, tiredness, and GI effects (nausea, vomiting, diarrhea). Griseofulvin may cause hepatotoxicity and photosensitivity in patients with porphyria. The drug is contraindicated for individuals with a history of porphyria or hepatocellular disease.

Drug Interactions. Griseofulvin induces hepatic drug-metabolizing enzymes and can thereby decrease the effects of warfarin. When this combination is used, the dosage of warfarin may need to be increased.

Preparations, Dosage, and Administration. Griseofulvin is formulated in two particle sizes: microsized and ultra-microsized. The microcrystalline form [Grifulvin V] is supplied in tablets (250 and 500 mg) and capsules (250 mg). The ultra-microcrystalline form [Gris-PEG] is supplied in tablets (125, 165, 250, and 330 mg).

Dosage depends to some degree upon the formulation (microsized or ultra-microsized). With microsized formulations, the usual adult dosage is 500 mg to 1 gm/day, and the usual pediatric dosage is 11 mg/kg/day. The ultra-microsized particles are better absorbed than the microsized particles, and hence doses of ultra-microcrystalline griseofulvin are about 30% lower than doses of microcrystalline griseofulvin.

Polyene Antibiotics

Nystatin

Actions, Uses, and Adverse Effects. Nystatin [Mycostatin, Nilstat, Nyaderm*, others] is a polyene antibiotic used only for candidiasis. Nystatin is the drug of choice for intestinal candidiasis, and is also employed to treat candidal infections of the skin, mouth, esophagus, and vagina. Nystatin can be administered orally and topically. There is no significant absorption from either route. Oral nystatin occasionally causes GI disturbance (nausea, vomiting, diarrhea). Topical application may produce local irritation.

Preparations, Dosage, and Administration. For oral administration, nystatin is supplied as a suspension and in tablets and lozenges; dosages range from 100,000 to 1 million units 3 to 4 times a day. Vaginal tablets are employed for vaginal candidiasis; the usual dosage is 100,000 units once a day for 2 weeks. Nystatin is supplied as a cream, ointment, and powder to treat candidiasis of the skin. The cream and ointment formulations are applied twice daily; the powder is applied 3 times daily.

Allylamines

Naftifine

Naftifine [Naftin] was the first allylamine available. Although approved only for topical treatment of dermatophytic infections, naftifine is active against a broad spectrum of pathogenic fungi. The drug works by inhibiting squalene epoxidase, and thereby inhibits synthesis of ergosterol, a key component of the fungal cell membrane. The most common adverse effects are burning and stinging. Absorption following topical administration is relatively low (about 6%). Systemic effects have not been reported. Naftifine is supplied in two formulations: 1% cream and 1% gel. The cream is applied once daily, the gel twice daily. Treatment usually lasts 4 weeks.

Terbinafine

Actions and Uses. Terbinafine [Lamisil] belongs to the same chemical family as naftifine and has the same mechanism of action: inhibition of squalene epoxidase with resultant inhibition of ergosterol synthesis. The drug is highly active against dermatophytes, and less active against *Candida* species. Terbinafine is available in topical and oral formulations. Topical therapy is used for ringworm infections (eg, tinea corporis, tinea cruris, tinea pedis). Oral therapy is used for ringworm and onychomycosis (fungal infection of the nails).

Adverse Effects. Adverse effects with topical terbinafine are minimal. The discussion that follows applies to oral therapy. The most common side effects are headache, diarrhea, dyspepsia, and abdominal pain. Oral terbinafine may also cause skin reactions and disturbance of taste. Of much greater concern, terbinafine may pose a risk of liver failure. Some terbinafine users have died of liver failure, and other have required a liver transplant. However, a causal link has not been established. Nonetheless, caution is advised. Baseline tests for serum alanine and aspartate aminotransferases (ALT and AST) are recommended. In addition, patients should be informed about signs of liver dysfunction (persistent nausea, anorexia, fatigue, vomiting, jaundice, right up-

per abdominal pain, dark urine, pale stools) and, if they appear, should discontinue terbinafine immediately and undergo evaluation of liver function. Terbinafine is not recommended for patients with pre-existing liver disease.

Preparations, Dosage, and Administration. Terbinafine for oral therapy is available in tablets (250 mg) and in granules (125 and 187.5 mg packet). The granules should be sprinkled on a spoonful of soft, nonacidic food, such as pudding or mashed potatoes, but not applesauce or fruit-based foods. The oral dosage for nail infections is 250 mg/day for 6 to 12 weeks, and the dosage for ringworm is 250 mg/day for 2 to 6 weeks. Terbinafine for topical therapy is available as a 1% gel. Application is done once or twice daily for 1 to 4 weeks.

Butenafine

Butenafine [Lotrimin Ultra Cream, Mentax] is chemically similar to naftifine and terbinafine, although butenafine is not a true allylamine. However, it does have the same mechanism of action: inhibition of squalene epoxidase with resultant inhibition of ergosterol synthesis. Butenafine is indicated for topical therapy of tinea pedis, tinea corporis, tinea cruris, and tinea versicolor. Absorption is minimal, and systemic side effects have not been reported. Local reactions include burning, stinging, erythema, irritation, and itching. Butenafine 1% cream is applied once daily for 2 to 4 weeks.

Other Drugs for Superficial Mycoses

Tolnaftate

Tolnaftate [Aftate, Tinactin, others] is employed topically to treat a variety of superficial mycoses. The drug is active against dermatophytes, but not against *Candida* species. The mechanism of antifungal action is unknown. Adverse effects (sensitization, irritation) are extremely rare. Tolnaftate is available in several formulations. Creams, gels, and solutions are most effective; powders are used adjunctively. The drug is applied twice daily for 2 to 4 weeks.

Undecylenic Acid

Undecylenic acid [Desenex, Cruex, others] is a topical agent used to treat superficial mycoses. The drug is active against dermatophytes but not *Candida* species. Its major indication is tinea pedis (athlete's foot). However, other drugs (tolnaftate, the azoles) are more effective.

Ciclopirox

Ciclopirox [Loprox, Penlac Nail Lacquer] is a broad-spectrum, topical antifungal drug. Benefits derive from chelating iron and aluminum present in metal-dependent enzymes that protect fungi from peroxides. Ciclopirox is used for infections of the skin (discussed here) and for infections of the fingernails and toenails (discussed above under *Onychomycosis*). The formulations used for skin infections are marketed as *Loprox*. The formulation used for nail infections is marketed as *Penlac Nail Lacquer*.

When applied to the skin, ciclopirox is active against dermatophytes and *Candida* species. The drug is effective against superficial candidiasis and tinea pedis, tinea cruris, and tinea corporis. Ciclopirox penetrates the epidermis to the dermis, but systemic absorption is minimal, and hence no significant systemic accumulation occurs. There is no toxicity from local application. For treatment of skin infections, ciclopirox is available as a 1% shampoo and as a 0.77% cream, gel, lotion, and suspension. The shampoo is used twice weekly for 4 weeks. The cream, gel, and suspension are applied twice daily for 2 to 4 weeks.

KEY POINTS

- Amphotericin B is a drug of choice for most systemic mycoses—despite its potential for serious harm.
- Amphotericin B binds to ergosterol in the fungal cell membrane, thereby making the membrane more permeable. The resultant leakage of intracellular cations reduces viability.
- Much of the toxicity of amphotericin B results from binding to cholesterol in host cell membranes.
- Because absorption of oral amphotericin B is poor, treatment of systemic mycoses requires intravenous administration.
- Amphotericin B infusion frequently causes fever, chills, rigors, nausea, and headache. Pretreatment with diphen-

- hydramine plus an analgesic (eg, acetaminophen) can reduce mild symptoms. A glucocorticoid can be used for severe reactions. Meperidine or dantrolene can reduce rigors.
- Amphotericin B causes renal injury in most patients. Kidney damage can be minimized by infusing 1 L of saline on the days amphotericin is infused.
- If possible, amphotericin B should not be combined with other nephrotoxic drugs (eg, aminoglycosides, cyclosporine, NSAIDs).
- Itraconazole, our prototype for the azole antifungal agents, is active against a broad spectrum of fungi.
- Itraconazole inhibits cytochrome P450, and thereby inhibits synthesis of ergosterol, an essential component of

the fungal cell membrane. As a result, cell membrane permeability increases, causing cellular components to leak out.

- Itraconazole is an alternative to IV amphotericin for many fungal infections. Advantages are lower toxicity and oral dosing.
- Itraconazole has two major adverse effects: cardioppression and liver damage.
- Itraconazole inhibits CYP3A4, and can thereby raise levels of many drugs. High levels of cisapride, pimozide, dofetilide, and quinidine can cause fatal dysrhythmias, and hence using these drugs with itraconazole is contraindicated.
- Drugs that reduce gastric acidity (eg, H₂ antagonists, proton pump inhibitors) can greatly reduce absorption of itraconazole.

- Topical clotrimazole, a member of the azole family of antifungals, is a drug of choice for many superficial mycoses caused by dermatophytes and *Candida* species.
- Onychomycosis (fungal infection of the fingernails and toenails) is difficult to treat and requires prolonged therapy. Oral therapy with terbinafine or itraconazole is the preferred treatment.
- Vulvovaginal candidiasis can be treated with a single oral dose of fluconazole or with short-term topical therapy (eg, one 1200-mg miconazole vaginal suppository).

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Summary of Major Nursing Implications

The implications summarized below pertain only to use of antifungal drugs against *systemic* mycoses.

AMPHOTERICIN B

Preadministration Assessment

Therapeutic Goal

Treatment of progressive and potentially fatal systemic fungal infections. Flucytosine may be given to enhance therapeutic effects.

Identifying High-Risk Patients

When used as it should be (ie, for life-threatening infections), amphotericin has no contraindications.

Implementation: Administration

Routes

Intravenous, intrathecal.

Intravenous Administration

Use aseptic technique when preparing infusion solutions. Infuse slowly (over 2 to 4 hours). Check the solution periodically for a precipitate and, if one forms, discontinue the infusion immediately. Therapy lasts several months; rotate the infusion site to reduce phlebitis and ensure availability of a usable vein. Dosage must be individualized. Alternate-day dosing may be ordered to reduce adverse effects.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

General Considerations. Amphotericin B can produce serious adverse effects. The patient should be under close supervision, preferably in a hospital.

Infusion Reactions. Amphotericin can cause fever, chills, rigors, nausea, and headache. Pretreatment with diphenhydramine plus acetaminophen can minimize these reactions. Give meperidine or dantrolene for rigors. If

other measures fail, give hydrocortisone to suppress symptoms. Rotate the infusion site and pretreat with heparin to minimize phlebitis. Infusion reactions can be reduced by using a lipid-based formulation rather than conventional amphotericin.

Nephrotoxicity. Almost all patients experience renal impairment. Monitor and record intake and output. Test kidney function every 3 to 4 days; if plasma creatinine content rises above 3.5 mg/dL, amphotericin dosage should be reduced. To reduce the risk of renal damage, infuse 1 L of saline on the days when amphotericin is given, avoid other nephrotoxic drugs (eg, aminoglycosides, cyclosporine, NSAIDs), and use a lipid-based formulation instead of conventional amphotericin.

Hypokalemia. Renal injury may cause hypokalemia. Measure serum potassium often. Correct hypokalemia with potassium supplements.

Hematologic Effects. Normocytic, normochromic anemia has occurred secondary to amphotericin-induced suppression of bone marrow. Hematocrit determinations should be performed to monitor for this anemia.

Minimizing Adverse Interactions

Nephrotoxic Drugs. Unless clearly required, amphotericin should not be combined with other nephrotoxic drugs, including aminoglycosides, cyclosporine, and NSAIDs.

ITRACONAZOLE

Preadministration Assessment

Therapeutic Goal

Treatment of systemic and superficial mycoses.

Baseline Data

Assess for heart disease or a history thereof. The prescriber may order baseline tests of liver function.

Summary of Major Nursing Implications*—cont'd

Identifying High-Risk Patients

Itraconazole is *contraindicated* for patients taking pimozide, quinidine, dofetilide, or cisapride.

Use with *great caution*, if at all, in patients with cardiac disease, significant pulmonary disease, active liver disease, or a history of liver injury with other drugs.

Implementation: Administration

Route

Oral.

Administration

Advise patients to take itraconazole capsules with food and/or a cola beverage to enhance absorption.

Advise patients using antacids and other drugs that reduce gastric acidity to take them at least 1 hour before itraconazole or 2 hours after.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Liver Injury. Rarely, itraconazole has been associated with fatal liver failure. If signs of liver injury appear, discontinue itraconazole and obtain tests of liver function. **Inform patients about signs of liver dysfunction (persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain, jaundice, dark urine, pale stools), and instruct them to notify the prescriber if these occur.**

Cardiac Suppression. Itraconazole can suppress ventricular function, posing a risk of heart failure. Monitor for signs and symptoms of heart failure, and discontinue itraconazole if they develop. **Inform patients about signs of heart failure (fatigue, cough, dyspnea, edema, jugular distention), and instruct them to seek immediate medical attention if they occur.**

Minimizing Adverse Interactions

Pimozide, Quinidine, Dofetilide, and Cisapride. By inhibiting CYP3A4, itraconazole can raise levels of these drugs, posing a risk of fatal dysrhythmias. Accordingly, concurrent use of these drugs with itraconazole is contraindicated.

Cyclosporine, Digoxin, Warfarin, and Sulfonylureas. By inhibiting CYP3A4, itraconazole can raise levels of these drugs. Monitor cyclosporine and digoxin blood levels. Monitor prothrombin time in patients taking warfarin. Monitor blood glucose in patients taking a sulfonylurea.

Drugs That Raise Gastric pH. Antacids, H₂ antagonists, proton pump inhibitors, and other drugs that decrease gastric acidity can reduce itraconazole absorption. **Advise patients using these agents to take them at least 1 hour before itraconazole or 2 hours after.**

*Patient education information is highlighted as blue text.

FLUCYTOSINE

Preadministration Assessment

Therapeutic Goal

Treatment of serious infections caused by *Candida* species and *Cryptococcus neoformans*. Flucytosine is usually combined with amphotericin B.

Baseline Data

Obtain baseline tests of renal function, hematologic status, and serum electrolytes.

Identifying High-Risk Patients

Use with *extreme caution* in patients with kidney disease or bone marrow suppression.

Implementation: Administration

Route

Oral.

Dosage and Administration

Treatment may require ingesting 10 or more capsules 4 times a day. **Advise patients to take capsules a few at a time over a 15-minute interval to minimize nausea and vomiting.** Dosage must be reduced in patients with renal impairment.

Ongoing Evaluation and Interventions

Monitoring Summary

Obtain weekly tests of liver function (serum transaminase and alkaline phosphatase levels) and hematologic status (leukocyte counts). In patients receiving amphotericin B concurrently, and in those with pre-existing renal impairment, monitor kidney function and flucytosine levels.

Minimizing Adverse Effects

Hematologic Effects. Flucytosine-induced bone marrow suppression can cause neutropenia, thrombocytopenia, and fatal agranulocytosis. Risk can be minimized by adjusting the dosage to keep plasma flucytosine levels below 100 mcg/mL. Obtain weekly leukocyte counts to monitor hematologic effects.

Hepatotoxicity. Mild and reversible liver dysfunction occurs frequently; severe hepatic damage is rare. Obtain weekly determinations of serum transaminase and alkaline phosphatase levels to evaluate liver function.

Minimizing Adverse Interactions

Amphotericin B. Kidney damage from amphotericin B may decrease flucytosine excretion, thereby increasing toxicity from flucytosine accumulation. When these drugs are combined, renal function and flucytosine levels must be monitored.

Antiviral Agents I: Drugs for Non-HIV Viral Infections

DRUGS FOR INFECTION WITH HERPES SIMPLEX VIRUSES AND VARICELLA-ZOSTER VIRUS

Acyclovir
Valacyclovir
Famciclovir
Topical Drugs for Herpes Labialis
Topical Drugs for Ocular Herpes Infections

DRUGS FOR CYTOMEGALOVIRUS INFECTION

Ganciclovir
Valganciclovir
Cidofovir
Foscarnet

DRUGS FOR HEPATITIS

Hepatitis C

Interferon Alfa
Ribavirin (Oral)
Protease Inhibitors: Boceprevir and Telaprevir

Hepatitis B

Interferon Alfa
Nucleoside Analogs

DRUGS FOR INFLUENZA

Influenza Vaccines
Neuraminidase Inhibitors
Adamantanes

DRUGS FOR RESPIRATORY SYNCYTIAL VIRUS INFECTION

Ribavirin (Inhaled)
Palivizumab

Antiviral drugs are discussed in this chapter and the one that follows. In this chapter, we consider drugs used to treat infections caused by viruses other than HIV. In Chapter 94, we consider drugs used against HIV infection. Drugs for non-HIV infections are summarized in Table 93-1.

Although antiviral therapy has made significant advances, our ability to treat viral infections remains limited. Compared with the dramatic advances made in antibacterial therapy over the past half-century, efforts to develop safe and effective antiviral drugs have been less successful. A major reason for this lack of success resides in the process of viral replication: Viruses are obligate intracellular parasites that use the biochemical machinery of host cells to reproduce. Because the viral growth cycle employs host-cell enzymes and substrates, it is difficult to suppress viral replication without doing sig-

TABLE 93-1 ■ Major Drugs for Non-HIV Viral Infections

Drug	Antiviral Spectrum
Drugs for Herpes Simplex Virus and Varicella-Zoster Virus Infections	
Systemic Drugs	
Acyclovir	HSV, VZV
Famciclovir	HSV, VZV
Foscarnet	HSV, VZV
Valacyclovir	HSV, VZV
Topical Drugs	
Vidarabine	HSV, VZV
Penciclovir	HSV
Trifluridine	HSV keratitis
Docosanol	HSV keratitis
Ganciclovir	HSV keratitis
Drugs for Hepatitis	
Alfa Interferons	
Interferon alfa-2b	HCV, HBV
Interferon alfacon-1	HCV
Peginterferon alfa-2a	HCV, HBV
Peginterferon alfa-2b	HCV
Protease Inhibitors	
Boceprevir	HCV
Telaprevir	HCV
Nucleoside Analogs	
Ribavirin (oral)	HCV
Adefovir	HBV*
Entecavir	HBV*
Lamivudine	HBV*
Telbivudine	HBV
Tenofovir	HBV*
Drugs for Cytomegalovirus Infection	
Ganciclovir	CMV
Valganciclovir	CMV
Cidofovir	CMV
Foscarnet	CMV
Drugs for Influenza	
Oseltamivir	Influenza A and B
Zanamivir	Influenza A and B
Drugs for Respiratory Syncytial Virus Infection	
Ribavirin (inhaled)	RSV
Palivizumab	RSV

CMV = cytomegalovirus, HBV = hepatitis B virus, HCV = hepatitis C virus, HSV = herpes simplex virus, RSV = respiratory syncytial virus, VZV = varicella-zoster virus.

*Also active against HIV.

TABLE 93-2 ■ Treatment of Herpes Simplex Virus and Varicella-Zoster Virus Infections

Infection	Drug	Route	Dosage	Duration
Herpes Simplex Virus Infections				
Encephalitis	Acyclovir	IV	10–15 mg/kg every 8 hr	14–21 days
Mucocutaneous in ICH	Acyclovir	IV	5 mg/kg every 8 hr	7–10 days
	Acyclovir	PO	400 mg 5 times/day	7–14 days
	Valacyclovir	PO	50 mg 2 times/day	7–10 days
	Famciclovir	PO	500 mg 2 times/day	7–10 days
	Foscarnet*	IV	400 mg 2–3 times/day	7–21 days
Neonatal	Acyclovir	IV	10–15 mg/kg every 8 hr	14 days
Orolabial	Acyclovir	Topical	5% cream 5 times/day	4 days
	Penciclovir	Topical	1% cream every 2 hr	4 days
	Docosanol	Topical	10% cream 5 times/day	4 days
Keratoconjunctivitis	Ganciclovir	Topical	See text	
	Trifluridine	Topical	See text	
	Vidarabine	Topical	See text	
Genital infections	See Chapter 95			
Varicella-Zoster Virus Infections				
Varicella	Acyclovir	PO	20 mg/kg (800 mg max) 4 times/day	5 days
Varicella in ICH*	Acyclovir	IV	10 mg/kg every 8 hr	7 days
Herpes zoster	Acyclovir	PO	800 mg 5 times/day	7–10 days
	Valacyclovir	PO	1 gm 3 times/day	7 days
	Famciclovir	PO	500 mg 3 times/day	7 days
Herpes zoster in ICH*	Acyclovir	IV	10 mg/kg every 8 hr	7 days
Acyclovir-resistant zoster	Foscarnet	IV	40 mg/kg every 28 hr	10 days

ICH = immunocompromised host.

*Reserve foscarnet for acyclovir-resistant infection.

nificant harm to the host. The antiviral drugs used clinically act by suppressing biochemical processes unique to viral reproduction. As our knowledge of viral molecular biology expands, additional virus-specific processes will be discovered, giving us new targets for drugs.

DRUGS FOR INFECTION WITH HERPES SIMPLEX VIRUSES AND VARICELLA-ZOSTER VIRUS

Herpes simplex virus (HSV) and *varicella-zoster virus* (VZV) are members of the herpesvirus group. HSV causes infection of the genitalia, mouth, face, and other sites. VZV is the cause of *varicella* (chickenpox) and *herpes zoster* (shingles), a painful condition resulting from reactivation of VZV that had been dormant within sensory nerve roots. Both conditions are discussed further in Chapter 68, along with the vaccine used to prevent chickenpox. Drugs for infection with HSV and VZV are summarized in Table 93-2. Genital herpes is discussed in Chapter 95.

Acyclovir

Acyclovir [Zovirax] is the agent of first choice for most infections caused by herpes simplex viruses and varicella-zoster virus. The drug can be administered topically, orally, and intravenously. Serious side effects are uncommon.

Antiviral Spectrum

Acyclovir is active only against members of the herpesvirus family, a group that includes *herpes simplex viruses* (HSVs), *varicella-zoster virus* (VZV), and *cytomegalovirus* (CMV). Of these, HSVs are most sensitive, VZV is moderately sensitive, and most strains of CMV are resistant.

Mechanism of Action

Acyclovir inhibits viral replication by suppressing synthesis of viral DNA. To exert antiviral effects, acyclovir must first undergo activation. The critical step in activation is conversion of acyclovir to acyclo-GMP by *thymidine kinase*. Once formed, acyclo-GMP is converted to acyclo-GTP, the compound directly responsible for inhibiting DNA synthesis. Acyclo-GTP suppresses DNA synthesis by (1) inhibiting viral DNA polymerase and (2) becoming incorporated into the growing strand of viral DNA, which blocks further strand growth.

The selectivity of acyclovir is based in large part on the ability of certain viruses to activate the drug. HSVs are especially sensitive to acyclovir because the drug is a much better substrate for thymidine kinase produced by HSVs than it is for mammalian thymidine kinase. Hence, formation of acyclo-GMP, the limiting step in the activation of acyclovir, occurs almost exclusively in cells infected with HSV. Cytomegalovirus is inherently resistant to the drug because acyclovir is a poor substrate for the form of thymidine kinase produced by this virus.

Resistance

Herpesviruses develop resistance to acyclovir by three mechanisms: (1) decreased production of thymidine kinase, (2) alteration of thymidine kinase such that it no longer converts acyclovir to acyclo-GMP, and (3) alteration of viral DNA polymerase such that it is less sensitive to inhibition. Of these mechanisms, thymidine kinase deficiency is the most common. Resistance is rare in immunocompetent patients, but many cases have been reported in transplant recipients and patients with AIDS. Lesions caused by resistant HSVs can be extensive and severe, progressing despite continued acyclovir therapy. Acyclovir-resistant HSVs and VZV usually respond to IV foscarnet or cidofovir, which are primarily used for treatment of cytomegalovirus infection (see below).

Therapeutic Uses

Mucocutaneous Herpes Simplex Infections. Herpes infections of the face and oropharynx are usually caused by HSV type 2 (HSV-2). For immunocompetent patients, oral acyclovir can be used to treat primary infections of the gums and mouth. Oral acyclovir can also be taken *prophylactically* to prevent episodes of recurrent herpes labialis (cold sores). However, there is no truly effective treatment for active herpes labialis. Mucocutaneous herpes infections can be especially severe in immunocompromised patients. For these people, intravenous acyclovir is the treatment of choice.

Varicella-Zoster Infections. High doses of oral acyclovir are effective for herpes zoster (shingles) in older adults. Oral therapy is also effective for varicella (chickenpox) in children, adolescents, and adults, provided that dosing is begun early (within 24 hours of rash onset). Intravenous acyclovir is the treatment of choice for varicella-zoster infection in the immunocompromised host.

Herpes Simplex Genitalis. The characteristics and treatment of genital HSV infection are discussed in Chapter 95.

Pharmacokinetics

Acyclovir may be administered topically, orally, and intravenously. Oral bioavailability is low, ranging from 15% to 30%. No significant absorption occurs with topical use. Once in the blood, acyclovir is distributed widely to body fluids and tissues. Levels achieved in cerebrospinal fluid are 50% of those in plasma. Elimination is renal, primarily as the unchanged drug. In patients with normal kidney function, acyclovir has a half-life of 2.5 hours. The half-life is prolonged by renal impairment, reaching 20 hours in anuric patients. Accordingly, dosages should be reduced in patients with kidney disease.

Adverse Effects

Intravenous Therapy. Intravenous acyclovir is generally well tolerated. The most common reactions are *phlebitis* and *inflammation* at the infusion site. Reversible *nephrotoxicity*, indicated by elevations in serum creatinine and blood urea nitrogen, occurs in some patients. The cause is deposition of acyclovir in renal tubules. The risk of renal injury is increased by dehydration and by use of other nephrotoxic drugs. Kidney damage can be minimized by infusing acyclovir slowly (over 1 hour) and by ensuring adequate hydration during the infusion and for 2 hours after.

Neurologic toxicity—agitation, tremors, delirium, hallucinations, and myoclonus—occurs rarely, primarily in patients

with renal impairment. In patients on dialysis, very low doses can cause severe neurotoxicity, characterized by delirium and coma.

Oral and Topical Therapy. Oral acyclovir is devoid of serious adverse effects. Renal impairment has not been reported. The most common reactions are nausea, vomiting, diarrhea, headache, and vertigo. Topical acyclovir frequently causes transient local burning or stinging; systemic reactions do not occur. Oral acyclovir is safe during pregnancy, and hence can be used to suppress recurrent genital herpes near term.

Preparations, Dosage, and Administration

Topical Ointment. Acyclovir [Zovirax] is supplied as a 5% ointment for topical therapy of *herpes genitalis* and *mild mucocutaneous HSV infection in the immunocompromised host*. Application is done 6 times a day at 3-hour intervals for 7 days. Patients should use a finger cot or rubber glove to avoid viral transfer to other parts of the body or to other people.

Topical Cream. Acyclovir [Zovirax] is supplied as a 5% cream for topical therapy of recurrent *herpes labialis* (cold sores) in patients at least 12 years old. Application is done 5 times a day for 4 days.

Oral. Oral acyclovir [Zovirax] is available in capsules (200 mg), tablets (400 and 800 mg), and a suspension (200 mg/5 mL). Dosages for patients with normal kidney function are given below. Dosages must be reduced for patients with renal impairment.

- For *initial episodes of herpes genitalis*, the usual dosage is 400 mg 3 times a day for 7 to 10 days.
- For *episodic recurrences of herpes genitalis*, the usual dosage is 400 mg 3 times a day for 5 days.
- For *long-term suppressive therapy of recurrent genital infections*, the usual dosage is 400 mg twice daily for up to 12 months.
- For *acute therapy of herpes zoster*, the dosage is 800 mg 5 times a day (at 4-hour intervals) for 7 to 10 days.
- For *varicella* (chickenpox), the dosage is 20 mg/kg (but no more than 800 mg) 4 times a day for 5 days. Treatment should begin at the earliest sign of rash.

Intravenous. For IV dosing, acyclovir is available in solution (50 mg/mL). Administration is by slow infusion (over 1 hour or more). Parenteral acyclovir must not be given by IV bolus or by IM or subQ injection. To minimize the risk of renal damage, hydrate the patient during the infusion and for 2 hours after. Dosages for patients with normal kidney function are given below. Dosages should be reduced for patients with renal impairment.

- For *mucocutaneous herpes simplex infection in the immunocompromised host*, the adult dosage is 5 mg/kg infused every 8 hours for 7 days. The dosage for children under 12 years is 250 mg/m² infused every 8 hours for 7 days.
- For *varicella-zoster infection in the immunocompromised host*, the adult dosage is 10 mg/kg infused every 8 hours for 7 days. The dosage for children under 12 years is 500 mg/m² infused every 8 hours for 7 days.
- For *severe episodes of herpes genitalis in the immunocompetent host*, the adult dosage is 5 to 10 mg/kg infused every 8 hours for 5 to 7 days (or until symptoms resolve). The dosage for children under 12 years is 250 mg/m² infused every 8 hours for 5 days.

Valacyclovir

Actions and Uses. Valacyclovir [Valtrex], a prodrug form of acyclovir, has three approved indications: (1) herpes zoster (shingles), (2) herpes simplex genitalis, and (3) herpes labialis (cold sores). In all three infections, benefits depend on conversion of valacyclovir to acyclovir, its active form. In a clinical trial in patients with *herpes zoster*, valacyclovir (1000 mg 3 times a day for 7 or 14 days) was somewhat more effective than acyclovir (800 mg 5 times a day for 7 days) in reducing the duration of pain and the duration of postherpetic neuralgia. In trials for patients with initial or recurrent *herpes genitalis*, valacyclovir (1000 mg twice a day) and acyclovir (200 mg 5 times a day) produced similar results. In another study, valacyclovir was shown to reduce—but not eliminate—the risk of transmitting genital herpes between monogamous heterosexual partners.

In patients receiving immunosuppressive drugs following a kidney transplant, prophylaxis with valacyclovir (2 gm 4 times a day for 90 days) can reduce the risk of CMV disease, a major complication of transplantation surgery.

Pharmacokinetics. Oral valacyclovir undergoes rapid absorption followed by rapid and essentially complete conversion to acyclovir. When acyclovir itself is given PO, bioavailability is only 15% to 30%. In contrast, when valacyclovir is given PO, the effective bioavailability of acyclovir is greatly increased—to about 55%. Hence, valacyclovir represents a more efficient way of getting acyclovir into the body. Following conversion of valacyclovir to acyclovir, the kinetics are the same as if acyclovir itself had been given.

Adverse Effects. In some immunocompromised patients, valacyclovir has produced a syndrome known as *thrombotic thrombocytopenic purpura/hemolytic uremic syndrome* (TTP/HUS). This syndrome, which can be fatal, has not occurred in immunocompetent patients. Valacyclovir is not approved for use in immunocompromised hosts. Aside from causing TTP/HUS, valacyclovir is generally well tolerated, producing the same side effects seen with oral acyclovir (eg, nausea, vomiting, diarrhea, headache, vertigo).

Preparations, Dosage, and Administration. Valacyclovir [Valtrex] is available in 500- and 1000-mg oral capsules. Dosing may be done without regard to meals. In patients with renal impairment, dosages should be reduced.

For patients with *herpes zoster*, the recommended dosage is 1000 mg 3 times a day for 7 days. Therapy should begin as soon as possible after symptom onset.

For patients with *herpes simplex genitalis*, the dosage is 1 gm twice daily for 10 days (for the initial episode), 500 mg twice daily for 3 days (for episodic recurrences), and 500 to 1000 mg once daily (for long-term suppression).

For patients with *herpes labialis*, the dosage is 2 gm twice, taken 12 hours apart. Dosing should begin as soon as possible after onset of symptoms.

Famciclovir

Famciclovir [Famvir] is a prodrug used to treat acute herpes zoster and genital herpes infection. Benefits are equivalent to those of acyclovir. Adverse effects are minimal.

Pharmacokinetics. Famciclovir undergoes rapid absorption from the GI tract followed by enzymatic conversion to *penciclovir*, its active form. Food decreases the rate of famciclovir absorption but not the extent. As a result, the amount of penciclovir produced is the same whether famciclovir is taken with or without food. Penciclovir is excreted in the urine, largely unchanged. The *plasma* half-life of penciclovir is about 2.5 hours. However, the half-life of penciclovir *within cells* is much longer. In patients with renal impairment, the plasma half-life of penciclovir is prolonged.

Mechanism of Action and Antiviral Spectrum. Penciclovir undergoes intracellular conversion to penciclovir triphosphate, a compound that inhibits viral DNA polymerase, and thereby prevents replication of viral DNA. Under clinical conditions, formation of penciclovir triphosphate requires viral thymidine kinase. As a result, inhibition of DNA synthesis is limited to cells that are infected, leaving the vast majority of host cells unharmed. *In vitro*, penciclovir is active against HSV type 1 (HSV-1), HSV-2, and VZV.

Therapeutic Use. Famciclovir is approved for treatment of acute herpes zoster (shingles) and herpes simplex genitalis. In patients with herpes zoster, the drug can decrease the time to full crusting from 7 days down to 5 days. Famciclovir does not decrease the *incidence* of postherpetic neuralgia, but can decrease the *duration* (from 112 days down to 61 days). In a trial comparing famciclovir with acyclovir, both drugs had equivalent effects against herpes zoster.

In patients with genital herpes simplex infection, famciclovir is active against the first episode and recurrent episodes. In addition, it can be used for long-term suppression.

Adverse Effects. Famciclovir is very well tolerated. In clinical trials, the incidence of side effects was the same as with placebo. Safety for use during pregnancy or breast-feeding and in children under the age of 18 has not been established.

Preparations, Dosage, and Administration. Preparations. Famciclovir [Famvir] is supplied in tablets (125, 250, and 500 mg) for oral dosing, with or without food.

Acute Herpes Zoster. The recommended dosage is 500 mg every 8 hours for 7 days. Treatment should start no later than 72 hours after symptom onset. In patients with renal impairment, the interval between doses should be increased to 12 hours or 24 hours, depending on the degree of impairment.

Herpes Simplex Genitalis. For initial episodes, the dosage is 250 mg 3 times a day for 5 to 10 days. For episodic recurrence, the dosage is 125 mg twice a day for 5 days (or two 1000-mg doses 12 hours apart). For long-term suppression, the dosage is 250 mg twice daily.

Topical Drugs for Herpes Labialis

We have three topical drugs for recurrent herpes labialis (cold sores). Two of these drugs—penciclovir and docosanol—are discussed below. The third drug—acyclovir—is discussed above.

Penciclovir Cream

Penciclovir [Denavir] is a topical drug indicated for recurrent herpes labialis, an infection caused by HSV-1 and HSV-2. The drug suppresses viral replication by inhibiting DNA polymerase, the enzyme that makes DNA. Penciclovir is supplied as a 1% cream to be applied every 2 hours (except when sleeping) for 4 days. In clinical trials, benefits were modest: The average time to healing and duration of pain were decreased by just half a day, from 5 days down to 4.5 days. The only common adverse effect is mild local erythema.

Docosanol Cream

Docosanol [Abreva] is a topical preparation indicated for recurrent herpes labialis. The drug is available over the counter as a 10% cream. Application is done 5 times a day, beginning at the first sign of recurrence. Benefits are modest. In one trial, treatment reduced the time to healing from 4.8 days down to 4.1 days—about the same response seen with penciclovir. Docosanol cream appears devoid of adverse effects.

Docosanol has a broad antiviral spectrum and a unique mechanism of action. Unlike penciclovir, which inhibits viral DNA synthesis (and thereby suppresses replication), docosanol blocks viral entry into host cells. The drug does not kill viruses and does not prevent them from binding to cells. As a result, viable virions can remain attached to the cell surface for a long time. Because docosanol does not affect processes of replication, it is unlikely to promote resistance.

Topical Drugs for Ocular Herpes Infections

Trifluridine Ophthalmic Solution

Trifluridine [Viroptic] is indicated only for topical treatment of ocular infections caused by HSV-1 and HSV-2. The drug is given to treat acute keratoconjunctivitis and recurrent epithelial keratitis. Antiviral actions result from inhibiting DNA synthesis. The most common side effects are localized burning and stinging. Edema of the eyelid occurs in about 3% of patients. Systemic absorption is minimal following topical administration, and hence the drug is devoid of systemic toxicity. Trifluridine is supplied as a 1% ophthalmic solution. Treatment consists of placing 1 drop on the cornea every 2 hours while the patient is awake, for a maximum of 9 drops/day. Once re-epithelialization of the cornea has occurred, the dosage is reduced to 1 drop every 4 hours. Treatment continues for 7 days.

Vidarabine Ointment

Topical vidarabine [Vira-A] is indicated for acute keratoconjunctivitis and recurrent epithelial keratitis caused by HSV-1 and HSV-2. Antiviral effects result from inhibition of viral DNA polymerase and from premature termination of the growing viral DNA chain. The most frequent side effects are burning sensations, photophobia, and lacrimation. Absorption of topical vidarabine is insignificant, and systemic toxicity has not been reported. Vidarabine is available in a 3% ointment for application to the eye. About one-half inch of ointment is administered into the lower conjunctival sac 5 times a day at 3-hour intervals. As a rule, treatment lasts for no more than 3 weeks.

Ganciclovir Gel

Ganciclovir 0.15% ophthalmic gel [Zirgan] is indicated for acute herpetic keratitis (inflammation and ulceration of the cornea caused by infection with a herpes simplex virus). As discussed below (under *Ganciclovir*), benefits derive from suppressing viral replication. Principal adverse effects are blurred vision (60%), eye irritation (20%), and red eyes (5%). Systemic effects are absent. The recommended dosage is 1 drop in the affected eye 5 times a day until symptoms abate, followed by 1 drop 3 times a day for 7 days. Instruct patients to apply drops directly to the affected eye, and to avoid contact lenses until lesions heal.

DRUGS FOR CYTOMEGALOVIRUS INFECTION

Cytomegalovirus (CMV) is a member of the herpesvirus group, which includes herpes simplex virus types 1 and 2, varicella-zoster virus (the cause of chickenpox), and Epstein-Barr virus (the cause of infectious mononucleosis).

Transmission of CMV occurs person to person—through direct contact with saliva, urine, blood, tears, breast milk, semen, and other body fluids. Infection can also be acquired by way of blood transfusion or organ transplantation. Infection with CMV is very common: Between 50% and 85% of Americans age 40 and older harbor the virus. After the initial infection, which has minimal symptoms in healthy people, the virus remains dormant within cells for life, without causing detectable injury or clinical illness. Hence, for most healthy people, CMV infection is of little concern. By contrast, people who are immunocompromised—owing to HIV infection, cancer chemotherapy, or use of immunosuppressive drugs—are at high risk of serious morbidity and even death, both from initial CMV infection and from reactivation of dormant CMV. Common sites for infection are the lungs, eyes, and GI tract. Among people with AIDS, CMV retinitis is the principal reason for loss of vision (see Chapter 94). The four drugs used against CMV are discussed below.

Ganciclovir

Ganciclovir [Cytovene, Vitrasert, Zirgan] is a synthetic antiviral agent with activity against herpesviruses, including CMV. Because the drug can cause serious adverse effects, especially granulocytopenia and thrombocytopenia, it should be used only for prevention and treatment of CMV infection in the immunocompromised host.

Mechanism of Action. Ganciclovir is converted to its active form, ganciclovir triphosphate, inside infected cells. As ganciclovir triphosphate, it suppresses replication of viral DNA by (1) inhibiting viral DNA polymerase and (2) undergoing incorporation into the growing DNA chain, which causes premature chain termination.

Pharmacokinetics. Bioavailability of oral ganciclovir is low: only 5% under fasting conditions and 9% when taken with food. Once in the blood, the drug is widely distributed to body fluids and tissues. Ganciclovir is excreted unchanged in the urine. In patients with normal renal function, the half-life is about 3 hours. In patients with renal impairment, the half-life is prolonged. Accordingly, dosages should be reduced in patients with kidney disease.

Therapeutic Use. Ganciclovir is used only to prevent and treat CMV infection in immunocompromised patients, including those with HIV infection and those receiving immunosuppressive drugs. Specific uses include:

- Treatment of sight-threatening CMV retinitis
- Treatment of CMV pneumonitis
- Treatment of acute CMV colitis
- Prevention of CMV infection in transplant recipients
- Preemptive treatment of patients with CMV antigenemia or viremia

In patients with AIDS, CMV retinitis has an incidence of 15% to 40%. Although most AIDS patients respond initially, the relapse rate is high. Accordingly, for most patients, maintenance therapy should continue indefinitely. The risk of relapse is higher with oral ganciclovir than with IV ganciclovir. Since viral resistance can develop during treatment, this possibility should be considered if the patient responds poorly.

Adverse Effects. Granulocytopenia and Thrombocytopenia. The adverse effect of greatest concern is bone marrow suppression, which can result in granulocytopenia (40%) and thrombocytopenia (20%). These effects, which are usually reversible, are more likely with IV therapy than with oral therapy. These hematologic responses can be exacerbated by concurrent therapy with zidovudine. Conversely, granulocytopenia can be reduced with granulocyte colony-stimulating factors (see Chapter 56). Because of the risk of adverse hematologic effects, blood cell counts must be monitored. Treatment should be interrupted if the absolute neutrophil count falls below $500/\text{mm}^3$ or if the platelet count falls below $25,000/\text{mm}^3$. Cell counts usually begin to recover within 3 to 5 days. Ganciclovir should be used with caution in patients with pre-existing cytopenias, in those with a history of cytopenic reactions to other drugs, and in those taking other bone marrow suppressants (eg, zidovudine, trimetrexate).

Reproductive Toxicity. Ganciclovir is teratogenic and embryotoxic in laboratory animals and probably in humans. Women should be advised to avoid pregnancy during therapy and for 90 days after ending treatment. At doses equivalent to those used therapeutically, ganciclovir inhibits spermatogenesis in mice; sterility is reversible with low doses and irreversible with high doses. Female infertility may also occur. Patients should be forewarned of these effects.

Other Adverse Effects. Incidental effects include nausea, fever, rash, anemia, liver dysfunction, and confusion and other central nervous system (CNS) symptoms. In mice, very high doses (1000 mg/kg) have caused cancer.

Preparations, Dosage, and Administration. Intravenous. Ganciclovir [Cytovene] is available as a powder (500 mg) to be reconstituted for IV infusion. Solutions are alkaline and must be infused into a freely flowing vein to avoid local injury. For treatment of CMV retinitis, the *initial dosage* for adults with normal renal function is 5 mg/kg (infused over 1 hour) every 12 hours for 14 to 21 days. Two *maintenance dosages* can be used: (1) 5 mg/kg infused over 1 hour once every day of the week or (2) 6 mg/kg infused over 1 hour once a day, 5 days a week. Dosages must be reduced for patients with renal impairment. Since many patients with AIDS must continue maintenance therapy for life, they need a permanent IV line and equipment for home infusion. Adequate hydration must be maintained in all patients to ensure renal excretion of ganciclovir.

Oral. Ganciclovir is supplied in 250- and 500-mg tablets for maintenance therapy in patients with CMV retinitis. The usual dosage is 1000 mg 3 times daily with food.

Ocular Implant. The ganciclovir ocular implant [Vitrasert] is indicated for CMV retinitis in patients with AIDS. Surgical implantation, which takes about 1 hour, is performed under local anesthesia on an outpatient basis. Vision is usually blurred for 2 to 4 weeks after the procedure. The implant must be replaced every 5 to 8 months. Clinical trials indicate that CMV retinitis progresses more slowly in patients who receive intraocular ganciclovir compared with those on IV ganciclovir.

Ocular Gel. As discussed above (under *Topical Drugs for Ocular Herpes Infections*), ganciclovir is available in a 0.15% gel, marketed as Zirgan, for treating herpetic keratitis.

Valganciclovir

Basic and Clinical Pharmacology. Valganciclovir [Valcyte] is a prodrug version of ganciclovir [Cytovene] with greater oral bioavailability (60% vs. 9%). Following absorption from the GI tract, valganciclovir is rapidly metabolized to ganciclovir, its active form—and eventually undergoes excretion as unchanged ganciclovir in the urine. Indications are CMV retinitis and prevention of CMV disease in high-risk organ transplant recipients. In patients with active CMV retinitis, oral valganciclovir is just as effective as intravenous ganciclovir—and much more convenient. In addition to its use

against CMV, valganciclovir has been used off-label to reduce transmission of genital herpes (see Chapter 95).

Adverse effects are the same as with ganciclovir. The principal concern is blood dyscrasias—granulocytopenia (27%), anemia (26%), and thrombocytopenia (6%)—secondary to bone marrow suppression. In addition, valganciclovir frequently causes diarrhea (41%), nausea (30%), vomiting (21%), fever (31%), and headache (22%). Valganciclovir is presumed to pose the same risks of mutagenesis, aspermatogenesis, and carcinogenesis as ganciclovir.

Preparations, Dosage, and Administration. Valganciclovir [Valcyte] is available in (1) 450-mg tablets and (2) a powder that makes a 50-mg/mL oral solution when reconstituted with 91 mL of purified water. All doses should be taken with food to enhance bioavailability.

For treatment of CMV retinitis, the adult dosage is 900 mg twice daily for 21 days, followed by 900 mg once daily for maintenance. Dosage must be reduced for patients with renal impairment.

For prevention of CMV disease in transplant recipients, the adult dosage is 900 mg once daily, starting within 10 days of transplantation and continuing until 100 days post-transplantation (or 200 days post-transplantation in kidney recipients).

Because valganciclovir has the potential for mutagenesis and carcinogenesis, the powder and tablets should be handled carefully. Tablets should be ingested intact, without crushing or chewing. Direct contact with the powder or broken tablets should be avoided. If contact does occur, the area should be washed with soap and water. When handling or disposing of the drug, health-care workers should follow the same guidelines established for cytotoxic anticancer drugs.

Cidofovir

Cidofovir [Vistide] is an IV drug with just one indication: CMV retinitis in patients with AIDS who have failed on ganciclovir or foscarnet. Alternative drugs for this infection are foscarnet, which is given IV, and ganciclovir, which may be administered IV, PO, or by ocular insert. Compared with IV foscarnet or IV ganciclovir, cidofovir has the distinct advantage of needing fewer infusions: Whereas foscarnet and ganciclovir must be infused daily, cidofovir is infused just once a week or every other week. The major adverse effect of the drug is kidney damage.

Mechanism of Action. Once inside cells, cidofovir is converted to cidofovir diphosphate, its active form. As the diphosphate, cidofovir causes selective inhibition of viral DNA polymerase, and thereby inhibits viral DNA synthesis. Intracellular concentrations of cidofovir diphosphate are too low to inhibit human DNA polymerases. Hence, host cells are spared.

Antiviral Spectrum and Therapeutic Use. Cidofovir is active against herpesviruses, including CMV, HSV-1, HSV-2, and VZV. However, the drug is approved only for CMV retinitis in patients with AIDS. Whether cidofovir is active against CMV infections in other patients or at other sites (eg, GI tract, lungs) is unknown. In clinical trials in patients with AIDS and established CMV retinitis, cidofovir significantly delayed progression of retinitis.

Pharmacokinetics. Cidofovir is administered by IV infusion and undergoes excretion by the kidneys. Probenecid competes with cidofovir for renal tubular secretion, and thereby delays elimination. Cidofovir has a prolonged intracellular half-life (17 to 65 hours), and hence a long interval (2 weeks) can separate doses. In contrast, IV foscarnet and ganciclovir must be infused daily.

Adverse Effects. Nephrotoxicity. The principal adverse effect is dose-dependent nephrotoxicity, manifesting as decreased renal function and symptoms of a Fanconi-like syndrome (proteinuria, glucosuria, bicarbonate wasting). To reduce the risk of renal injury, all patients must receive probenecid and IV hydration therapy with each infusion. Also, serum creatinine and urine protein should be checked within 48 hours prior to each dose and, if these values indicate kidney damage, cidofovir should be withheld or the dosage reduced. Cidofovir is contraindicated for patients taking other drugs that can injure the kidney, and for patients with proteinuria (2+ or greater) or baseline serum creatinine greater than 1.5 mg/dL.

Other Adverse Effects. Neutropenia develops in about 20% of patients, and hence neutrophil counts should be monitored. Ocular disorders—iritis, uveitis, or ocular hypotony (low intraocular pressure)—can also occur. In animal studies, cidofovir was carcinogenic and teratogenic, and caused hypospemia. Adverse effects are more likely in patients taking antiretroviral drugs (ie, drugs for HIV).

Preparations, Dosage, and Administration. Cidofovir [Vistide] is supplied in solution (75 mg/mL) in 5-mL ampules. To reduce the risk of renal injury, cidofovir infusions must be accompanied by IV hydration therapy and (4) probenecid.

Each cidofovir dose—for induction or maintenance—consists of 5 mg/kg infused IV over 1 hour. For induction, two doses are given 1 week apart. For maintenance, one dose is given every 2 weeks. The size of each dose must be reduced for patients with renal impairment. If impairment is severe, cidofovir should be withheld.

Oral probenecid must accompany each infusion. The dosage is 2 gm given 3 hours before the infusion, 1 gm given 1 hour after the infusion, and another 1 gm given 8 hours after that. Ingesting food before each dose can decrease probenecid-induced nausea and vomiting. An antiemetic may also be used.

Hydration is accomplished by infusing 1 L of 0.9% saline solution over 1 to 2 hours immediately before infusing cidofovir. For patients who can tolerate it, 1 L more can be infused over 1 to 3 hours, beginning when the cidofovir infusion begins or as soon as it is over.

Foscarnet

Foscarnet, formerly available as *Foscavir*, is an IV drug active against all known herpesviruses, including CMV, HSV-1, HSV-2, and VZV. Compared with ganciclovir, foscarnet is more difficult to administer, less well tolerated, and much more expensive (the cost to the pharmacy is about \$20,000 a year). The major adverse effect is renal injury.

Mechanism of Action. Foscarnet, an analog of pyrophosphate, inhibits viral DNA polymerases and reverse transcriptases, and thereby inhibits synthesis of viral nucleic acids. At the concentrations achieved clinically, the drug does not inhibit host DNA replication. Unlike many other antiviral drugs, which must undergo conversion to an active form, foscarnet is active as administered.

Therapeutic Use. Foscarnet has two approved indications: (1) CMV retinitis in patients with AIDS and (2) acyclovir-resistant mucocutaneous HSV and VZV infection in the immunocompromised host. CMV retinitis resistant to ganciclovir may respond to foscarnet.

Pharmacokinetics. Foscarnet has low oral bioavailability and must be administered IV. The drug is poorly soluble in water and does not penetrate cells easily. As a result, it must be given in large doses with large volumes of fluid. Between 10% and 28% of each dose is deposited in bone; the remainder is excreted unchanged in the urine. Because foscarnet is eliminated by the kidneys, dosages must be reduced in patients with renal impairment. The plasma half-life is 3 to 5 hours.

Adverse Effects and Interactions. In general, foscarnet is less well tolerated than ganciclovir. However, unlike ganciclovir, foscarnet does not cause granulocytopenia or thrombocytopenia.

Nephrotoxicity. Renal injury, as evidenced by a rise in serum creatinine, is the most common dose-limiting toxicity. Most patients develop some degree of renal impairment. Renal injury occurs most often during the second week of therapy. The risk of nephrotoxicity is increased by concurrent use of other nephrotoxic drugs, including amphotericin B, aminoglycosides (eg, gentamicin), and pentamidine. Prehydration with IV saline may reduce the risk of renal injury. Renal function (creatinine clearance) should be monitored closely and the dosage should be reduced if renal impairment develops.

Electrolyte and Mineral Imbalances. Foscarnet frequently causes hypocalcemia, hypokalemia, hypomagnesemia, and hypo- or hyperphosphatemia. Ionized serum calcium may be reduced despite normal levels of total serum calcium. Patients should be informed about symptoms of low ionized calcium (eg, paresthesias, numbness in the extremities, perioral tingling) and instructed to report these. Severe hypocalcemia can result in dysrhythmias, tetany, and seizures. Serum levels of calcium, magnesium, potassium, and phosphorus should be measured frequently. Special caution is required in patients with pre-existing electrolyte, cardiac, or neurologic abnormalities. The risk of hypocalcemia is increased by concurrent use of pentamidine.

Other Adverse Effects. Common reactions include fever (65%), nausea (47%), anemia (33%), diarrhea (30%), vomiting (26%), and headache (26%). In addition, foscarnet can cause fatigue, tremor, irritability, genital ulceration, abnormal liver function tests, neutropenia, and seizures.

Preparations, Dosage, and Administration. Foscarnet is supplied in solution (24 mg/mL) for IV infusion. An infusion pump is essential to reduce the risk of accidental overdose. Infusions may be administered through a central venous line or a peripheral vein. When a central line is used, a concentrated (24 mg/mL) solution may be given. When a peripheral vein is used, the solution should be diluted to 12 mg/mL. For patients with normal kidney function, the initial dosage is 60 mg/kg (for CMV infection) or 40 mg/kg (for HSV infection) infused over 1 hour (or longer) every 8 hours for 2 to 3 weeks. The maintenance dosage (for CMV or HSV infection) is 90 to 120 mg/kg infused over 2 hours once daily. All dosages must be reduced for patients with renal impairment.

TABLE 93-3 ■ Characteristics of Hepatitis A, Hepatitis B, and Hepatitis C

Point of Comparison	Hepatitis A	Hepatitis B	Hepatitis C
Causative agent	Hepatitis A virus	Hepatitis B virus	Hepatitis C virus
Percent of Americans ever infected	29–34	4.3–5.6	1.3–1.9
Percent of infections that become chronic	0	3–5	Over 70
New acute infections in the United States (2009)	21,000	38,000	16,000
U.S. residents with chronic infection	None	0.8–1.4 million	2.7–3.9 million
Annual deaths in the United States from chronic infection	None	1800	15,000
People worldwide with chronic infection	None	350 million	170 million
Method of prevention	Hepatitis A vaccine	Hepatitis B vaccine	None available
Preferred treatment	None	Interferon alfa <i>or</i> lamivudine	Peginterferon alfa <i>plus</i> ribavirin <i>plus</i> either boceprevir <i>or</i> telaprevir

DRUGS FOR HEPATITIS

Viral hepatitis is the most common liver disorder, affecting millions of Americans. The disease can be caused by six different hepatitis viruses, labeled A, B, C, D, E, and G. All six can cause *acute* hepatitis, but only B, C, and D also cause *chronic* hepatitis. Acute hepatitis lasts for 6 months or less and is characterized by liver inflammation, jaundice, and elevation of serum alanine aminotransferase (ALT) activity. In most cases, acute hepatitis resolves spontaneously, and hence intervention is generally unnecessary. In contrast, chronic hepatitis can lead to cirrhosis, hepatocellular carcinoma, and life-threatening liver failure, and hence treatment should be considered.

Most cases (90%) of chronic hepatitis are caused by either hepatitis B virus (HBV) or hepatitis C virus (HCV). Accordingly, our discussion focuses on hepatitis B and hepatitis C. About 1.5% of Americans are infected with HBV or HCV, which is 5 times more than the number infected with HIV. Comparisons between hepatitis A, B, and C are summarized in Table 93-3. Vaccines for hepatitis A and B are discussed in Chapter 68. Drugs for hepatitis B and C are discussed below.

HEPATITIS C

About 2.7 million Americans have chronic hepatitis C. Transmission occurs primarily through exchange of blood. Whether sexual transmission occurs is controversial. Furthermore, if sexual transmission *does* occur, the risk of transmission between monogamous heterosexual partners is extremely low. Among people who acquire HCV, 75% to 85% develop active infection. However, most people with chronic hepatitis C have

no symptoms, although they can transmit HCV to others. Chronic HCV infection undergoes slow progression, and, in some people, eventually causes liver failure, cancer, and death. Chronic hepatitis C is the leading reason for liver transplantations, and kills about 15,000 Americans each year—more than are killed by HIV. Currently, treatment is recommended only for patients with HCV viremia, persistent elevation of ALT, and evidence of hepatic fibrosis and inflammation upon liver biopsy. For years, dual therapy with *pegylated interferon alfa (peginterferon alfa) plus ribavirin* has been the treatment of choice for chronic hepatitis C. However, adding a protease inhibitor—either boceprevir or telaprevir—greatly improves outcomes, and hence triple therapy—*peginterferon alfa plus ribavirin plus either boceprevir or telaprevir*—is likely to become the new standard of care. There is no vaccine for hepatitis C.

It is important to note that not all hepatitis C viruses are the same. There are 6 genotypes of HCV, and more than 50 subtypes. In the United States, 75% of HCV infections are caused by HCV genotype 1, which, unfortunately, is less responsive to treatment than other HCV genotypes. Before drug therapy is initiated, HCV genotype should be determined.

Interferon Alfa

Human interferons are naturally occurring compounds with complex antiviral, immunomodulatory, and antineoplastic actions. The interferon family has three major classes, designated alpha, beta, and gamma. All of the interferons used for hepatitis belong to the alpha class (Table 93-4). In the discussion below, these compounds are referred to collectively as *interferon alfa*. None of these agents can be used orally, and hence administration is parenteral—almost always subQ. Commercial production is by recombinant DNA technology.

TABLE 93-4 ■ Interferon Alfa Preparations: Dosages for Chronic Hepatitis B and Hepatitis C

Generic Name	Trade Name	Adult Dosage	
		Chronic Hepatitis B	Chronic Hepatitis C
Conventional Interferon Alfa Preparations			
Interferon alfa-2b	Intron A	5 million IU subQ daily or 10 million IU subQ 3 times/wk	3 million IU subQ or IM 3 times/wk
Interferon alfacon-1	Infergen	(not used)	<i>Monotherapy:</i> 9 mcg subQ 3 times/wk <i>With ribavirin:</i> 15 mcg subQ daily
Long-Acting Interferon Alfa Preparations			
Peginterferon alfa-2a	Pegasys	180 mcg subQ once/wk	180 mcg subQ once/wk
Peginterferon alfa-2b*	PegIntron, Unitron PEG ♦	(not used)	<i>Monotherapy:</i> 1 mcg/kg subQ once/wk <i>With ribavirin:</i> 1.5 mcg/kg subQ once/wk

IU = international units.

*Peginterferon alfa-2b is also marketed as *Sylatron* for treatment of melanoma.

Mechanism of Action. Interferon alfa has multiple effects on the viral replication cycle. After binding to receptors on host cell membranes, the drug blocks viral entry into cells, synthesis of viral messenger RNA and viral proteins, and viral assembly and release.

Conventional Versus Long-Acting Interferons. The alfa interferons can be divided into two groups—conventional and long acting—based on their time course of action (see Table 93-4). The conventional preparations have short half-lives, and hence must be administered frequently—at least 3 times a week. In contrast, the long-acting preparations are administered less frequently—just once a week—making them more convenient. In addition, with the long-acting preparations, blood levels remain high between doses, and hence clinical responses are better.

How are long-acting interferons made? By conjugating a conventional interferon (eg, interferon alfa-2b) with polyethylene glycol (PEG), in a process known as *pegylation*. Therapeutic effects of the pegylated product are due solely to its interferon component. The PEG component serves only to delay elimination. At this time, two long-acting interferons are available: *pegylated interferon (peginterferon) alfa-2a* [Pegasys] and *peginterferon alfa-2b* [PegIntron, Unitron PEG ♦].* Because of their convenience and superior efficacy, these products are preferred to conventional interferons. However, please note that several side effects—*injection-site reactions*, *dose-related neutropenia*, and *thrombocytopenia*—are more common with pegylated interferons than with the conventional formulations.

Effects in Chronic Hepatitis C. In patients with chronic hepatitis C, responses are equally modest with all forms of interferon alfa. After 12 months of treatment, serum ALT normalizes in 40% to 50% of patients, and serum levels of HCV-RNA (a marker for HCV in blood) become undetectable

in 30% to 40%. Unfortunately, about half of these people relapse when treatment is stopped; sustained responses are maintained in only 5% to 15% of patients. As discussed below, combining interferon alfa with ribavirin, with or without a protease inhibitor, can improve response rates.

Adverse Effects. All formulations of interferon alfa produce the same spectrum of adverse effects, some of which can be life threatening. The incidence is higher with the long-acting preparations.

The most common side effect is a *flu-like syndrome* characterized by fever, fatigue, myalgia, headache, and chills. The incidence is about 50%. Fortunately, symptoms tend to diminish with continued therapy. Some symptoms (fever, headache, myalgia) can be reduced with acetaminophen.

Interferon alfa frequently causes *neuropsychiatric effects*—especially *depression*. Suicidal ideation and suicide have occurred. The risk of depression is increased by large doses and prolonged treatment. The mechanism underlying depression is unknown. In many patients, depression responds to antidepressant drugs (eg, paroxetine). If depression persists, a reduction in dosage or cessation of treatment is indicated.

Prolonged or high-dose therapy can cause fatigue, thyroid dysfunction, heart damage, and bone marrow suppression, manifesting as neutropenia and thrombocytopenia.

Other adverse effects include alopecia and GI effects: nausea, diarrhea, anorexia, and vomiting. Injection-site reactions (inflammation, bruising, itching, irritation) are common, especially with long-acting formulations. Also, interferon may induce or exacerbate autoimmune diseases, such as thyroiditis and autoimmune chronic hepatitis.

Ribavirin (Oral)

Actions and Therapeutic Use. Oral ribavirin [Rebetol, Ribasphere, Copegus], combined with subQ peginterferon alfa, is the traditional treatment of choice for HCV infection.

*Peginterferon alfa-2b is also marketed as *Sylatron* for treatment of melanoma.

When used alone against HCV, ribavirin is not effective: Treatment produces a transient normalization of serum ALT, but does not reduce serum HCV-RNA. Combining ribavirin with interferon alfa greatly improves response rates. Ribavirin is a nucleoside analog with a broad spectrum of antiviral activity—but, its mechanism of action remains unclear.

In addition to its use against HCV, ribavirin is available as an aerosol for treating children infected with respiratory syncytial virus. This use is discussed below under *Ribavirin (Inhaled)*.

Pharmacokinetics. Ribavirin is well absorbed following oral administration. In plasma, the drug does not undergo protein binding. After leaving the vasculature, ribavirin is readily taken up by cells. Perhaps because of this cellular sequestration, ribavirin has a prolonged half-life, estimated at 6 to 12 days. As a result, when dosing stops, it can take weeks to clear the drug from the body.

Clinical Trials. The objective of hepatitis C therapy is to elicit a sustained virologic response (SVR), defined as loss of detectable serum HCV-RNA that persists for at least 6 months after treatment. By this criterion, treatment with ribavirin plus conventional interferon alfa for 24 to 48 weeks produces an SVR in 30% to 40% of previously untreated patients. In trials using peginterferon alfa, response rates were even higher. For example, in one trial, the response rate was 68% with peginterferon alfa plus ribavirin versus only 51% with conventional interferon alfa plus ribavirin. As discussed below, adding a protease inhibitor to the regimen produces an even greater SVR.

Adverse Effects. Although ribavirin and interferon alfa are generally well tolerated, both drugs can cause significant adverse effects. As noted above, interferon alfa frequently causes *flu-like symptoms*, and occasionally causes *severe depression*. The principal concerns with ribavirin are *hemolytic anemia* and *fetal injury*.

Hemolytic Anemia. Hemolytic anemia, characterized by a hemoglobin (Hb) level below 10 gm/dL, develops in 10% to 13% of patients receiving dual therapy with ribavirin/interferon alfa. Onset is typically 1 to 2 weeks after starting treatment. Hemolytic anemia can worsen heart disease, and may lead to nonfatal or fatal myocardial infarction. Owing to the risk of anemia, ribavirin should be avoided in patients with significant heart disease and in those with hemoglobinopathies, including sickle cell anemia and thalassemia major. Because anemia can develop rapidly, Hb determinations should be made before treatment, 2 weeks and 4 weeks into treatment, and periodically thereafter.

Fetal Injury. Ribavirin is both embryo-lethal and teratogenic. In laboratory animals, the drug has caused fetal death as well as malformations of the skull, palate, eyes, jaw, limbs, GI tract, and skeleton—all at doses as low as one-twentieth of those used to treat humans. Accordingly, *ribavirin is classified in Food and Drug Administration (FDA) Pregnancy Risk Category X, and therefore is contraindicated for use during pregnancy*. Pregnancy must be ruled out before starting ribavirin. Also, pregnancy testing must be done every month during treatment and for 6 months after treatment stops. To avoid pregnancy, couples should use *two* reliable forms of birth control during treatment and for 6 months after stopping. Furthermore, if ribavirin is used in conjunction with a *protease inhibitor*, hormonal contraceptives may not work, and

hence two *barrier* contraceptives should be used, as discussed below under *Protease Inhibitors*.

Among men being treated, ribavirin can be present in sperm. At this time, we don't know if ribavirin-containing sperm will be teratogenic upon fertilizing an ovum. Until more is known, prudence dictates that couples avoid pregnancy if the male partner is receiving ribavirin.

Other Adverse Effects. In addition to flu-like symptoms, depression, anemia, and birth defects, ribavirin/interferon alfa can cause many other adverse effects. Among these are autoimmune disorders, infections, pancreatitis, neutropenia, and injury to the eyes and lungs.

Preparations, Dosage, and Administration. For treatment of chronic hepatitis C, ribavirin *must be combined with interferon alfa*; the drug is not effective when used alone. For combined therapy, peginterferon alfa is preferred to conventional interferon alfa. Duration of therapy is prolonged, typically 24 to 48 weeks.

Preparations. Ribavirin is available (1) in 200-mg capsules marketed as *Rebetol* and *Ribasphere*; (2) in tablets (200, 400, and 600 mg), marketed as *Copegus* and *Ribasphere*; and (3) an oral solution (40 mg/mL), marketed as *Rebetol*.

Dosage for Ribasphere Capsules, Rebetol Oral Solution, and Rebetol Capsules (Combined with Interferon Alfa-2b). Administration is PO, and dosage depends on patient weight. For patients weighing 75 kg or less, the dosage is 1000 mg/day (400 mg in the morning and 600 mg in the evening). For patients weighing more than 75 kg, the dosage is 1200 mg/day (600 mg in the morning and 600 mg in the evening).

Dosage for Copegus Tablets and Ribasphere Tablets (Combined with Peginterferon Alfa-2a). Dosing is done PO with food. Dosage depends on patient weight and the strain (genotype) of the hepatitis C virus.

- **For Genotype 1 or 4.** For patients weighing 75 kg or less, the dosage is 1000 mg/day (400 mg in the morning and 600 mg in the evening). For patients weighing more than 75 kg, the dosage is 1200 mg/day (600 mg in the morning and 600 mg in the evening).
- **For Genotype 2 or 3.** For all patients, regardless of weight, the dosage is 800 mg/day (400 mg in the morning and 400 mg in the evening).

Dosage for Interferon Alfa Used with Ribavirin. Dosage of interferon alfa depends on the specific preparation employed. For example, the dosage for peginterferon alfa-2a [Pegasys] is 180 mcg subQ once a week, and the dosage for peginterferon alfa-2b [PegIntron, Unitron PEG \blacklozenge] is 1.5 mcg/kg subQ once a week.

Protease Inhibitors: Boceprevir and Telaprevir

In 2011, the FDA approved two protease inhibitors—boceprevir and telaprevir—for treatment of chronic hepatitis C, making them the first new drugs for hepatitis C in 20 years. Both drugs inhibit viral protease, an enzyme required for HCV replication. When combined with peginterferon alfa plus ribavirin, these drugs greatly enhance antiviral effects. As a result, triple therapy with a protease inhibitor plus peginterferon alfa plus ribavirin is likely to replace dual therapy with peginterferon alfa/ribavirin as the standard of care for HCV infection. However, despite their efficacy, the protease inhibitors do have drawbacks: Both drugs are expensive, and both can be difficult to use, owing to adverse effects and extensive drug interactions.

Boceprevir

Therapeutic Use. Boceprevir [Victrelis] is indicated for chronic hepatitis C caused by genotype 1 HCV in adults with compensated (stable) liver disease. The drug must always be used in conjunction with peginterferon alfa and ribavirin. It must never be used alone.

Triple therapy with boceprevir/peginterferon alfa/ribavirin is much more effective than traditional dual therapy with interferon alfa/ribavirin. In a trial known as SPRINT-2, boceprevir triple therapy was compared with dual therapy in previously untreated patients, some of whom were black and some of whom were nonblack. The result? Among the black patients, an SVR was obtained in 47% of those receiving triple therapy, compared with only 23% of those receiving dual therapy. Results were even more dramatic among the non-black patients: An SVR was obtained in 68% of those receiving triple therapy compared with only 40% of those receiving dual therapy.

The benefits of boceprevir triple therapy are especially dramatic in previously treated patients who failed to respond to dual therapy. For example, in the RESPOND-2 trial, which enrolled 403 patients who had failed with dual therapy, an SVR was obtained in 59% to 66% of those given boceprevir triple therapy, compared with only 21% of those re-treated with dual therapy.

Mechanism of Action. Boceprevir inhibits a protease specific to HCV (NS3/4A serine protease), and thereby arrests HCV replication. As discussed in Chapter 94, viral proteases act during the replication cycle to cleave large polypeptides into their smaller, functional forms. Hence, by inhibiting protease activity, boceprevir prevents replicating HCV from progressing to its mature, infectious state.

Pharmacokinetics. Boceprevir is administered orally, and plasma levels peak about 2 hours after dosing. Any food, be it low fat or high fat, increases absorption by about 65%. Boceprevir undergoes metabolism in the liver—partly by CYP3A4 (the 3A4 isozyme of cytochrome P450) and partly by other pathways—followed by excretion in the feces. The half-life is 3.4 hours.

Adverse Effects. Among patients receiving triple therapy with boceprevir/interferon alfa/ribavirin, the most common adverse effects are fatigue (57%), nausea (45%), altered taste (40%), chills (34%), insomnia (32%), vomiting (18%), anemia (47%), and neutropenia (19%). Anemia and neutropenia are significantly more common than when peginterferon/ribavirin are used without boceprevir. To monitor for hematologic effects, complete blood counts should be obtained at baseline, and then at weeks 4, 8, and 12 of treatment.

Effect in Pregnancy. Boceprevir alone is safe during pregnancy (FDA Pregnancy Risk Category B). However, the drug is not used alone. Rather, it is always combined with ribavirin (a teratogenic, embryolethal drug) plus peginterferon. The triple combination—ribavirin, peginterferon, and boceprevir—is very dangerous to the fetus, and classified in FDA Pregnancy Risk Category X. Accordingly, before women use the combination, pregnancy must be ruled out and two effective forms of contraception must be implemented. Furthermore, because the triple combination can render hormonal contraceptives ineffective, two nonhormonal contraceptives should be employed. Options include a copper-T intrauterine device, a diaphragm with spermicidal jelly, a cervical cap with spermicidal jelly, a male condom with spermicidal jelly, and a female condom with spermicidal jelly (but not a male condom combined with a female condom).

Not only is the combination dangerous for women should they become pregnant while using it, it is dangerous for a pregnant woman whose male partner is using it. Accordingly,

the combination is contraindicated for any man whose female partner is pregnant.

Drug Interactions. Boceprevir is subject to many drug interactions. Why? First, boceprevir is both a substrate for and inhibitor of CYP3A4. Hence, drugs that induce or inhibit CYP3A4 can alter levels of boceprevir, and boceprevir can alter levels of drugs that are CYP3A4 substrates. Second, boceprevir inhibits P-glycoprotein, the transporter that pumps drugs out of cells in the intestine, liver, kidney, and other sites (see Chapter 4). By doing so, boceprevir can alter levels of drugs that are P-glycoprotein substrates. Important interactions between boceprevir and other drugs are summarized in Table 93-5.

Preparations, Dosage, and Administration. Boceprevir [Victrelis] is supplied in 200-mg capsules. The usual dosage is 800 mg 3 times a day (every 7 to 9 hours). Instruct patients to take the capsules with a meal or light snack to enhance absorption.

For treatment of chronic hepatitis C, boceprevir must be combined with peginterferon alfa and ribavirin. Treatment begins with 4 weeks of peginterferon plus ribavirin. After that, patients take all three drugs—peginterferon alfa, ribavirin, and boceprevir—for another 24 or 32 weeks, depending on the decline in plasma HCV-RNA, the presence or absence of cirrhosis, and the response to prior treatment. Following treatment with all three drugs, patients who responded slowly should receive 12 more weeks of treatment with two drugs: peginterferon plus ribavirin.

Telaprevir

Actions and Therapeutic Use. Telaprevir [Incivek] has the same mechanism as boceprevir (suppression of HCV replication through inhibition of HCV protease) and the same indication (treatment of genotype 1 chronic hepatitis C in combination with interferon alfa and ribavirin). In clinical trials, triple therapy with telaprevir/interferon alfa/ribavirin was much more effective than dual therapy with interferon alfa/ribavirin. For example, in previously untreated patients, an SVR was seen in 79% of those receiving triple therapy, compared with 46% of those receiving dual therapy. Even more dramatically, in previously treated patients who failed to respond to dual therapy, an SVR was seen in 66% of those receiving triple therapy, compared with only 16% of those receiving dual therapy.

Pharmacokinetics. Administration is oral, and food greatly enhances absorption. Compared with dosing on an empty stomach, dosing with a low-fat meal increases absorption by 117%, and dosing with a high-fat meal increases absorption by 330%. Telaprevir undergoes extensive hepatic metabolism, primarily by CYP3A4, followed by excretion in the feces. At steady state, the half-life is 9 to 11 hours.

Adverse Effects. Among patients receiving triple therapy with telaprevir/interferon alfa/ribavirin, the most common adverse effects are rash (56%), fatigue (56%), itching (47%), nausea (39%), diarrhea (26%), vomiting (13%), hemorrhoids/anorectal discomfort (12%), altered taste (10%), and anemia (36%). Anemia is significantly more common than when peginterferon/ribavirin is used without telaprevir. To monitor for anemia, determine hemoglobin levels at baseline, and then every 4 weeks during treatment. Rash and other skin reactions with the telaprevir combination can be severe, sometimes progressing to Stevens-Johnson syndrome. Advise patients to report any skin changes or itching, but not to discontinue treatment unless the provider says so.

Effect in Pregnancy. Like boceprevir, telaprevir by itself is safe in pregnant women (FDA Pregnancy Risk Category B). However, the triple combination used clinically—telaprevir plus ribavirin plus interferon alfa—is classified in FDA Pregnancy Risk Category X, owing to the presence of ribavirin, a highly teratogenic, embryotoxic drug. Accordingly, before the combination is used, pregnancy must be ruled out, and two nonhormonal forms of contraception must be implemented. (Like the boceprevir triple combination, the telaprevir triple combination can reduce the efficacy of hormonal contraceptives, and hence hormonal contraceptives should be avoided.) As with the boceprevir triple combination, the telaprevir triple combination is contraindicated for any man whose female partner is pregnant (as well as for any women who is pregnant).

Drug Interactions. Like boceprevir, telaprevir interacts with many other drugs. The reasons are largely the same as with boceprevir: Telaprevir is a substrate for and inhibitor of CYP3A4, and also a substrate for and

TABLE 93-5 • Drug Interactions for Boceprevir and Telaprevir

Boceprevir	Telaprevir	Boceprevir	Telaprevir
DRUGS THAT ARE CONTRAINDICATED		DRUGS THAT SHOULD BE USED WITH CAUTION—cont'd	
Antiseizure Drugs		Calcium Channel Blockers	
Carbamazepine Phenobarbital Phenytoin	None contraindicated	<i>Levels increased:</i> Felodipine, nifedipine, nifedipine	<i>Levels increased:</i> Amlodipine, diltiazem, felodipine, nifedipine, nisoldipine, verapamil
Statins		Glucocorticoids	
Lovastatin Simvastatin	Atorvastatin Lovastatin Simvastatin	<i>Boceprevir levels decreased:</i> Dexamethasone (avoid) <i>Levels increased:</i> Budesonide, fluticasone (avoid)	<i>Telaprevir levels decreased:</i> Dexamethasone (avoid) <i>Levels increased:</i> Budesonide, fluticasone, methylprednisolone, prednisone (avoid)
Phosphodiesterase-5 Inhibitors		HIV Protease Inhibitors	
Sildenafil* Tadalafil*	Sildenafil* Tadalafil*	<i>Boceprevir levels decreased:</i> Ritonavir; effect of other protease inhibitors on boceprevir and vice versa unknown	<i>Telaprevir levels decreased:</i> Ritonavir (all ritonavir combinations except atazanavir/ritonavir not recommended)
Ergot Derivatives		HIV Reverse Transcriptase Inhibitors	
Dihydroergotamine Ergonovine Ergotamine Methylergonovine	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	<i>Boceprevir levels decreased:</i> Efavirenz (avoid)	<i>Levels decreased:</i> Efavirenz and telaprevir decrease each other's levels <i>Levels increased:</i> Tenofovir
Benzodiazepines		Immunosuppressants	
Midazolam (oral) Triazolam	Midazolam (oral) Triazolam	<i>Levels increased:</i> Cyclosporine, sirolimus, tacrolimus	<i>Levels increased:</i> Cyclosporine, sirolimus, tacrolimus
Others		Macrolides	
Alfuzosin Cisapride Drospirenone Pimozide Rifampin St. John's wort	Alfuzosin Cisapride Pimozide Rifampin St. John's wort	<i>Levels increased:</i> Clarithromycin (consider clarithromycin dose reduction in renal impairment)	<i>Levels increased:</i> Clarithromycin, erythromycin, telithromycin
DRUGS THAT SHOULD BE USED WITH CAUTION		Opioids	
Antiseizure Drugs		<i>Levels increased or decreased:</i> Buprenorphine, methadone	<i>Levels increased or decreased:</i> Methadone
<i>Boceprevir levels decreased, contraindicated:</i> Carbamazepine, phenobarbital, phenytoin	<i>Telaprevir levels decreased, use caution:</i> Carbamazepine, phenobarbital, phenytoin	Phosphodiesterase-5 Inhibitors	
Antidysrhythmic Drugs		<i>Levels increased:</i> Sildenafil,* tadalafil,* vardenafil	<i>Levels increased:</i> Sildenafil,* tadalafil,* vardenafil
<i>Levels increased:</i> Amiodarone, bepridil, digoxin, flecainide, propafenone, quinidine	<i>Levels increased:</i> Amiodarone, bepridil, digoxin, flecainide, lidocaine (systemic), propafenone, quinidine	Statins	
Antidepressants		<i>Levels increased, use caution:</i> Atorvastatin <i>Levels increased, contraindicated:</i> Lovastatin, simvastatin	<i>Levels increased, contraindicated:</i> Atorvastatin, lovastatin, simvastatin
<i>Levels increased:</i> Desipramine, trazodone	<i>Levels increased:</i> Desipramine, trazodone <i>Levels decreased:</i> Escitalopram	Others	
Azole Antifungals		Bosentan: Levels increased	
<i>Boceprevir and azole levels increased:</i> Itraconazole, ketoconazole, posaconazole, voriconazole	<i>Telaprevir and azole levels increased:</i> Itraconazole, ketoconazole, posaconazole <i>Telaprevir level increased, azole level increased or decreased:</i> Voriconazole	Colchicine: Levels increased	
Benzodiazepines		Ethinyl estradiol: Levels decreased, causing potential contraceptive failure	
<i>Levels increased:</i> Alprazolam, IV midazolam (oral midazolam contraindicated)	<i>Levels increased:</i> Alprazolam, IV midazolam (oral midazolam contraindicated) <i>Levels decreased:</i> Zolpidem	Rifabutin: Boceprevir levels decreased, rifabutin levels increased (avoid)	
		Salmeterol: Levels increased (avoid)	
		Warfarin: INR may increase or decrease	
		INR may increase or decrease	

INR = international normalized ratio.

*Contraindicated at the high dosage used for pulmonary arterial hypertension; use caution at the lower dosage used for erectile dysfunction.

TABLE 93-6 • Drugs for Chronic Hepatitis B

Drug	Route	Relapse Rate*	Adverse Effects	Resistance Rate	Active Against HIV
Interferon Alfa Preparations					
Interferon alfa-2b [Intron A]	SubQ	Moderate	Flu-like symptoms, fatigue, neutropenia, depression	Zero	No
Peginterferon alfa-2a [Pegasys]	SubQ	Moderate	Same as interferon alfa-2b	Zero	No
Nucleoside Analogs					
Lamivudine [Epivir HBV, Heptovir♦]	PO	High	Well tolerated; lactic acidosis and hepatomegaly are possible	15%–30% in yr 1; 70% by yr 5	Yes
Adefovir [Hepsera]	PO	High	Nephrotoxic at high doses; lactic acidosis and hepatomegaly are possible	Zero in yr 1; 29% by yr 5	Yes
Entecavir [Baraclude]	PO	High	Well tolerated; lactic acidosis and hepatomegaly are possible	Zero in yr 1; 1% or less by yr 3	Yes
Tenofovir [Viread]	PO	High	Weakness, headache, GI reactions; lactic acidosis and hepatomegaly are possible	—	Yes
Telbivudine [Tyzeka, Sebivo♦]	PO	Moderate	Myopathy, lactic acidosis, hepatomegaly are possible	6%–12% in yr 1; 9%–22% by yr 2	No

*Following discontinuation of treatment.

inhibitor of P-glycoprotein. Major interactions are summarized in Table 93-5.

Preparations, Dosage, and Administration. Telaprevir [Incivek] is supplied in 375-mg tablets. The usual dosage is 750 mg 3 times a day (every 7 to 9 hours). To enhance absorption, patients should take the tablets with a high-fat meal or snack (eg, bagel with cream cheese, one-half cup nuts, 3 tablespoons peanut butter, 1 cup ice cream, 2 ounces potato chips).

For treatment of chronic hepatitis C, telaprevir *must be combined with peginterferon alfa and ribavirin*. Treatment begins with 12 weeks of all three drugs. After that, patients take two drugs—peginterferon plus ribavirin—for another 12 or 36 weeks, depending on the decline in plasma HCV-RNA and the response to prior treatment.

HEPATITIS B

In the United States, about 1.25 million people have chronic hepatitis B. Transmission is primarily through exchange of blood or semen. Between 45% and 60% of exposed adults develop acute hepatitis. Of these, about 11,000 require hospitalization for deep fatigue, muscle pain, and jaundice. In adults, acute infection usually leads to viral clearance by the immune system. As a result, only 3% to 5% of infected adults develop chronic infection. However, when chronic infection does develop, it can lead to cirrhosis, hepatic failure, hepatocellular carcinoma, and death. The best strategy against HBV is prevention: All children should receive HBV vaccine before entering school (see Chapter 68).

Seven drugs are used for chronic HBV. Two are alfa interferons—*interferon alfa-2b* [Intron A] and *peginterferon alfa-2a* [Pegasys]—and five are nucleoside analogs: *lamivudine* [Epivir HBV, Heptovir♦], *adefovir* [Hepsera], *entecavir* [Baraclude], *telbivudine* [Tyzeka, Sebivo♦], and *tenofovir* [Viread]. The alfa interferons are administered subQ; the nucleoside analogs are administered PO. The interferons are more effective than the nucleoside analogs, but are also more

expensive and less well tolerated. Development of resistance is common with lamivudine and telbivudine, and relatively rare with the other five drugs. Four agents—lamivudine, adefovir, entecavir, and tenofovir—are also active against HIV, and hence may promote emergence of resistant HIV in people co-infected with that virus.

With all seven drugs—and especially the nucleoside analogs—the rate of relapse following cessation of treatment is high. As a result, treatment is usually prolonged, thereby amplifying concerns about adverse effects and drug cost. To decrease unnecessary drug exposure and expense, current guidelines recommend treatment only for patients at highest risk, indicated by elevated aminotransferase levels, or histologic evidence of moderate or severe hepatic inflammation or advanced fibrosis. We do not yet know if treatment should continue lifelong, or if clinical benefit is sustained if treatment is stopped after several years. Given that relapse is common, patients should be followed closely if these drugs are withdrawn. Comparisons between the seven drugs are summarized in Table 93-6.

Interferon Alfa

Only two forms of interferon alfa—*interferon alfa-2b* [Intron A] and *peginterferon alfa-2a* [Pegasys]—are approved for chronic hepatitis B. Both preparations are administered subQ (see Table 93-4). In clinical trials, treatment for 4 months reduced serum ALT and improved liver histology in about 40% of recipients. Remissions have been prolonged in some patients, and resistance has not been reported. Unfortunately, although alfa interferons are effective, they are also expensive, and adverse effects—flu-like syndrome, depression, fatigue, and leukopenia—are common. The basic pharmacology of interferon alfa and its use in hepatitis C are discussed above.

Nucleoside Analogs

Lamivudine

Lamivudine [Epivir HBV, Heptovir[®]] is a nucleoside analog approved for infections caused by HBV or HIV. The drug was originally developed for HIV infection, and was later approved for HBV. Formulations and dosages for treating HIV and HBV infections differ, and hence must not be considered interchangeable. The basic pharmacology of lamivudine is discussed in Chapter 94. Discussion here is limited to treatment of HBV.

Lamivudine suppresses HBV replication by inhibiting viral DNA synthesis. The process begins with intracellular conversion of lamivudine to lamivudine triphosphate, the drug's active form. As the triphosphate, lamivudine undergoes incorporation into the growing DNA chain, and thereby causes premature chain termination.

Lamivudine offers at least some benefit to most patients. In one trial, 52 weeks of daily lamivudine normalized serum ALT in 72% of patients, and reduced liver inflammation and fibrosis in 56%. Unfortunately, the rate of relapse is high when treatment stops. Also, emergence of resistance is a concern: Resistant isolates appear in 24% of patients after 1 year of continuous treatment, 42% after 2 years, 53% after 3 years, and 70% after 4 years.

At the dosage employed to treat hepatitis B, side effects are minimal. In clinical trials, the incidence of most side effects was no greater than with placebo. *Lactic acidosis*, *pancreatitis*, and *severe hepatomegaly* are rare but dangerous complications. If one of these conditions develops, lamivudine should be discontinued.

For treatment of HBV, lamivudine [Epivir HBV, Heptovir[®]] is formulated in 100-mg tablets and a 5-mg/mL oral solution. The adult dosage is 100 mg once daily (compared with 150 mg twice daily for HIV). The pediatric dosage is 3 mg/kg once daily (compared with 4 mg/kg twice daily for HIV). Since lamivudine is eliminated primarily by renal excretion, dosage must be reduced in patients with renal impairment.

Adefovir

Therapeutic Use. Adefovir [Hepsera] is indicated for oral therapy of chronic hepatitis B. The drug was originally developed to fight HIV infection, but was not approved owing to a high incidence of nephrotoxicity at the doses required. The doses used for hepatitis B are much lower, and hence the risk of renal injury is lower too.

Approval for chronic hepatitis B was based on two randomized, placebo-controlled trials, both lasting 48 weeks. In one trial, significant improvement was seen in 53% of those taking adefovir, compared with only 25% of those taking placebo. Results of the second trial were similar: Improvement was seen in 64% of those taking adefovir, compared with 35% of those taking placebo.

Mechanism of Action. Adefovir is a nucleoside analog with a mechanism similar to that of acyclovir. Both drugs inhibit viral DNA synthesis, and both must be converted to their active form within the body. Activation of adefovir is mediated by cellular kinases—enzymes that convert the drug into adefovir diphosphate, a compound with two actions: (1) it directly inhibits viral DNA polymerase (by competing with deoxyadenosine triphosphate, a natural substrate for the enzyme); and (2) it undergoes incorporation into the growing strand of viral DNA, and thereby causes premature strand termination. Host cells are spared because adefovir diphosphate is a poor inhibitor of human DNA polymerase.

Pharmacokinetics. Bioavailability is about 60% following oral administration, both in the presence and absence of food. Plasma levels peak about 2 hours after dosing. Elimination is renal, by a combination of glomerular filtration and active tubular secretion. In patients with normal kidney function, the half-life is 7.5 hours. In patients with renal impairment, the half-life is significantly increased.

Adverse Effects. *Nephrotoxicity* is the principal concern. Increased serum creatinine, a sign of kidney damage, was seen in 4% of patients who received 48 weeks of therapy, and in 9% of patients who received 96 weeks of therapy. To reduce risk, kidney function should be assessed at baseline and periodically thereafter, paying special attention to patients at high risk (ie, patients with pre-existing renal impairment and those taking nephrotoxic drugs [eg, cyclosporine, tacrolimus, aminoglycosides, vancomycin, aspirin and other nonsteroidal anti-inflammatory drugs]).

When adefovir is discontinued, patients may experience *acute exacerbation of hepatitis B*. In clinical trials, serum ALT levels rose dramatically in 25% of patients when treatment was stopped. Liver function should be assessed periodically following adefovir withdrawal.

Drug Interactions. Drugs that are eliminated by active tubular secretion can compete with adefovir for renal excretion. As a result, if one of these agents were combined with adefovir, excretion of adefovir, the other drug, or both could be decreased, causing their plasma levels to rise.

Precautions. Because adefovir is related to the nucleoside analogs used against HIV, there is a concern that, if the patient were infected with HIV, giving adefovir in the low doses employed against HBV could allow emergence of HIV viruses resistant to nucleoside analogs. Accordingly, HIV infection should be ruled out before adefovir is used.

The nucleoside analogs used to treat HIV infection can cause lactic acidosis and severe hepatomegaly. Hence, there is concern that adefovir can cause these effects too. If the patient develops clinical or laboratory findings that suggest lactic acidosis or pronounced hepatotoxicity, adefovir should be withdrawn.

Preparations, Dosage, and Administration. Adefovir [Hepsera] is supplied in 10-mg tablets. For patients with good kidney function, the dosage is 10 mg once a day, taken with or without food. For patients with impaired kidney function, as indicated by reduced creatinine clearance (CrCl), the dosing interval should be increased. Adjusted dosages are as follows:

- CrCl 20 to 49 mL/min—10 mg every 48 hours
- CrCl below 20 mL/min (not requiring dialysis)—10 mg every 72 hours
- Patients on hemodialysis—10 mg once a week, taken after dialysis

Entecavir

Therapeutic Use. Entecavir [Baraclude], approved in 2005, is indicated for oral therapy of chronic hepatitis B. Candidates for treatment should have evidence of active viral replication along with persistently elevated serum aminotransferases or histologic evidence of active disease. In clinical trials, entecavir was more effective than lamivudine. In patients with lamivudine-resistant HBV, responses to entecavir were somewhat reduced, but were still better than responses to lamivudine. Recent evidence indicates that, with long-term use (3 years) entecavir can reverse fibrosis and cirrhosis.

Mechanism of Action. Entecavir is a nucleoside analog that undergoes conversion to entecavir triphosphate (its active form) within the body. As entecavir triphosphate, the drug inhibits HBV DNA polymerase, and thereby prevents viral replication. Entecavir triphosphate is a weak inhibitor of human DNA polymerases, both nuclear and mitochondrial, and hence host cells are spared. Like lamivudine and adefovir, entecavir may impede HIV replication, and hence may promote emergence of resistant HIV.

Pharmacokinetics. Entecavir is available in tablets and solution for oral dosing. Bioavailability with both formulations is the same. Plasma levels peak 0.5 to 1.5 hours after dosing. Entecavir undergoes extensive distribution to body tissues, with little binding to plasma proteins. Metabolism is minimal. Entecavir is neither a substrate for, inhibitor of, nor inducer of cytochrome P450 enzymes. Excretion is via the urine, primarily as unchanged drug. The half-life is about 5.5 days.

Adverse Effects and Precautions. Entecavir is very well tolerated. The most common adverse effects are dizziness, headache, fatigue, and nausea—and even these occur in less than 5% of patients.

Patients treated with other nucleoside analogs have developed lactic acidosis and severe hepatomegaly, and hence there is concern that entecavir may cause these effects too. If the patient develops clinical or laboratory findings that suggest lactic acidosis or pronounced hepatotoxicity, entecavir should be withdrawn.

Acute severe exacerbations of hepatitis B have developed following discontinuation of entecavir and other drugs for hepatitis B. Accordingly, if entecavir is discontinued, liver function should be monitored closely for several months.

Preparations, Dosage, and Administration. Entecavir [Baraclude] is available in tablets (0.5 and 1 mg) and an oral solution (0.05 mg/mL). Dosing is done once a day, either 2 hours before eating or 2 hours after

Dosage depends on renal function (as indicated by CrCl) and on the infection's sensitivity to lamivudine.

If the infection is *lamivudine sensitive*, daily dosages are as follows:

- CrCl 50 mL/min or higher—0.5 mg
- CrCl 30 to 49 mL/min—0.25 mg
- CrCl below 30 mL/min (not requiring dialysis)—0.15 mg
- Patients on hemodialysis—0.05 mg taken after dialysis

If the infection is *lamivudine resistant*, daily dosages are as follows:

- CrCl 50 mL/min or higher—1 mg
- CrCl 30 to 49 mL/min—0.5 mg
- CrCl below 30 mL/min (not requiring dialysis)—0.3 mg
- Patients on hemodialysis—0.05 mg taken after dialysis

Telbivudine

Therapeutic Use. Telbivudine [Tyzeka, Sebivo[®]], approved in 2006, is a nucleoside analog indicated for chronic HBV infection in adults and adolescents 16 years of age or older. Patients must have evidence of active HBV replication, plus either persistent elevations in serum ALT or aspartate aminotransferase (AST) or histologic evidence of active liver disease. In nucleoside-naïve patients, telbivudine is at least as effective as lamivudine (as indicated by suppression of HBV DNA and either normalization of ALT or loss of serum HBeAg, a hepatitis B antigen). As with lamivudine, resistance can be significant: After 2 years of treatment with telbivudine, resistance develops in 9% to 22% of patients. Patients resistant to telbivudine show cross-resistance to lamivudine. In contrast to lamivudine, entecavir, and adefovir, telbivudine is not active against HIV.

Mechanism of Action. Telbivudine is a thymidine nucleoside analog that undergoes intracellular conversion to its active form: telbivudine triphosphate. As the triphosphate, it inhibits HBV replication in two ways. First, it directly inhibits HBV DNA polymerase (by competing with the natural substrate, thymidine triphosphate). Second, it undergoes incorporation in the growing viral DNA chain, and thereby causes chain termination.

Adverse Effects. The most common adverse effects are fever, fatigue/malaise, arthralgia, myalgia, cough, headache, and GI symptoms (eg, abdominal pain, nausea, vomiting, diarrhea, dyspepsia). Some patients have developed symptomatic myopathy, characterized by persistent muscle pain, tenderness, or weakness. Lactic acidosis and severe hepatomegaly have occurred with other nucleoside analogs, but have not been reported with telbivudine. As with other drugs for hepatitis B, severe exacerbations can occur when treatment is discontinued.

Drug Interactions. No significant interactions have been reported. However, since telbivudine is eliminated primarily by renal excretion, drugs that impair renal function may raise its level. Also, other drugs that cause muscle injury may increase risk in patients taking telbivudine. Telbivudine is neither a substrate for nor inhibitor of CYP isozymes, and hence will not be affected by drugs that inhibit or induce CYP isozymes, nor will it affect drugs that are metabolized by these isozymes.

Preparations, Dosage, and Administration. Telbivudine [Tyzeka, Sebivo[®]] is supplied in 600-mg tablets and an oral solution (100 mg/5 mL). The usual dosage for adults and children is 600 mg once a day, taken with or without food. For patients with renal impairment, as indicated by reduced CrCl, the dosing interval should be increased. For patients with hepatic impairment, no dosage adjustment is required. Dosages are as follows:

- CrCl 50 mL/min or higher—600 mg once daily
- CrCl 30 to 49 mL/min—600 mg once every 48 hours
- CrCl below 30 mL/min (not requiring dialysis)—600 mg once every 72 hours
- Patients on hemodialysis—600 mg once every 96 hours, taken after hemodialysis

Tenofovir

Like lamivudine and adefovir, tenofovir [Viread] was originally approved for HIV infection, and then later approved for HBV in adults. The basic pharmacology of tenofovir is presented in Chapter 94. Consideration here is limited to its use against HBV. When compared directly with adefovir in patients with HBV, tenofovir was considerably more effective. However, as with other nucleoside analogs, discontinuation of treatment is followed by exacerbation of hepatitis. Adverse effects include weakness, headache, lactic acidosis with hepatomegaly, and GI reactions: diarrhea, vomiting, and flatulence. Like some other nucleoside analogs, tenofovir can impede HIV replication, and hence may promote emergence of resistant HIV. Tenofovir is supplied in 300-mg tablets for oral dosing. The recommended dosage for HBV is 300 mg once daily, the same dosage we use for HIV.

DRUGS FOR INFLUENZA

Influenza is a serious respiratory tract infection that constitutes a major cause of morbidity and mortality worldwide. During the 1918–1919 global pandemic, more than 500,000 people died in the United States and up to 50 million people died worldwide. Complications of influenza (eg, bronchitis, pneumonia) cause up to 300,000 American hospitalizations a year. Annual deaths vary widely, depending on the strain of flu in circulation. For example, between 1976 and 2007, annual deaths ranged from a low of 3300 to a high of 49,000. The cost of influenza is huge: Direct and indirect expenses total between \$3 billion and \$5 billion annually.

Influenza is caused by influenza viruses, of which there are two major types: *influenza A* and *influenza B*. Type A influenza viruses cause far more infections than type B influenza viruses (about 96% vs. 4%). The influenza A viruses are further subclassified on the basis of two types of surface antigens: hemagglutinin (H) and neuraminidase (N). The predominant subgroups of seasonal influenza A viruses in circulation today are known as H1N1 and H3N2, because of the specific types of hemagglutinin and neuraminidase that they carry. Keep in mind, however, that viral strains undergo constant evolution. As a result, the strains of H1N1 and H3N2 in circulation this year are likely to differ from the strains of H1N1 and H3N2 in circulation next year. Because of this ongoing evolution, the World Health Organization (WHO) has established a global network of laboratories to monitor the emergence and spread of new variants.

Influenza is a highly contagious infection spread via aerosolized droplets produced by coughing or sneezing. The virus enters the body through mucous membranes of the nose, mouth, or eyes. Viral replication takes place in the respiratory tract. Symptoms begin 2 to 4 days after exposure, and last 5 to 6 days. Influenza is characterized by fever, cough, chills, sore throat, headache, and myalgia (muscle pain). For typical patients, infection results in 5 to 6 days of restricted activity, 3 to 4 days of bed disability, and 3 days of absence from work or school. In the United States, the influenza “season” begins in November and extends through March or April.

Influenza is managed by vaccination and with drugs. Vaccination is the primary management strategy; drug therapy is secondary. The drugs for influenza fall into two groups: *adamantanes*, which have been used for decades, and *neuraminidase inhibitors*, which are relatively new. Nearly all strains of influenza currently in circulation are resistant to the adamantanes, but remain sensitive to the neuraminidase inhibitors. Accordingly, neuraminidase inhibitors are recommended, but adamantanes are not. For very current information on influenza vaccines and drugs, you can look online at www.cdc.gov/flu, a comprehensive web site maintained by the Centers for Disease Control and Prevention (CDC).

Influenza Vaccines

Annual vaccination is the best protection against influenza. Because influenza viruses are constantly evolving, influenza vaccines must continuously change too. Each year, manufac-

TABLE 93-7 ■ Influenza Vaccines

Vaccine	Route	Formulation	Mercury Content* (mcg/0.5-mL dose)	Ovalbumin Content (mcg/0.5-mL dose)	Approved Age Group
Inactivated Influenza Vaccines					
Afluria	IM	0.5-mL single-dose syringe	None	1 or less	6 months and older [†]
		5-mL multidose vial	25	1 or less	6 months and older [†]
Fluarix	IM	0.5-mL single-dose syringe	None	0.05 or less	3 yr and older
FluLaval	IM	5-mL multidose vial	25	1 or less	18 yr and older
Fluvirin	IM	0.5-mL single-dose syringe	1 or less	1 or less	4 yr and older
		5-mL multidose vial	25	1 or less	4 yr and older
Fluzone	IM	0.25-mL single-dose syringe	None	— [‡]	6–35 months
		0.5-mL single-dose syringe	None	— [‡]	3 yr and older
		0.5-mL single-dose vial	None	— [‡]	3 yr and older
		5-mL multidose vial	24	— [‡]	3 yr and older
Fluzone High-Dose	IM	0.5-mL single-dose syringe	None	— [‡]	65 yr and older
Fluzone Intradermal	ID	0.1-mL single-dose syringe	None	— [‡]	18–64 yr
Live, Attenuated Influenza Vaccine					
FluMist	Nasal	0.2-mL single-dose sprayer	None	§	2–49 yr

ID = intradermal, IM = intramuscular.

*Mercury, in the form of thimerosal, is used as a preservative in some vaccines.

[†]Although Afluria is approved for children as young as 6 months, ACIP recommends avoiding Afluria in children under the age of 9 years, owing to a possible risk of fever and febrile seizures in younger children.

[‡]Information not included in the package insert, but available upon request from the manufacturer: Sanofi Pasteur, 1-800-822-2463.

[§]Insufficient data available to use FluMist in egg-allergic persons.

urers produce a new vaccine directed against the three strains of influenza virus deemed most likely to cause disease during the upcoming flu season. Identification of the three strains is done jointly by the CDC, FDA, and WHO.

Types of Influenza Vaccines

Two basic kinds of flu vaccine are available: (1) *inactivated influenza vaccine* and (2) *live, attenuated influenza vaccine*, also known as LAIV. The inactivated vaccine is administered by *IM or intradermal injection*. The live, attenuated vaccine is administered by *intranasal spray*. Both kinds of vaccine are directed against the same three influenza strains, and both are reformulated annually.

At this time, there are eight influenza vaccines on the market (Table 93-7). Six of these vaccines—Afluria, Fluarix, FluLaval, Fluvirin, Fluzone, and Fluzone High-Dose—are given by IM injection, one—Fluzone Intradermal—is given by intradermal injection, and one—FluMist—is given by intranasal spray. As indicated in Table 93-7, some of the IM products contain trace amounts of mercury. The table also shows that the eight vaccines differ regarding the age groups for which they are approved. Of note, Fluzone High-Dose is approved only for older people, and intranasal FluMist is approved only for people 2 to 49 years old, and hence cannot be used by two large groups considered at high risk, namely, the very young and the elderly.

Composition

As noted, the vaccines that we develop each year for seasonal influenza contain antigens derived from three different strains of influenza viruses. For example, the vaccine developed for

the 2011–2012 flu season contained antigens from these three strains:

An *A/California/7/2009 (H1N1)*-like virus
An *A/Perth/16/2009 (H3N2)*-like virus
A *B/Brisbane/60/2008*-like virus

The first two strains are type A influenza viruses, and the third strain is a type B influenza virus. Of note, the first virus in the list is the same virus used to create a vaccine against the H1N1 variant that caused a global pandemic in 2009. Also of note, the vaccine created for the 2011–2012 flu season is identical to the vaccine created for the 2010–2011 flu season. There was no need to change the antigens because the predominant circulating strains of influenza viruses did not change that year.

Efficacy

Protection begins 1 to 2 weeks after vaccination and generally lasts 6 months or longer. However, among elderly vaccinees, protection may be lost in 4 months or even less. Efficacy of vaccination depends on the age and health status of the vaccinee, and on how well the vaccine matches the strains of influenza virus in circulation that year. Efficacy of the inactivated vaccine and the LAIV is about equal.

Because the influenza virus evolves rapidly, influenza vaccines are reformulated annually. Accordingly, to maintain protection, revaccination is required each year. Furthermore, since antibody titers can decline fairly quickly, annual revaccination is recommended even if the formulation does *not* change, as was the case for the 2010–2011 and 2011–2012 flu seasons.

Adverse Effects

Adverse effects differ for the inactivated vaccine versus the LAIV. However, with both vaccines, significant adverse effects are rare.

Inactivated Influenza Vaccine. Adverse effects are uncommon, except for possible soreness at the site of IM or intradermal injection. People who have not been vaccinated previously may experience fever, myalgia, and malaise lasting 1 or 2 days.

Influenza vaccination may carry a very small risk of *Guillain-Barré syndrome* (GBS), a severe, paralytic illness. In 1976, swine flu vaccine was associated with GBS. However, there has been no clear link between GBS and influenza vaccines used since then. If there is a risk, it is very small, estimated at 1 to 2 cases per million vaccinees—much smaller than the risk posed by severe influenza.

Live, Attenuated Influenza Vaccine. LAIV has been given to millions of people, and reports of serious adverse events have been very rare. As of August 16, 2005, the Vaccine Adverse Event Reporting System had received 460 reports regarding LAIV. Among these were seven cases of possible anaphylaxis, two cases of GBS, and one case of Bell's palsy. More commonly, vaccinees experience mild, transient effects. Among children 5 to 17 years old, the most common reactions have been runny nose, nasal congestion, cough, headache, vomiting, muscle aches, and fever. Among adults 18 to 49 years old, the most common reactions have been runny nose, headache, sore throat, and cough.

Precautions and Contraindications

People with acute febrile illness should defer vaccination until symptoms abate. Minor illnesses (eg, common cold), with or without fever, do not preclude vaccination.

Influenza vaccines are contraindicated for persons with hypersensitivity to eggs. Why? Because the vaccines are produced from viruses grown in eggs, and hence may contain trace amounts of egg proteins. Individuals suspected of egg hypersensitivity should undergo a skin test before receiving the vaccine. If the test is positive, the vaccine should be withheld.

Who Should Be Vaccinated?

The Advisory Committee on Immunization Practices (ACIP) now recommends annual vaccination for *all people age 6 months and older*. This recommendation, made in February 2010, is much more inclusive than recommendations made in the past. Furthermore, although an annual flu shot is recommended for everyone, an annual shot is especially important for persons at high risk of flu complications, and for those who live with or care for persons at high risk. Persons at high risk include the following:

- Children younger than 5 years, and especially children younger than 2 years
- Children age 18 or under receiving long-term aspirin therapy
- Pregnant women
- People age 65 and older
- People who are morbidly obese
- People who live in nursing homes and other long-term care facilities
- American Indians/Alaskan Natives

- People who are immunosuppressed (eg, owing to HIV infection or use of immunosuppressant drugs)
- People with certain chronic medical conditions, including spinal cord injury; asthma; anemia; diabetes; heart, kidney, or lung disease; and neurologic disorders, such as epilepsy or cerebral palsy, that can lead to breathing or swallowing problems

Important note: These people at high risk should only receive the *inactivated* influenza vaccine. They should not receive the live influenza vaccine. Why? Because safety of the live vaccine has not been evaluated in this population.

Who Should NOT Be Vaccinated?

As noted immediately above, people at high risk for flu complications, including pregnant women, should not receive the *live* influenza vaccine. Instead, they should receive the *inactivated* vaccine. In addition, some people should not receive *either* vaccine without a physician's approval. In this group are:

- People who have a severe allergy to chicken eggs
- People who have had a severe reaction to influenza vaccination in the past
- People who have experienced GBS
- People who have a moderate or severe illness with a fever (these individuals should wait until symptoms abate)

When Should Vaccination Be Done?

In the United States, flu season usually peaks in January or February, but can also peak as early as October or as late as May. To ensure full protection, the best time to vaccinate is October or November. However, for people who missed the best time, vaccinating as late as April may be of help. Influenza vaccine may be given at the same time as other vaccines, including pneumococcal vaccine.

Dosage and Administration

Inactivated Influenza Vaccine: Intramuscular. Inactivated influenza vaccines for IM dosing are available under six trade names: Afluria, Fluarix, FluLaval, Fluvirin, Fluzone, and Fluzone High-Dose. Fluzone High-Dose is approved only for patients age 65 and older. Only Afluria and Fluzone are approved for patients as young as 6 months. However, although Afluria is approved for younger children, ACIP recommends using it only for children age 9 years and older. Why? Because Afluria may increase the risk of fever and febrile seizures in younger children.

Intramuscular vaccination is done into the anterolateral aspect of the thigh (for infants and young children) or into the deltoid muscle (for older children, adolescents, and adults).

Dosage is a function of age and vaccination history. Most vaccinees require just 1 injection a year. However, children under 9 years old who have not been vaccinated before require 2 injections, administered at least 1 month apart. The dosage volume is 0.25 mL for persons ages 6 months through 35 months, and 0.5 mL for persons age 3 years and older.

Inactivated Influenza Vaccine: Intradermal. *Fluzone Intradermal*, introduced in 2011, is the first influenza vaccine formulated for intradermal injection. Vaccinees should be 18 through 64 years old. Compared with the IM flu vaccines, the intradermal vaccine contains less antigen/dose (9 mcg vs. 15 mcg) and is injected in a smaller volume (0.1 mL vs. 0.5 mL). The preferred injection site is over the deltoid muscle.

Live, Attenuated Influenza Vaccine. LAIV [FluMist] is supplied in a single-dose, 0.2-mL sprayer for intranasal administration to persons ages 2 through 49 years—but not to persons at high risk for influenza complications, including pregnant women. Most vaccinees get just one dose a year. However, children age 2 through 8 years who have not been vacci-

nated before require two doses, administered at least 1 month apart. FluMist is unstable at room temperature, and hence must be stored frozen.

Avian Influenza. The FDA has approved an inactivated vaccine against avian H5N1 influenza. It is not available commercially in the United States, but is being included in the CDC's Strategic National Stockpile in case H5N1 avian influenza strains become able to spread efficiently between humans. The vaccine is given as 2 IM injections, 1 month apart.

Neuraminidase Inhibitors

The neuraminidase inhibitors, introduced in 1999, are active against influenza A and influenza B. As of 2011, more than 99% of strains responsible for seasonal influenza were susceptible. In contrast, the adamantanes have only low activity against influenza A, and no activity against influenza B (see below). Accordingly, the neuraminidase inhibitors are the current drugs of choice for influenza treatment. At this time, two neuraminidase inhibitors are available: oseltamivir and zanamivir. Neither drug should be considered an alternative to vaccination.

Oseltamivir

Therapeutic Effects. Oseltamivir [Tamiflu] is an oral drug approved for prevention and treatment of influenza in patients age 1 year and older. When used for *treatment*, dosing must begin early—no later than 2 days after symptom onset, and preferably much sooner. Why? Because benefits decline greatly when treatment is delayed: When treatment is started within 12 hours of symptom onset, symptom duration is reduced by more than 3 days; when started within 24 hours, symptom duration is reduced by less than 2 days; and when started within 36 hours, symptom duration is reduced by only 29 hours. In addition to reducing symptom duration, oseltamivir can reduce symptom severity and the incidence of complications (sinusitis, bronchitis). Unfortunately, in the real world, patients may be unable to obtain and fill a prescription soon enough for the drug to be of significant benefit.

Oseltamivir has been studied for its ability to *prevent* influenza in residents of nursing homes, in family members of someone with the flu, and in the community at large. When used in nursing homes, most of whose residents had been vaccinated, oseltamivir decreased the incidence of influenza from 4.4% down to 0.4%. When used to protect family members, the drug decreased the incidence of influenza from 12% down to 1%. And when given to unvaccinated individuals during a community outbreak of influenza, it reduced the incidence of infection from 4.8% down to 1.2%.

Mechanism of Action. Antiviral effects derive from inhibiting *neuraminidase*, a viral enzyme required for replication. As a result of neuraminidase inhibition, newly formed viral particles are unable to bud off from the cytoplasmic membrane of infected host cells. Hence, viral spread is stopped. Oseltamivir is active against most strains of influenza A and influenza B responsible for seasonal influenza, as well as most isolates of influenza A type H5N1 (the cause of *avian flu*). In addition, the drug is active against the so-called *swine flu*, the variant of influenza A type H1N1 that caused the influenza pandemic in 2009. Emergence of resistance over the course of treatment is rare.

Pharmacokinetics. Oseltamivir is well absorbed following oral administration. In the liver, the drug undergoes conversion to oseltamivir carboxylate, its active form. Bioavailability of the carboxylate is 80%.

Plasma levels of active drug peak 2.5 to 6 hours after dosing. The plasma half-life is 6 to 10 hours. The drug is eliminated in the urine, primarily as the carboxylate form.

Adverse Effects. Oseltamivir is generally well tolerated. The most common side effects are nausea (9.9%) and vomiting (9.4%). Nausea can be reduced by giving oseltamivir with food.

Rarely, oseltamivir has caused *severe hypersensitivity reactions*, including anaphylaxis and serious skin reactions (eg, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome). If an allergic reaction develops, oseltamivir should be discontinued.

Rarely, oseltamivir has been associated with *neuropsychiatric effects*, mainly in younger patients. Reported reactions include delirium and abnormal behavior, which has led to injury and even death. However, since influenza itself can cause these reactions, they cannot be ascribed with certainty to oseltamivir.

Interaction with Live Influenza Vaccine. In theory, oseltamivir can blunt responses to LAIV. Accordingly, oseltamivir should be discontinued at least 2 days before giving LAIV. Following dosing with LAIV, at least 2 weeks should elapse before starting oseltamivir.

Preparations, Dosage, and Administration. Oseltamivir [Tamiflu] is available in capsules (30, 45, and 75 mg) and as a powder (360 mg) to be reconstituted to a 6-mg/mL oral suspension. Dosing can be done with or without food, although dosing with food can reduce nausea.

Treatment of Influenza. For treatment, the dosage for patients age 13 years and older is 75 mg twice daily for 5 days, beginning no later than 2 days after the onset of symptoms. Dosage should be reduced to 75 mg once daily in patients with significant renal impairment. The dosage for children 1 year old through 12 years old is based on body weight as follows: under 15 kg, 30 mg twice daily; 15 to 23 kg, 45 mg twice daily; 23 to 40 kg, 60 mg twice daily; and over 40 kg, 75 mg twice daily.

Prevention of Influenza. For prevention, the dosage is *one-half the dosage used for treatment*. This is accomplished by switching from twice-daily dosing to once-daily dosing. Hence, for patients age 13 years and older, the dosage is 75 mg once a day. The dosage for children 1 year old through 12 years old is based on body weight as follows: under 15 kg, 30 mg once daily; 15 to 23 kg, 45 mg once daily; 23 to 40 kg, 60 mg once daily; and over 40 kg, 75 mg once daily.

Candidates for prophylactic therapy include family members of someone with flu and residents of nursing homes. To protect family members, dosing should begin within 48 hours of exposure and should continue for 10 days. To protect residents of nursing homes or high-risk members of the community at large, dosing can be done continuously for up to 42 days.

Zanamivir

Actions and Uses. Zanamivir [Relenza], administered by oral inhalation, is approved for *treatment* of acute uncomplicated influenza in patients at least 7 years old, and for *prophylaxis* of influenza in people at least 5 years old. As with oseltamivir, benefits derive from inhibiting viral neuraminidase, an enzyme required for viral replication. Like oseltamivir, zanamivir is well tolerated, except in patients with underlying airway disease.

Clinical Trials. Zanamivir is moderately effective at shortening the duration of influenza symptoms. In Phase III clinical trials, improvement in symptoms was defined as (1) the absence of fever and (2) mild or no headache, myalgia, cough, or sore throat. In patients taking zanamivir (10 mg twice daily for 5 days, beginning no later than 36 hours after the onset of symptoms), the average duration of symptoms was 5 days, compared with 6.5 days for patients taking placebo. In addition, zanamivir reduced the incidence of complications (sinusitis, bronchitis) requiring antibacterial drugs.

In a 4-week trial conducted during the influenza season, once-daily treatment with 10 mg of inhaled zanamivir was 84% effective at preventing febrile illness.

Pharmacokinetics. Zanamivir is formulated as a dry powder for oral inhalation. The drug is poorly absorbed from the GI tract, and hence cannot be administered by mouth. Most (70% to 90%) of an inhaled dose is depos-

sted in the oropharynx and throat. About 10% to 20% reaches the tracheo-bronchial tree and lungs. Between 4% and 17% of each dose undergoes absorption into the systemic circulation. Zanamivir has a plasma half-life of 2.5 to 5 hours and is eliminated unchanged in the urine. No metabolites have been detected.

Adverse Effects and Interactions. In patients with healthy lung function, serious adverse effects are uncommon. Because zanamivir is administered as an inhaled powder, patients may experience cough or throat irritation. Also, as with oseltamivir, there have been rare reports of severe allergic reactions and neuropsychiatric effects.

In patients with pre-existing lung disorders (eg, asthma, chronic obstructive pulmonary disease), zanamivir may cause severe bronchospasm and respiratory decline. Some patients have required immediate treatment or hospitalization. Deaths have occurred. However, given the impact of flu itself on lung function, it's not clear that zanamivir was the cause. Nonetheless, owing to the potential risk, zanamivir is not recommended for patients with underlying airway disease.

Zanamivir appears devoid of drug interactions. However, like oseltamivir, zanamivir may blunt responses to LAIV, and hence should be stopped 2 days before giving LAIV, and should not be started for 2 weeks after giving LAIV.

Preparations, Dosage, and Administration. Zanamivir [Relenza] is supplied in blister packs that contain 5 mg of powdered drug. Administration is by oral inhalation using the *Diskhaler* provided by the manufacturer.

Influenza Treatment. The dosage for adults and children is 10 mg (two 5-mg inhalations) twice daily for 5 days. Each 10-mg dose should be separated by 12 hours. However, on the first day of treatment, less separation (as little as 2 hours) is permitted if the first dose cannot be taken early enough in the day to allow 12 hours between doses. Patients who are using an inhaled bronchodilator (eg, albuterol) should administer the bronchodilator before inhaling zanamivir.

Influenza Prevention. The dosage for adults and children is 10 mg (two 5-mg inhalations) once daily. Note that this is one-half the dosage used for treatment.

Adamantanes

The adamantanes—*amantadine* [Symmetrel] and *rimantadine* [Flumadine]—were the first influenza drugs available. These agents have moderate activity against influenza A, and none against influenza B. With amantadine, adverse CNS effects are common, and with both drugs, resistance can develop rapidly. In the United States, resistance among influenza A isolates has risen sharply, from just 2% in 2003 to 91% by 2005. Because most current strains of influenza A are resistant, and because all strains of influenza B are resistant, the CDC recommends against using these drugs for *any* influenza patients, whether infected with influenza A or influenza B. For more information on amantadine and rimantadine, refer to the seventh edition of this text.

DRUGS FOR RESPIRATORY SYNCYTIAL VIRUS INFECTION

Respiratory syncytial virus (RSV) infection is a major cause of lower respiratory tract disease. Symptomatic infection with RSV is most likely in the very young, the elderly, and persons with disorders involving the respiratory tract, heart, or immune system. In the United States, RSV infection is the most common cause of lower respiratory tract disease in infants and young children, leading to between 51,000 and 82,000 hospitalizations each year. Among children 5 years old and younger, RSV is the leading cause of viral death. The death rate from RSV in the elderly is also high. Like influenza, infection with RSV is seasonal, with most cases occurring in the winter (December through March). Only two antiviral drugs—ribavirin and palivizumab—are approved for RSV. Unfortunately, neither drug is very effective.

Ribavirin (Inhaled)

Ribavirin, a broad-spectrum antiviral drug, is available in two formulations: aerosol and oral. The aerosol formulation, marketed as Virazole, is used for infection with RSV. The oral formulation, marketed as Rebetol, Ribasphere, and Copegus, is used for chronic hepatitis C. Discussion here focuses on RSV. Use for hepatitis C is discussed above.

Antiviral Actions. Ribavirin [Virazole] is virustatic. The drug is active against RSV, HCV, influenza virus (types A and B), and HSV. Although several biochemical actions of the drug have been described, it is not known which (if any) is responsible for antiviral effects.

Use in RSV Infection. Ribavirin is labeled only for severe viral pneumonia caused by RSV in carefully selected, hospitalized infants and young children. Unfortunately, benefits are usually minimal—and the cost is high (over \$1300/day). Ribavirin should not be used for mild RSV infections.

Pharmacokinetics. For treatment of RSV, ribavirin is administered by oral inhalation. The drug is absorbed from the lungs and achieves high concentrations in respiratory tract secretions and erythrocytes. Concentrations in plasma remain low. The drug is metabolized to active and inactive products. Excretion is via the urine (30% to 55%) and feces (15%). Ribavirin that is sequestered in erythrocytes remains in the body for weeks.

Adverse Effects. Inhalation of ribavirin produces little or no systemic toxicity. However, although generally safe, inhaled ribavirin does pose a hazard to infants undergoing mechanical assistance of ventilation: The drug can precipitate in the respiratory apparatus, thereby interfering with safe and effective respiratory support. Consequently, ribavirin should not be administered to infants who need respiratory assistance. In some infants, and in adults who have asthma or chronic obstructive lung disease, ribavirin has caused deterioration of pulmonary function. Accordingly, respiratory function should be carefully monitored. If deterioration occurs, ribavirin should be discontinued. When administered systemically (PO or IV), ribavirin frequently causes anemia. This has not been reported with inhalational therapy.

Use in Pregnancy. Ribavirin is *contraindicated for use during pregnancy*. Although studies in primates indicate no effect on the developing fetus, ribavirin has proved either teratogenic or embryolethal in nearly all other species tested. No studies in humans have been performed. *Ribavirin is classified under FDA Pregnancy Risk Category X*: The risk of use during pregnancy clearly outweighs any potential benefits. Because of the risk of significant drug exposure, pregnant women should not directly care for patients undergoing ribavirin aerosol therapy.

Preparations, Dosage, and Administration. For treatment of RSV, ribavirin [Virazole] is supplied as a powder (6 gm/100-mL vial) to be reconstituted for aerosol administration. According to the manufacturer, only one device—the Viratek Small Particle Aerosol Generator (SPAG) model SPAG-2—should be employed for ribavirin administration. The SPAG-2 is used to deliver ribavirin to an infant oxygen hood. Treatment is given 12 to 18 hours a day for no less than 3 days and no more than 1 week. The drug should not be administered to patients who require ventilatory assistance. To reconstitute powdered ribavirin, dissolve 6 gm of the drug in sterile water for injection or inhalation, transfer this concentrated solution to the SPAG-2 reservoir, and dilute to a final volume of 300 mL using sterile water for injection or inhalation. The final concentration of ribavirin is 20 mg/mL. This solution is aerosolized and inhaled by the patient.

Palivizumab

Actions and Uses. Palivizumab [Synagis] is a monoclonal antibody indicated for preventing RSV infection in premature infants and in young children with chronic lung disease. The antibody binds to a surface protein on RSV and thereby prevents replication. In clinical trials, the rate of hospitalization was 1.8% for premature infants treated with palivizumab, compared with 8.1% for those receiving placebo. In young children with chronic lung disease, the hospitalization rate was 7.9% for those receiving the antibody, versus 12.8% for those receiving placebo.

Adverse Effects. Except for *hypersensitivity reactions*, which are rare, palivizumab appears devoid of significant adverse effects. Acute hypersensitivity reactions have occurred with initial drug use and with subsequent use. Very rarely (less than 1 in 100,000 cases), palivizumab has caused anaphylaxis, but only with re-exposure, not with the initial dose. If a *mild* hypersensitivity reaction occurs, cautious use of palivizumab can continue. However, if a *severe* reaction occurs, the drug should be stopped and never used again. Severe reactions are managed with parenteral epinephrine and supportive care.

Preparations, Dosage, and Administration. Palivizumab [Synagis] is supplied in solution (50 and 100 mg/mL). The dosage is 15 mg/kg once a month, injected IM into the anterolateral aspect of the thigh. Dosing should commence before the RSV season (December through March in the United States) and continue until the season ends. The cost for a full season of treatment is about \$7000. However, although this seems high, it could save more than \$50,000 by avoiding hospitalization.

KEY POINTS

- Because viruses use host-cell enzymes and substrates to reproduce, it is difficult to suppress viral reproduction without also harming cells of the host.
- Acyclovir is the drug of choice for most infections caused by herpes simplex viruses and varicella-zoster virus.
- Following conversion to its active form, acyclovir suppresses viral reproduction by inhibiting viral DNA polymerase and by causing premature termination of viral DNA strand growth. Because the active form of acyclovir is not a good inhibitor of human DNA polymerase, cells of the host are spared.
- Acyclovir is eliminated unchanged by the kidneys. Accordingly, dosage must be reduced in patients with renal impairment.
- Intravenous acyclovir can injure the kidneys. Renal damage can be minimized by infusing acyclovir slowly and by ensuring adequate hydration during and after the infusion.
- Ganciclovir is the drug of choice for prophylaxis and treatment of CMV infection in immunocompromised patients, including those with AIDS.
- Ganciclovir does not cure CMV retinitis in patients with AIDS, and hence, in most cases, treatment must continue for life.
- Like acyclovir, ganciclovir becomes activated within infected cells, after which it inhibits viral DNA polymerase and causes premature termination of viral DNA strand growth.
- Like acyclovir, ganciclovir is excreted unchanged in the urine. Hence, dosage must be reduced in patients with renal impairment.
- The major adverse effects of ganciclovir are granulocytopenia and thrombocytopenia.
- Chronic hepatitis is caused primarily by HBV and HCV.
- Hepatitis B can be prevented by vaccination. There is no vaccine for hepatitis C.
- Hepatitis C is treated with interferon alfa, ribavirin, and HCV protease inhibitors (boceprevir and telaprevir).
- HCV protease inhibitors prevent replicating HCV from progressing to its mature, infectious form.
- Ribavirin is not effective against HCV when used alone, and hence is always combined with interferon alfa.
- HCV protease inhibitors greatly enhance the effects of interferon alfa plus ribavirin, and hence are always combined with both of those drugs.
- For years, the treatment of choice for hepatitis C has been dual therapy with peginterferon alfa plus ribavirin. However, triple therapy with a protease inhibitor plus peginterferon alfa plus ribavirin is much more effective, and hence is likely to replace dual therapy as standard of care. The principal adverse effects of interferon alfa are a flu-like syndrome and severe depression.
- The principal adverse effects of ribavirin are hemolytic anemia and fetal death or malformation.
- Owing to its adverse effects on the fetus, ribavirin is contraindicated for use during pregnancy.
- The HCV protease inhibitors are subject to a large number of drug interactions.
- Hepatitis B can be treated with interferon alfa or a nucleoside analog, such as lamivudine.
- Rarely, lamivudine causes lactic acidosis and severe hepatomegaly.
- Vaccination is the best way to prevent influenza.
- Influenza vaccination is recommended for everyone age 6 months and older.
- Because influenza viruses evolve rapidly, influenza vaccines must be reformulated each year, and persons wanting protection must receive the new vaccine each year.
- Two types of influenza vaccine are available: inactivated influenza vaccine (administered by IM or intradermal injection) and live, attenuated influenza vaccine, aka LAIV (administered by nasal spray).
- We have two types of antiviral drugs for influenza: neuraminidase inhibitors and adamantanes.
- Neuraminidase inhibitors (oseltamivir and zanamivir) are highly active against all current strains of influenza A and B, whereas the adamantanes (amantadine and rimantadine) are not. Accordingly, the neuraminidase inhibitors are the current drugs of choice for treatment and prophylaxis of influenza.
- In theory, neuraminidase inhibitors can blunt responses to LAIV, and hence should be discontinued 2 days before giving an LAIV and not started until 2 weeks after giving an LAIV.
- Resistance to neuraminidase inhibitors is uncommon.

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Summary of Major Nursing Implications*

ACYCLOVIR

Preadministration Assessment

Therapeutic Goal

Treatment of infections caused by herpes simplex viruses and varicella-zoster virus.

Identifying High-Risk Patients

Use with *caution* in patients with dehydration or renal impairment and in those taking other nephrotoxic drugs.

Implementation: Administration

Routes

Topical, oral, IV.

Dosage

Oral and IV dosages must be reduced in patients with renal impairment.

Administration

Topical. Advise patients to apply the drug with a finger cot or rubber glove to avoid viral transfer to other body sites or other people.

Oral. Dosages vary widely for different indications (see Table 93-2).

Intravenous. Give by slow IV infusion (over 1 hour or more). Never give by IV bolus.

Implementation: Measures to Enhance Therapeutic Effects

Inform patients with herpes simplex genitalis that acyclovir only decreases symptoms; it does not eliminate the virus and does not produce cure. Advise patients to cleanse the affected area with soap and water 3 to 4 times a day, drying thoroughly after each wash. Advise patients to avoid all sexual contact while lesions are present, and to use a condom even when lesions are absent.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Observe for decreased clinical manifestations of herpes simplex and varicella-zoster infections. Virologic testing may also be performed.

Minimizing Adverse Effects

Nephrotoxicity. Intravenous acyclovir can precipitate in renal tubules, causing reversible kidney damage. To minimize risk, infuse acyclovir slowly and ensure adequate hydration during the infusion and for 2 hours after. Exercise caution in patients with pre-existing renal impairment and in those who are dehydrated or taking other nephrotoxic drugs.

GANCICLOVIR

Preadministration Assessment

Therapeutic Goal

Treatment and prevention of CMV infection in immunocompromised patients, including those with AIDS and those taking immunosuppressive drugs following an organ transplant.

Topical treatment of acute keratitis caused by HSV.

Baseline Data

Obtain a complete blood count and platelet count.

Identifying High-Risk Patients

Ganciclovir is *contraindicated* during pregnancy and for patients with neutrophil counts below $500/\text{mm}^3$ or platelet counts below $25,000/\text{mm}^3$.

Use with *caution* in patients taking zidovudine or nephrotoxic drugs (eg, amphotericin B, cyclosporine) and in patients with a history of cytopenic reactions to other drugs.

Implementation: Administration

Routes

Oral, IV, intraocular, topical to the eye.

Dosage

Oral and IV dosages must be reduced in patients with renal impairment. AIDS patients with CMV retinitis must take ganciclovir for life.

Administration

Intravenous. Give by slow IV infusion (over 1 hour or more). Ensure adequate hydration to promote renal excretion.

Oral. Advise patients to take oral ganciclovir with food.

Intraocular Implants. Surgical implants are replaced every 5 to 8 months.

Topical to the Eye. Advise patients to apply ganciclovir gel drops directly to the affected eye, and to avoid contact lenses until lesions heal.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Granulocytopenia and Thrombocytopenia. Ganciclovir suppresses bone marrow function when given IV or PO. Obtain complete blood counts and platelet counts frequently. Discontinue ganciclovir if the neutrophil count falls below $500/\text{mm}^3$ or the platelet count falls below $25,000/\text{mm}^3$. The risk of granulocytopenia can be reduced by giving granulocyte colony-stimulating factors. The risk of granulocytopenia is increased by concurrent therapy with zidovudine (a drug for AIDS).

Reproductive Toxicity. In animals, ganciclovir is teratogenic and embryotoxic and suppresses spermatogenesis. Warn patients against becoming pregnant. Inform male patients about possible sterility.

*Patient education information is highlighted as blue text.

Antiviral Agents II: Drugs for HIV Infection and Related Opportunistic Infections

Pathophysiology

- Characteristics of HIV

- Transmission of HIV

- Clinical Course of HIV Infection

Classification of Antiretroviral Drugs

Nucleoside/Nucleotide Reverse Transcriptase

- Inhibitors

- Zidovudine

- Other NRTIs

Non-nucleoside Reverse Transcriptase Inhibitors

- Efavirenz

- Other NNRTIs

Protease Inhibitors

- Group Properties

- Lopinavir/Ritonavir

- Other Protease Inhibitors

Raltegravir, an Integrase Strand Transfer Inhibitor

Enfuvirtide, an HIV Fusion Inhibitor

Maraviroc, a CCR5 Antagonist

Management of HIV Infection

- Screening and Diagnosis

- Laboratory Tests

- Treatment of Adult and Adolescent Patients

- Treatment of Infants and Young Children

- Treatment of Pregnant Patients

Preventing HIV Infection with Drugs

- Treatment as Prevention

- Pre-exposure Prophylaxis

- Postexposure Prophylaxis

- Preventing Perinatal HIV Transmission

Prophylaxis and Treatment of Opportunistic Infections

HIV Vaccines

Keeping Current

In this chapter we discuss drug therapy of infection with the *human immunodeficiency virus* (HIV), the microbe that causes *acquired immunodeficiency syndrome* (AIDS). HIV promotes immunodeficiency by killing CD4 T lymphocytes (CD4 T cells), which are key components of the immune system (see Chapter 67). As a result of HIV-induced immunode-

ficiency, patients are at risk of opportunistic infections and certain neoplasms.

It is important to appreciate that HIV infection is not synonymous with AIDS, which develops years after HIV infection is acquired. The definition of AIDS, established by the Centers for Disease Control and Prevention (CDC) in 1993, is a syndrome in which the individual is HIV positive and has either (1) CD4 T-cell counts below 200 cells/mL or (2) an AIDS-defining illness. Included in the CDC's long list of AIDS-defining illnesses are *Pneumocystis pneumonia*, cytomegalovirus retinitis, disseminated histoplasmosis, tuberculosis, and Kaposi's sarcoma.

Since being identified as a new disease in 1981, AIDS has become a global epidemic. In the United States, nearly 1.2 million people are now infected, about 50,000 more become infected each year, and nearly 600,000 have died since the epidemic began. Worldwide, an estimated 33 million people are now infected, and about 25 million have died, including 270,000 children in 2007 alone. However, there is good news: According to a United Nations report, released in 2011, the number of new HIV infections and HIV-related deaths is on the decline, due in large part to more widespread use of HIV drugs.

Therapy of HIV infection has made dramatic advances. Today, standard *antiretroviral therapy* (ART) consists of three or four drugs. These combinations, often referred to as *HAART* (for *highly active antiretroviral therapy*), can decrease plasma HIV to levels that are undetectable with current technology, and can thereby delay or reverse loss of immune function, decrease certain AIDS-related complications, preserve health, prolong life, and decrease HIV transmission. In the United States, ART has reduced AIDS-related deaths by 72%—from a peak of 50,000 in 1995 to 16,000 in 2008. However, these benefits have not come without a price: ART is expensive, poses a risk of long-term side effects and serious drug interactions, and must continue lifelong. Accordingly, if treatment is to succeed, patients must be highly motivated and well informed about all aspects of the treatment program. A strong support network is extremely valuable too.

ART cannot cure HIV infection. Although treatment *can* greatly reduce HIV levels—often rendering the virus undetectable—discontinuation has consistently been followed by a rebound in HIV replication. Because ART does not eliminate HIV, patients continue to be infectious and must be warned to avoid behaviors that can transmit the virus to others.

Understanding this chapter requires a basic understanding of the immune system. Accordingly, you may find it helpful to read Chapter 67 before proceeding.

PATHOPHYSIOLOGY

Characteristics of HIV

HIV is a *retrovirus*. Like all other viruses, retroviruses lack the machinery needed for self-replication, and hence are obligate intracellular parasites. However, in contrast to other viruses, retroviruses have positive-sense, single-stranded RNA as their genetic material. Accordingly, in order to replicate, retroviruses must first transcribe their RNA into DNA. The enzyme employed for this process is viral *RNA-dependent DNA polymerase*, commonly known as *reverse transcriptase*. (The enzyme is called reverse transcriptase to distinguish it from DNA-dependent RNA polymerase, the host enzyme that transcribes DNA into RNA, which is the usual ["forward"] transcription process.) The name *retrovirus* is derived from the first two letters of *reverse* and *transcriptase*.

There are two types of HIV, referred to as HIV-1 and HIV-2. HIV-1 is found worldwide, whereas HIV-2 is found mainly in West Africa. Although HIV-1 and HIV-2 differ with respect to genetic makeup and antigenicity, they both cause similar disease syndromes. Not all drugs that are effective against HIV-1 are also effective against HIV-2.

Target Cells

The principal cells attacked by HIV are *CD4 T cells* (helper T lymphocytes). As discussed in Chapter 67, these cells are essential components of the immune system. They are required for production of antibodies by B lymphocytes and

for activation of cytolytic T lymphocytes. Accordingly, as HIV kills CD4 T cells, the immune system undergoes progressive decline. As a result, infected individuals become increasingly vulnerable to opportunistic infections, a major cause of death among people with AIDS. HIV targets CD4 T cells because the CD4 proteins on the surface of these cells provide points of attachment for HIV (see below). Without such a receptor, HIV would be unable to connect with and penetrate these cells. Once HIV has infected a CD4 T cell, the cell dies in about 1.25 days. It is important to appreciate that only a few percent of CD4 T cells circulate in the blood; the vast majority reside in lymph nodes and other lymphoid tissues.

In addition to infecting CD4 T cells, HIV infects *macrophages* and *microglial cells* (the central nervous system [CNS] counterparts of macrophages), both of which carry CD4 proteins. Since macrophages and microglial cells are resistant to destruction by HIV, they can survive despite being infected. As a result, they serve as a reservoir of HIV during chronic infection.

Structure of HIV

The structure of HIV is very simple. As shown in Figure 94-1, the HIV *virion* (ie, the entire virus particle) consists of *nucleic acid* (RNA) surrounded by *core proteins*, which in turn are surrounded by a *capsid* (protein shell), which in turn is surrounded by a *lipid bilayer envelope* (derived from the membrane of the host cell).

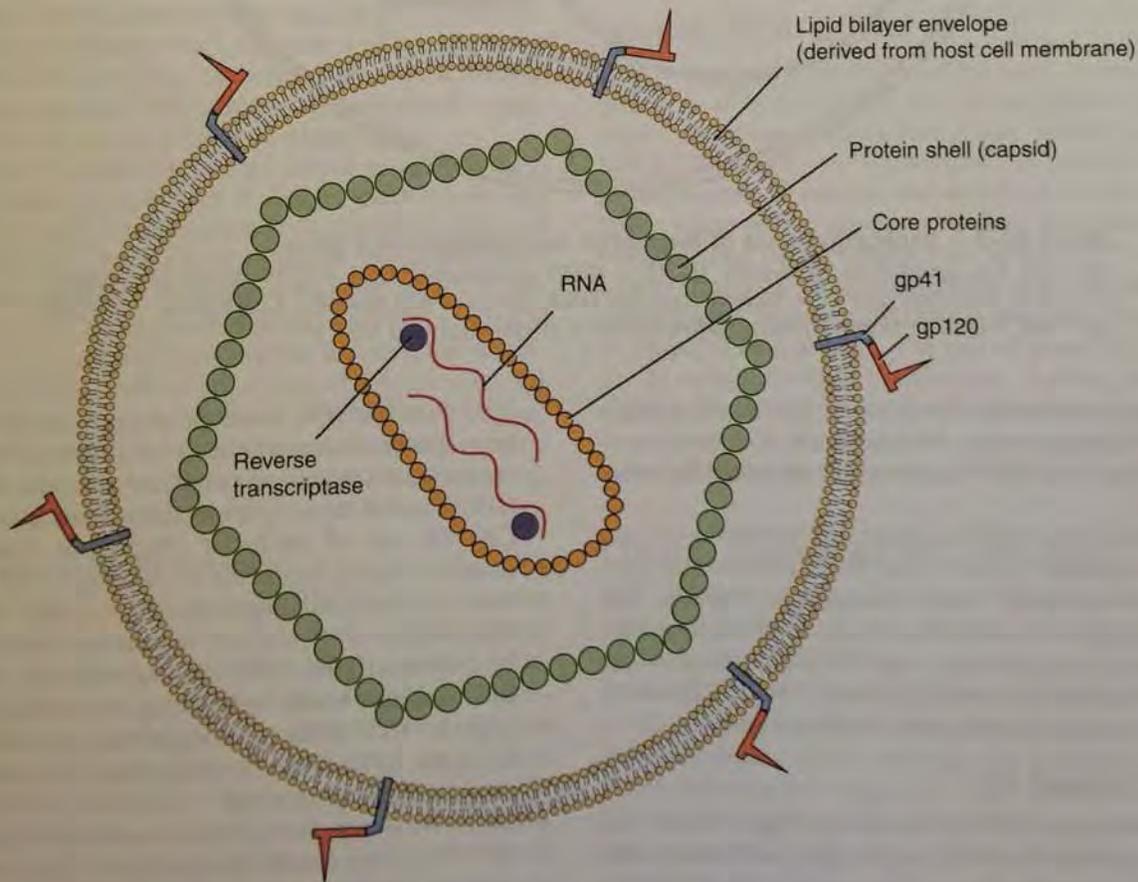


Figure 94-1 • Structure of the human immunodeficiency virus.

Note that HIV has two single strands of RNA, and that each strand is associated with a molecule of reverse transcriptase. (gp41 = glycoprotein 41, gp120 = glycoprotein 120.)

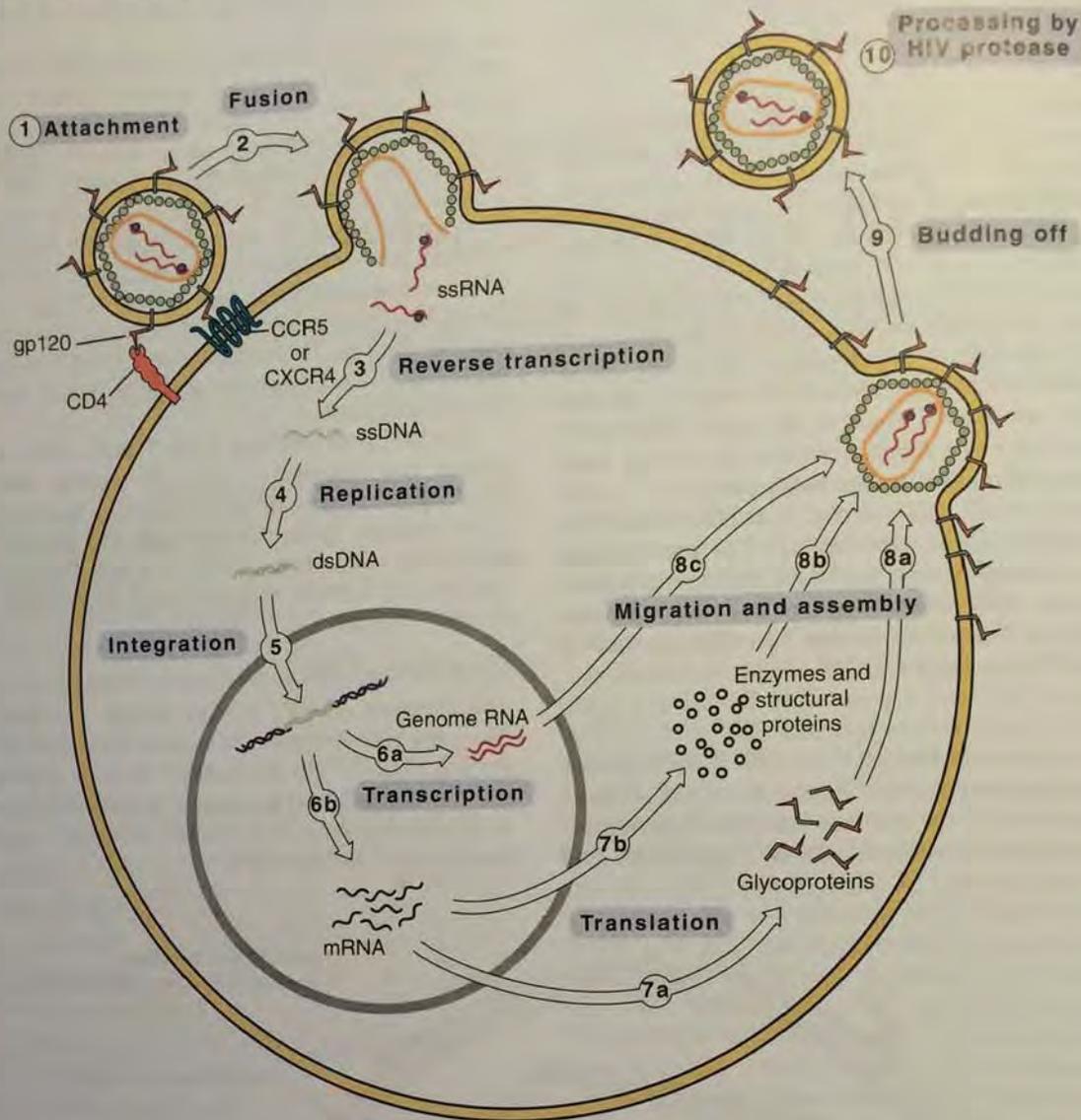


Figure 94-2 ■ Replication cycle of the human immunodeficiency virus.

See text for description of events. (CCR5 = CCR5 co-receptor, CD4 = CD4 receptor, CXCR4 = CXCR4 co-receptor, dsDNA = double-stranded DNA, gp120 = glycoprotein 120, mRNA = messenger RNA, ssDNA = single-stranded DNA, ssRNA = single-stranded RNA.)

The central core contains two separate but identical single strands of RNA, each with its own molecule of *reverse transcriptase* attached. The RNA serves as the template for DNA synthesis.

The outer envelope of HIV contains *glycoproteins* that are needed for attachment to host cells. Each glycoprotein (gp) consists of two subunits, known as *gp41* and *gp120*. The smaller protein (*gp41*) is embedded in the lipid bilayer of the viral envelope; the larger protein (*gp120*) is connected firmly to *gp41*. (The numbers 41 and 120 simply indicate the mass of these glycoproteins in thousands of daltons.)

Replication Cycle of HIV

The replication cycle of HIV is depicted in Figure 94-2. The numbered steps below correspond to the numbers in the figure.

- **Step 1**—The cycle begins with attachment of HIV to the host cell. The primary connection takes place between

gp120 on the HIV envelope and a *CD4* protein on the host cell membrane. Other host proteins, known as co-receptors, act in concert with *CD4* to tighten the bond with HIV. Two of these co-receptors—known as *CCR5* and *CXCR4*—are of particular importance. One drug—*maraviroc*—blocks HIV entry by binding *CCR5*.

- **Step 2**—The lipid bilayer envelope of HIV fuses with the lipid bilayer of the host cell membrane. Fusion is followed by release of HIV RNA into the host cell. One drug—*enfuvirtide*—works by blocking the fusion process.
- **Step 3**—HIV RNA is transcribed into single-stranded DNA by HIV *reverse transcriptase*. Twelve antiretroviral drugs inhibit this enzyme.
- **Step 4**—Reverse transcriptase converts the single strand of HIV DNA into double-stranded HIV DNA.
- **Step 5**—Double-stranded HIV DNA becomes integrated into the host's DNA, under the direction of a viral enzyme known (*aptly*) as *integrase*. One drug—*raltegravir*—inhibits this enzyme.

- **Step 6**—HIV DNA undergoes transcription into RNA. Some of the resulting RNA becomes the genome for daughter HIV virions (step 6a). The rest of the RNA is messenger RNA that codes for HIV proteins (step 6b).
- **Step 7**—Messenger RNA is translated into HIV glycoproteins (step 7a) and HIV enzymes and structural proteins (step 7b).
- **Step 8**—The components of HIV migrate to the cell surface and assemble into a new virus. Prior to assembly, HIV glycoproteins become incorporated into the host cell membrane (step 8a). In steps 8b and 8c, the other components of the virion migrate to the cell surface, where they undergo assembly into the new virus.
- **Step 9**—The newly formed virus buds off from the host cell. As indicated, the outer envelope of the virion is derived from the cell membrane of the host.
- **Step 10**—In this step, which occurs either during or immediately after budding off, HIV undergoes final maturation under the influence of *protease*, an enzyme that cleaves certain large polyproteins into their smaller, functional forms. If protease fails to cleave these proteins, HIV will remain immature and noninfectious. HIV protease is the target of several important drugs.

Replication Rate

HIV replicates rapidly during *all* stages of the infection. During the initial phase of infection, replication is massive. Why? Because (1) the population of CD4 cells is still large, thereby providing a large viral breeding ground; and (2) the host has not yet mounted an immune response against HIV, hence replication can proceed unopposed. As a result of massive replication, plasma levels of HIV can exceed 10 million virions/mL. During this stage of high viral load, patients often experience an *acute retroviral syndrome* (see below).

Over the next few months, as the immune system begins to attack HIV, plasma levels of HIV undergo a sharp decline and then level off. A typical steady-state level is between 1000 and 100,000 virions/mL. Please note, however, that steady-state numbers can be deceptive. The plasma half-life of HIV is only 6 hours; that is, every 6 hours, half of the HIV virions in plasma are lost. Accordingly, in order to maintain the steady-state levels typically seen during chronic HIV infection, the actual rate of *replication* is between 1 and 10 billion virions/day. Despite this high rate of ongoing replication, infected persons typically remain asymptomatic for about 10 years, after which symptoms of advanced HIV disease appear.

Mutation and Drug Resistance

HIV mutates rapidly. Why? Because HIV reverse transcriptase is an error-prone enzyme. Hence, whenever it transcribes HIV RNA into single-stranded DNA and then into double-stranded DNA, there is a high probability of introducing base-pair errors. In fact, according to one estimate, up to 10 incorrect bases may be incorporated into HIV DNA during each round of replication. Because of these errors, HIV can rapidly mutate from a drug-sensitive form into a drug-resistant form. The probability of developing resistance in the individual patient is directly related to the total viral load. Hence, the more virions the patient harbors, the greater the likelihood that at least one will become resistant. To minimize the emergence of resistance, patients must be treated with a combina-

TABLE 94-1 ■ Acute Retroviral Syndrome: Associated Signs and Symptoms

- Fever (96%)
- Lymphadenopathy (74%)
- Pharyngitis (70%)
- Rash and mucocutaneous ulceration (70%)
 - Erythematous maculopapular rash with lesions on face and trunk and sometimes extremities, including palms and soles
 - Mucocutaneous ulceration involving mouth, esophagus, or genitals
- Myalgia or arthralgia (54%)
- Diarrhea (32%)
- Headache (32%)
- Nausea and vomiting (27%)
- Hepatosplenomegaly (14%)
- Weight loss (13%)
- Thrush (12%)
- Neurologic symptoms (12%)
 - Meningoencephalitis or aseptic meningitis
 - Peripheral neuropathy or radiculopathy
 - Facial palsy
 - Guillain-Barré neuritis
 - Brachial neuritis
 - Cognitive impairment or psychosis

tion of antiretroviral drugs. This is the same strategy we employ to prevent emergence of resistance when treating tuberculosis (see Chapter 90).

Transmission of HIV

HIV is transmitted sexually and by other means. The virus is present in all body fluids of infected individuals. Transmission can be via intimate contact with semen, vaginal secretions, and blood. The disease can be transmitted by sexual contact, transfusion, sharing IV needles, and accidental needle sticks. In addition, it can be transmitted to the fetus by an infected mother, usually during the perinatal period. Initially, HIV infection was limited largely to homosexual males, injection-drug users, and hemophiliacs. However, the disease can now be found routinely in the population at large. The risk of acquiring HIV sexually can be reduced by male circumcision, limiting sexual partners, and use of condoms—as well as by complete sexual abstinence. In addition, acquisition can be prevented with drugs, as discussed below under *Preventing HIV Infection with Drugs*.

Clinical Course of HIV Infection

HIV infection follows a triphasic clinical course. During the initial phase, HIV undergoes massive replication, causing blood levels of HIV to rise very high. As a result, between 50% and 90% of patients experience a flu-like *acute retroviral syndrome*. Signs and symptoms include fever, lymphadenopathy, pharyngitis, rash, myalgia, and headache (Table 94-1). Soon, however, the immune system mounts a counterattack, causing HIV levels to fall. As a result, symptoms of the acute syndrome fade. Very often, the acute retroviral syndrome is perceived as influenza, and hence goes unrecognized for what it really is.

The middle phase of HIV infection is characterized by prolonged *clinical latency*. Blood levels of HIV remain rela-

tively low, and most patients are asymptomatic. However, as noted above, HIV continues to replicate despite apparent dormancy. Because of persistent HIV replication, CD4 T cells undergo progressive decline. The average duration of clinical latency is 10 years.

During the late phase of HIV infection, CD4 T cells drop below a critical level (200 cells/mL), rendering the patient highly vulnerable to opportunistic infections and certain neoplasms (eg, Kaposi's sarcoma). The late phase is when AIDS occurs.

Many patients with HIV infection experience neurologic complications. Both the peripheral and central nervous systems may be involved. *Peripheral neuropathies* affect 20% to 40% of patients and may develop at any time over the course of HIV infection. In contrast, *CNS complications* usually occur late in the disease. Symptoms of CNS injury include decreased cognition, reduced concentration, memory loss, mental slowness, and motor complaints (eg, ataxia, tremors). Neuronal injury may be the direct result of HIV infection, or may develop secondary to an opportunistic infection in the CNS.

CLASSIFICATION OF ANTIRETROVIRAL DRUGS

At this time, we have five types of antiretroviral drugs. Three types—*reverse transcriptase inhibitors*, *integrase strand transfer inhibitors* (INSTIs), and *protease inhibitors* (PIs)—inhibit enzymes required for HIV replication. The other two types—*fusion inhibitors* and *chemokine receptor 5 (CCR5) antagonists*—block viral entry into cells. As discussed below, the reverse transcriptase inhibitors are subdivided into two groups: *nucleoside/nucleotide reverse transcriptase inhibitors* (NRTIs), which are structural analogs of nucleosides or nucleotides, and (2) *non-nucleoside reverse transcriptase inhibitors* (NNRTIs). Drugs that belong to these groups are listed in Table 94-2. All NRTIs, NNRTIs, PIs, INSTIs, and CCR5 antagonists are administered orally, and one NRTI—zidovudine—may also be given IV. The one fusion inhibitor available—enfuvirtide [Fuzeon]—is administered subQ.

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

The nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) were the first drugs used against HIV infection, and remain mainstays of therapy today. In fact, these drugs constitute the backbone of all treatment regimens. As their name suggests, the NRTIs are chemical relatives of naturally occurring nucleosides or nucleotides, the building blocks of DNA. Antiretroviral effects derive from suppressing synthesis of viral DNA by reverse transcriptase. To be effective, all of the NRTIs must first undergo intracellular conversion to their active (triphosphate) forms. The NRTIs have few drug interactions, and most can be taken without regard to meals. Rarely, these agents cause a potentially fatal syndrome characterized by lactic acidosis and hepatomegaly with steatosis; pregnant women taking two NRTIs may be at increased risk. At this time, seven NRTIs are available. Major properties are summarized in Table 94-3.

Zidovudine

Zidovudine [Retrovir] was the first NRTI available and will serve as our prototype for the group. The drug is an analog of thymidine, a naturally occurring nucleoside. When employed in combination with other antiretroviral drugs, zidovudine can decrease viral load, increase CD4 T-cell counts, delay onset of disease symptoms, and reduce symptom severity. The drug's principal dose-limiting toxicities are *severe anemia* and *neutropenia*. Abbreviations for this agent are ZDV (for zidovudine) and AZT (for azidothymidine, its original name).

Mechanism of Antiviral Action

Zidovudine inhibits HIV replication by suppressing synthesis of viral DNA. To do this, zidovudine must first undergo intracellular conversion to its active form, zidovudine triphosphate (ZTP). As ZTP, the drug acts as a substrate for reverse transcriptase. However, when ZTP becomes incorporated into the growing DNA strand, it prevents reverse transcriptase from adding more bases. As a result, further growth of the strand is blocked. In addition to causing premature strand termination, ZTP competes with natural nucleoside triphosphates for binding to the active site of reverse transcriptase; the result is competitive inhibition of the enzyme.

Therapeutic Use

Zidovudine is used to treat infection with HIV-1. Because monotherapy with any antiretroviral drug can rapidly lead to resistance, zidovudine should always be combined with other antiretroviral agents. Zidovudine penetrates to the CNS better than most other antiretroviral drugs, and hence can be especially valuable for relieving cognitive symptoms. Zidovudine is also the drug of choice for preventing mother-to-infant HIV transmission during labor and delivery. The role of zidovudine and other agents in the management of HIV infection is discussed at length later in the chapter.

Pharmacokinetics

Zidovudine is readily absorbed in the presence or absence of food, and distributes to all tissues, including the CNS. After entering the blood, some of the drug is taken up by cells and converted to ZTP, the active form. The remainder undergoes rapid hepatic conversion to an inactive metabolite. Both zidovudine and its inactive metabolite are eliminated by renal excretion. The *plasma* half-life of the drug is 1.1 hours, and the *intracellular* half-life is 7 hours.

Adverse Effects

Anemia and Neutropenia from Bone Marrow Suppression. Severe anemia and neutropenia are the principal toxic effects. Multiple transfusions may be required. The risk of hematologic toxicity is increased by high-dose therapy, advanced HIV infection, deficiencies in vitamin B₁₂ and folic acid, and concurrent use of drugs that are myelosuppressive, nephrotoxic, or directly toxic to circulating blood cells. Anemia and neutropenia generally resolve following zidovudine withdrawal.

Hematologic status (hemoglobin concentration and neutrophil counts) should be determined before treatment and at least every 4 weeks thereafter. Hemoglobin levels may fall significantly within 2 to 4 weeks; neutrophil counts may not fall until after week 6. For patients who develop severe anemia (hemoglobin below 5 gm/dL or down 25% from baseline) or severe neutropenia (neutrophil count below 750 cells/mL or down 50% from baseline), zidovudine should be interrupted until there is evidence of bone marrow recovery. If neutropenia and anemia are less severe, a reduction in dosage

TABLE 94-2 ■ Classification of Antiretroviral Drugs

Generic Name	Trade Name	Abbreviation
DRUGS THAT INHIBIT HIV ENZYMES		
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		
Single-Drug Products		
Abacavir	Ziagen	ABC
Didanosine	Videx	ddI
Emtricitabine	Emtriva	FTC
Lamivudine	Epivir	3TC
Stavudine	Zerit	d4T
Tenofovir	Viread	TDF
Zidovudine	Retrovir	ZDV
Fixed-Dose Combinations		
Abacavir/lamivudine	Epzicom	ABC/3TC
Abacavir/lamivudine/zidovudine	Trizivir	ABC/3TC/ZDV
Zidovudine/lamivudine	Combivir	ZDV/3TC
Emtricitabine/tenofovir	Truvada	FTC/TDF
Emtricitabine/tenofovir/efavirenz*	Atripla	FTC/TDF/EFV
Emtricitabine/tenofovir/rilpivirine†	Complera	FTC/TDF/RPV
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Delavirdine	Rescriptor	DLV
Efavirenz	Sustiva	EFV
Etravirine	Intelence	ETR
Nevirapine	Viramune	NVP
Rilpivirine	Edurant	RPV
Protease Inhibitors		
Atazanavir	Reyataz	ATV
Darunavir	Prezista	DRV
Fosamprenavir	Lexiva, Telzir*	FPV
Indinavir	Crixivan	IDV
Nelfinavir	Viracept	NFV
Ritonavir	Norvir	RTV
Saquinavir	Invirase	SQV
Tipranavir	Aptivus	TPV
Lopinavir/ritonavir	Kaletra	LPV/r
Integrase Strand Transfer Inhibitor		
Raltegravir	Isentress	RAL
DRUGS THAT BLOCK HIV ENTRY INTO CELLS		
Fusion Inhibitor		
Enfuvirtide	Fuzeon	T-20
CCR5 Antagonist		
Maraviroc	Selzentry, Celsentri*	MVC

*Efavirenz is an NNRTI, not an NRTI.

†Rilpivirine is an NNRTI, not an NRTI.

may be sufficient. Transfusions may permit some patients to continue drug use.

Granulocyte colony-stimulating factors may be given to reverse zidovudine-induced neutropenia. Also, if erythropoietin levels are not already elevated, *epoetin alfa* (recombinant erythropoietin) can be given to reduce transfusion requirements in patients with anemia. Granulocyte colony-stimulating factors and epoetin alfa are discussed in Chapter 56.

Lactic Acidosis with Hepatic Steatosis. Rarely, zidovudine causes a syndrome of lactic acidosis with severe hepatomegaly (liver enlargement) and hepatic steatosis (fatty degeneration of the liver). Symptoms include nausea, vomiting, abdominal pain, malaise, fatigue, anorexia, and hyperventilation (blowing off carbon dioxide can reduce acidosis). Left

untreated, the syndrome can be fatal. Diagnosis is based on lactic acid measurement in *arterial* blood. If clinically significant lactic acidosis is present, zidovudine should be discontinued. Lactic acidosis is caused by toxicity to mitochondria.

Combining NRTIs during pregnancy may increase the risk of lactic acidosis. Fatalities have occurred in pregnant women who were taking the NRTIs didanosine and stavudine. Because lactic acidosis and hepatic steatosis are potential side effects of *all* NRTIs, it may be prudent to avoid combining any of these drugs during pregnancy.

Other Adverse Effects. Gastrointestinal effects (anorexia, nausea, vomiting, diarrhea, abdominal pain, stomach upset) occur on occasion. Possible *CNS reactions* include headache, insomnia, confusion, anxiety, nervousness, and seizures. Additional adverse effects include *myopathy* (damage to

TABLE 94-3 ■ Properties of Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

	Abacavir (ABC)	Didanosine (ddl)	Emtricitabine (FTC)
Trade Name	Ziagen	Videx, Videx EC	Emtriva
Formulations	Tablets: 300 mg PO soln: 20 mg/mL	EC capsules: 125, 200, 250, 400 mg Buffered powder for PO soln: 100, 167, 250 mg	Capsules: 200 mg PO soln: 10 mg/mL
Dosage	300 mg 2 times/day or 600 mg once/day	EC capsules: ≥60 kg: 400 mg once/day (or 250 mg once/day with tenofovir) <60 kg: 250 mg once/day (or 200 mg once/day with tenofovir) PO solution: ≥60 kg: 200 mg 2 times/day <60 kg: 125 mg 2 times/day	Capsules: 200 mg once/day PO soln: 240 mg once/day
Impact of Food	Take without regard to meals—but alcohol increases levels by 41%	Take 30 min before meals or 2 hr after	Take without regard to meals
Bioavailability	83%	30%–40%	93%
Serum Half-life	1.5 hr	1.5 hr	10 hr
Intracellular Half-life	12–26 hr	More than 20 hr	More than 20 hr
Elimination	Metabolized by alcohol dehydrogenase, then excreted in the urine	Partial metabolism followed by renal excretion	Renal excretion
Adverse Effects	<ul style="list-style-type: none"> • Lactic acidosis* • Potentially fatal hypersensitivity reactions (fever, rash, nausea, vomiting, fatigue, abdominal pain, respiratory symptoms) • Possible increased risk of MI 	<ul style="list-style-type: none"> • Lactic acidosis* • Pancreatitis • Peripheral neuropathy • GI: nausea, diarrhea • Retinal changes, optic neuritis • Insulin resistance/diabetes • Possible increased risk of MI 	<ul style="list-style-type: none"> • Minimal toxicity • Lactic acidosis* • Hyperpigmentation of palms and soles • GI: nausea, diarrhea • Headache • Rash • In patients co-infected with HBV, withdrawing emtricitabine may result in severe acute exacerbation of hepatitis.

BMD = bone mineral density, EC = enteric coated, HBV = hepatitis B virus, MI = myocardial infarction, WHO = World Health Organization.

*Lactic acidosis with hepatic steatosis is a rare but potentially fatal toxicity associated with all NRTIs.

Adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, prepared by the Panel on Clinical Practices for Treatment of HIV Infection, convened by the DHHS, as updated on October 14, 2011.

muscle fibers), nail pigmentation, insulin resistance/diabetes, hyperlipidemia, and lipodystrophy.

Drug Interactions

Drugs that are myelosuppressive, nephrotoxic, or directly toxic to circulating blood cells can increase the risk of zidovudine-induced hematologic toxicity. Notable among these is *ganciclovir*, an antiviral agent used to treat cytomegalovirus retinitis, a common infection in patients with AIDS. Other drugs of concern include dapson, pentamidine, pyrimethamine, trimethoprim/sulfamethoxazole, amphotericin B, flucytosine, vincristine, vinblastine, and doxorubicin.

Preparations, Dosage, and Administration

Preparations. Zidovudine [Retrovir] is available in three oral formulations—capsules (100 mg), tablets (300 mg), and solution (10 mg/mL)—and a solution for IV use (10 mg/mL). The drug is also available in combination with lamivudine under the trade name Combivir, and in combination with lamivudine and abacavir under the trade name Trizivir.

Oral Therapy. The recommended dosage is 300 mg twice a day or 200 mg 3 times a day. The dosage for treating CNS effects (cognitive slowing, motor slowing, dementia) is 1200 mg/day (ie, twice the normal dosage).

Hematologic monitoring should be done every 2 weeks. If severe anemia or severe neutropenia develops, treatment should be interrupted until there is evidence of bone marrow recovery. If anemia or neutropenia is mild, a reduction in dosage may be sufficient.

Intravenous Therapy: Adults with *Pneumocystis Pneumonia*. Intravenous zidovudine is indicated for adults with AIDS who have a history of cytologically confirmed *Pneumocystis pneumonia* or a CD4 T-cell count below 200 cells/mL. The IV dosage is 1 to 2 mg/kg (infused over 1 hour) every 4 hours around-the-clock. Rapid infusion and bolus injection must be avoided. Intravenous therapy should be stopped as soon as oral therapy is appropriate.

Intravenous solutions are prepared by withdrawing the calculated dose from the stock vial and diluting it to 4 mg/mL (or less) in 5% dextrose for injection. The solution should not be mixed with biologic or colloidal fluids (eg, blood products, protein solutions) and should be administered within 8 hours (if held at room temperature) or within 24 hours (if held under refrigeration).

Intravenous Therapy: Preventing Mother-to-Infant Transmission. Intravenous dosing of the mother during labor and the infant after birth is discussed below under *Preventing Perinatal HIV Transmission*.

Lamivudine (3TC)	Stavudine (d4T)	Tenofovir (TDF)	Zidovudine (ZDV)
Epivir Tablets: 150, 300 mg PO soln: 10 mg/mL	Zerit Capsules: 15, 20, 30, 40 mg PO soln: 1 mg/mL	Viread Tablets: 300 mg	Retrovir Capsules: 100 mg Tablets: 300 mg PO soln: 10 mg/mL IV soln: 10 mg/mL
Adults: 150 mg 2 times/day or 300 mg once/day Children: 4 mg/kg 2 times/day (max 150 mg 2 times/day)	>60 kg: 40 mg 2 times/day <60 kg: 30 mg 2 times/day Note: WHO recommends 30 mg 2 times/day regardless of weight	300 mg once/day	200 mg 3 times/day or 300 mg 2 times/day
Take without regard to meals	Take without regard to meals	Take without regard to meals	Take without regard to meals
86%	86%	39% (with food)	60%
5-7 hr	1 hr	17 hr	1.1 hr
18-22 hr	7.5 hr	More than 60 hr	7 hr
Renal excretion (unchanged)	Partial metabolism followed by renal excretion	Renal excretion	Hepatic metabolism followed by renal excretion
<ul style="list-style-type: none"> Minimal toxicity Lactic acidosis* In patients co-infected with HBV, withdrawing lamivudine may result in severe acute exacerbation of hepatitis. 	<ul style="list-style-type: none"> Lactic acidosis* Pancreatitis Peripheral neuropathy Rapidly progressive neuromuscular weakness (rare) Lipoatrophy Hyperlipidemia Insulin resistance/diabetes 	<ul style="list-style-type: none"> Lactic acidosis* Asthenia Headache GI: nausea, diarrhea, vomiting, flatulence Renal insufficiency Osteomalacia Possible decreased BMD In patients co-infected with HBV, withdrawing tenofovir may result in severe acute exacerbation of hepatitis. 	<ul style="list-style-type: none"> Lactic acidosis* Bone marrow suppression: anemia, neutropenia GI intolerance Headache Insomnia Myopathy Nail pigmentation Hyperlipidemia Lipoatrophy Insulin resistance/diabetes

Other NRTIs

Didanosine

Actions and Uses. Didanosine [Videx, Videx EC], also known as dideoxyinosine (ddI), is an analog of inosine, a naturally occurring nucleoside. The drug is taken up by host cells, where it undergoes conversion to its active form, dideoxyadenosine triphosphate (ddATP). Like the active form of zidovudine, ddATP suppresses viral replication primarily by causing premature termination of the growing DNA strand. In addition, ddATP competes with natural nucleoside triphosphates for binding to the active center of reverse transcriptase, and thereby further suppresses DNA synthesis. In clinical trials, didanosine increased CD4 T-cell counts, decreased viremia, and reduced symptoms in patients with AIDS.

Didanosine is approved only for HIV-1 infection. Because monotherapy with any antiretroviral drug can rapidly lead to resistance, the regimen should always include other antiretroviral drugs.

Pharmacokinetics. Didanosine is administered orally, and bioavailability is low (about 35%). Absorption is greatly reduced by food and gastric acidity. To decrease gastric acidity, and thereby enhance absorption, older formulations of didanosine [Videx] contain buffering agents; newer formulations [Videx EC] are protected by an enteric coating. Didanosine crosses the blood-brain barrier poorly; levels in cerebrospinal fluid are only 20% of those in plasma. Much of the drug (35% to 60%) is excreted unchanged in the

urine. The plasma half-life in patients with normal renal function is 1.5 hours, but is 3 times longer in patients with renal failure. The intracellular half-life is more than 20 hours.

Adverse Effects. Pancreatitis. Pancreatitis, which can be fatal, is the major dose-limiting toxicity. The incidence is 3% to 17%. Patients should be monitored for indications of developing pancreatitis (increased serum amylase in association with increased serum triglycerides; decreased serum calcium; and nausea, vomiting, or abdominal pain). If evolving pancreatitis is diagnosed, didanosine should be withdrawn. The risk of pancreatitis is increased by a history of pancreatitis or alcoholism and by use of IV pentamidine. Caution should be exercised in such patients.

Lactic Acidosis with Hepatic Steatosis. Like all other NRTIs, didanosine can cause lactic acidosis with hepatic steatosis. Fatalities have occurred in several pregnant women taking didanosine plus stavudine. Accordingly, the manufacturer warns against combining these drugs during pregnancy, unless resistance to all other antiretrovirals leaves no option. Because lactic acidosis and hepatic steatosis are potential side effects of all NRTIs, it may be prudent to avoid combining didanosine with any of these drugs during pregnancy.

Other Adverse Effects. Additional adverse effects include diarrhea (28%), peripheral neuropathy (20%), chills or fever (12%), and rash or pruritus (9%). Postmarketing data indicate the drug may also cause retinal

changes, optic neuritis, and insulin resistance/diabetes, and may increase the risk of myocardial infarction (MI). In contrast to zidovudine, didanosine causes minimal bone marrow suppression.

Drug Interactions. For treatment of HIV infection, didanosine can be used in various regimens (see Table 94-8). Buffered didanosine formulations can interfere with the absorption of drugs that require gastric acidity, including delavirdine and indinavir. Ribavirin and allopurinol can increase levels of didanosine, and may thereby pose a risk of toxicity. Accordingly, these combinations should be avoided.

Preparations, Dosage, and Administration. Didanosine is available in two formulations: enteric-coated capsules [Videx EC], and a buffered powder for oral solution [Videx].

Both Formulations. Because absorption is greatly reduced by food, didanosine should be administered on an empty stomach, either 30 minutes before meals or 2 hours after. Because didanosine is eliminated by the kidneys, dosage must be reduced in patients with renal impairment.

Enteric-Coated Capsules. Didanosine enteric-coated capsules [Videx EC] are available in four strengths: 125, 200, 250, and 400 mg. For patients who weigh 60 kg or more, the dosage is 400 mg once daily (or 250 mg once daily with tenofovir). For patients who weigh less than 60 kg, the dosage is 250 mg once daily (or 200 mg once daily with tenofovir).

Buffered Powder for Oral Solution. Didanosine powder for oral solution is available in bottles (2 and 4 gm) for pediatric use. Prior to dispensing, the pharmacist must reconstitute the powder to make a 20-mg/mL solution. Dosage is 200 mg twice daily (for patients over 60 kg) or 125 mg twice daily (for patients under 60 kg).

Stavudine

Actions and Uses. Stavudine [Zerit], also known as didehydrodeoxythymidine (d4T), is an analog of thymidine, a naturally occurring nucleoside. Following uptake by cells, stavudine is converted to its active form, stavudine triphosphate. The active drug then suppresses HIV replication by (1) causing premature termination of the growing DNA strand and (2) competing with natural nucleoside triphosphates for binding to reverse transcriptase.

Stavudine is indicated only for infection with HIV-1. Like all other drugs for HIV, stavudine should be combined with other antiretroviral agents to decrease the risk of resistance.

Pharmacokinetics. Stavudine is administered orally, and bioavailability is high (86%). Food has little or no effect on absorption. Penetration to the CNS is good. Elimination is by a combination of hepatic metabolism and renal excretion. The plasma half-life is 1 hour, and the intracellular half-life is 7.5 hours.

Adverse Effects. Peripheral Neuropathy. Like didanosine, stavudine can cause peripheral neuropathy. In clinical trials, neuropathy developed in 15% to 21% of patients. Patients should be informed about early symptoms of neuropathy (numbness, tingling, or pain in hands and feet) and instructed to report them immediately. Neuropathy may resolve if the drug is withdrawn. If symptoms resolve completely, resumption of treatment may be considered, but the dosage should be reduced.

Pancreatitis. Stavudine can cause pancreatitis. Although the incidence is low (1%), pancreatitis can be fatal. Patients should be monitored for indications of pancreatitis, and, if evolving pancreatitis is diagnosed, stavudine should be withdrawn.

Lactic Acidosis with Hepatic Steatosis. Like all other NRTIs, stavudine can cause lactic acidosis and hepatic steatosis. In fact, the incidence with stavudine may be higher than with all other NRTIs. As noted, fatal lactic acidosis has developed in several pregnant women taking stavudine plus didanosine. Accordingly, the manufacturer warns against combining these drugs during pregnancy, unless resistance to all other antiretrovirals leaves no option. Because lactic acidosis is a potential side effect of all NRTIs, it may be prudent to avoid combining stavudine with any NRTI during pregnancy.

Neuromuscular Weakness. Rarely, stavudine causes ascending demyelinating polyneuropathy, resulting in neuromuscular weakness. Symptoms begin months after initiation of treatment, but then progress rapidly, producing dramatic motor weakness within days to weeks. Some patients may require mechanical ventilation owing to respiratory paralysis. Patients who experience symptoms should discontinue all antiretroviral drugs. Recovery takes several months, and may never be complete.

Other Adverse Effects. Postmarketing reports indicate that stavudine may cause hyperlipidemia, lipoatrophy, and insulin resistance/diabetes.

Drug Interactions. Like stavudine, didanosine can cause peripheral neuropathy. Accordingly, the combination should be used with caution.

Preparations, Dosage, and Administration. Stavudine [Zerit] is available in capsules (15, 20, 30, and 40 mg) and a powder for oral solution (1 mg/mL). Dosing may be done with or without food. The adult dosage is

40 mg twice a day (for patients over 60 kg) and 30 mg twice a day (for patients under 60 kg).

Lamivudine

Actions and Uses. Lamivudine [Epivir], also known as dideoxy-3-thiacytidine (3TC), is an analog of cytidine, a naturally occurring nucleoside. Following uptake by cells, the drug is converted to its active form, lamivudine triphosphate, which then suppresses HIV replication by (1) causing premature termination of the growing DNA strand and (2) competing with natural nucleoside triphosphates for binding to reverse transcriptase.

Lamivudine is approved for treating infection with HIV-1 and hepatitis B virus (HBV). The formulation used for HIV-1 is marketed as Epivir, and the formulation for HBV is marketed as Epivir HBV (see Chapter 93). Like all other drugs used against HIV, lamivudine should be combined with at least one other antiretroviral agent, so as to decrease the risk of resistance.

Pharmacokinetics. Lamivudine is administered orally, and bioavailability is high (86%). Food reduces the rate of absorption but not the extent. The drug is eliminated intact in the urine. The plasma half-life is 5 to 7 hours, and the intracellular half-life is 18 to 22 hours.

Adverse Effects. Of all the NRTIs, lamivudine is the best tolerated. Side effects are minimal. Some patients experience insomnia and headache, but these effects usually fade in a few weeks.

Like all other NRTIs, lamivudine poses a small risk of potentially fatal lactic acidosis. Combining NRTIs may increase the risk of lactic acidosis in pregnant women, and hence should be avoided when feasible.

In patients co-infected with HBV, withdrawal of lamivudine may result in severe acute exacerbation of hepatitis.

Preparations, Dosage, and Administration. For treatment of HIV, lamivudine [Epivir] is available alone in tablets (150 and 300 mg) and an oral solution (10 mg/mL). The drug is also available in three fixed-dose combinations: lamivudine/zidovudine [Combivir], lamivudine/abacavir [Epzicom], and lamivudine/abacavir/zidovudine [Trizivir]. The dosage for adults is 300 mg/day once daily or 150 mg twice daily. The dosage for children ages 3 months to 16 years is 4 mg/kg twice daily (up to a maximum of 150 mg twice daily). In patients with renal impairment, dosage should be reduced. Lamivudine may be administered with or without food.

Abacavir

Actions and Use. Abacavir [Ziagen], also known as ABC, is an analog of guanine, a naturally occurring pyrimidine. The drug is taken up by host cells, and then undergoes conversion to its active form, carbovir triphosphate, an analog of deoxyguanosine triphosphate. Carbovir triphosphate suppresses viral replication by causing premature termination of the growing DNA strand and by competing with natural nucleoside triphosphates for binding to the active center of reverse transcriptase.

Abacavir is approved only for HIV-1 infection. Because monotherapy with any antiretroviral drug can rapidly lead to resistance, abacavir should always be combined with other antiretroviral agents.

Pharmacokinetics. Abacavir is administered orally, and bioavailability is high (83%). Absorption is not affected by food. Penetration to cerebrospinal fluid is good. The drug is converted to inactive metabolites by alcohol dehydrogenase. Metabolites are excreted in the urine. The plasma half-life is 1.5 hours, and the intracellular half-life is 12 to 26 hours.

Adverse Effects. Hypersensitivity Reactions. Hypersensitivity reactions occur in 5% to 8% of patients. These reactions, which usually develop during the first 6 weeks of treatment, can be severe and even fatal. Symptoms include fever, rash (typically maculopapular or urticarial), myalgia, arthralgia, and GI disturbances (nausea, vomiting, diarrhea, abdominal pain). A severe reaction can result in liver failure, renal failure, anaphylaxis, and death. If a hypersensitivity reaction occurs, abacavir should be withdrawn and never used again.

Abacavir hypersensitivity reactions can manifest initially as respiratory symptoms (eg, pharyngitis, dyspnea, cough). Because abacavir hypersensitivity can rapidly prove fatal, early recognition is critical. Accordingly, if respiratory symptoms develop, abacavir hypersensitivity should be suspected, even though alternative diagnoses (eg, pneumonia, bronchitis, pharyngitis, flu-like illness) are possible. If a clear differentiation between acute respiratory illness and abacavir hypersensitivity cannot be made, abacavir should be withdrawn and never used again.

A specific genetic variation, known as HLA-B*5701, is strongly associated with abacavir hypersensitivity. Therefore, all candidates for abacavir should be screened for this variation. Patients who test positive for HLA-B*5701 should not receive the drug, and abacavir hypersensitivity should be noted on their allergy list. Those who test negative are less likely to experience hypersensitivity, but should be counseled about the symptoms of the reaction nonetheless.

Myocardial Infarction. There has been concern that abacavir may increase the risk of myocardial infarction (MI). However, a 2011 report from the Food and Drug Administration (FDA) seems to have put this concern to rest. After analyzing 26 randomized controlled trials, the FDA found no statistically significant association between MI and abacavir-containing regimens.

Other Adverse Effects. Abacavir can cause nausea (13%), nausea with vomiting (9%), diarrhea (7%), and headache (10%). Like all other NRTIs, abacavir poses a small risk of potentially fatal lactic acidosis with hepatic steatosis. Combining NRTIs may increase the risk of lactic acidosis in pregnant women, and hence should be avoided when feasible.

Drug Interactions. Alcohol can compete with abacavir for metabolism by alcohol dehydrogenase, and can thereby increase abacavir levels substantially (about 40%). The clinical significance of this interaction is unclear. Nonetheless, it would seem prudent to minimize alcohol consumption. Significant interactions with drugs other than alcohol have not been reported.

Preparations, Dosage, and Administration. Preparations. Abacavir [Ziagen] is available in 300-mg tablets and a 20-mg/mL oral solution. In addition, abacavir is available in two fixed-dose combinations: abacavir/lamivudine [Epzicom] and abacavir/zidovudine/lamivudine [Trizivir].

Dosage and Administration. Abacavir may be taken with or without food. The adult dosage is 300 mg twice daily or 600 mg once daily. The pediatric dosage is 8 mg/kg twice daily, but should not exceed 300 mg twice daily.

Tenofovir Disoproxil Fumarate

Mechanism of Action. Tenofovir disoproxil fumarate (TDF) [Viread] is a nucleotide reverse transcriptase inhibitor—not a nucleoside reverse transcriptase inhibitor. The drug is discussed in this section because nucleotides and nucleosides are very similar (a nucleotide is simply a nucleoside with a phosphate group added) and hence have similar effects on reverse transcriptase. Once inside cells, TDF undergoes conversion to tenofovir, and then to tenofovir diphosphate, its active form. Like the NRTIs, tenofovir diphosphate inhibits viral DNA synthesis in two ways: (1) it competes with the natural substrate (in this case, deoxyadenosine triphosphate) for binding to reverse transcriptase, and (2) after being incorporated into the growing DNA chain, it causes premature chain termination. Toxicity results in part from inhibiting mitochondrial DNA polymerase.

Therapeutic Use. Tenofovir was originally approved only for HIV-1, but is now approved for HBV too. To delay emergence of resistant HIV, the regimen should always include other antiretroviral drugs.

Pharmacokinetics. Tenofovir is administered orally, and bioavailability is low (25% in the absence of food and 39% in the presence of food). Blood levels peak about 1 hour after dosing. Binding to plasma proteins is low. Tenofovir is eliminated primarily by the kidneys; both glomerular filtration and active tubular secretion are involved. Because elimination is renal, tenofovir can accumulate to dangerous levels if kidney function is impaired. Tenofovir has a prolonged half-life—17 hours in plasma and more than 60 hours within cells—and hence can be administered just once a day.

Adverse Effects. Tenofovir is generally well tolerated. The most common reactions are asthenia (8%), headache (6%), and mild to moderate GI effects: nausea (11%), diarrhea (9%), vomiting (5%), and flatulence (4%).

Because tenofovir can suppress HBV, patients co-infected with HBV may experience a severe exacerbation of hepatitis when tenofovir is withdrawn.

Postmarketing data indicate that tenofovir can reduce bone mineral density (BMD), and can thereby increase the risk of osteoporotic fractures of the hip, vertebrae, and wrist.

Rarely, tenofovir has been associated with renal toxicity, indicated by elevated serum creatinine and proteinuria. Since tenofovir is excreted by the kidneys, renal damage increases the risk of drug accumulation to dangerous levels.

Like other NRTIs, tenofovir poses a small risk of potentially fatal lactic acidosis with hepatic steatosis. Combining NRTIs may increase risk in pregnant women, and hence should be avoided when feasible.

Drug Interactions. Tenofovir has little or no effect on the metabolism of other drugs. However, combining tenofovir with another drug that undergoes active tubular secretion could lead to the accumulation of tenofovir, the other drug, or both. Through a mechanism that has not been determined, tenofovir can raise plasma levels of didanosine. Accordingly, patients using the combination should be monitored for long-term didanosine toxicity.

Preparations, Dosage, and Administration. Preparations. Tenofovir, by itself, is available in 300-mg tablets under the name Viread. The drug is also available in three fixed-dose combinations: tenofovir/emtricitabine [Truvada], tenofovir/emtricitabine/efavirenz [Atripla], and tenofovir/emtricitabine/rilpivirine [Complera].

Dosage and Administration. The recommended dosage is 300 mg once a day, taken with or without food. If the patient is also taking didanosine, tenofovir should be administered 2 hours before didanosine or 1 hour after. Patients with significant renal impairment (creatinine clearance below 60 mL/min) should not use the drug.

Emtricitabine

Actions and Uses. Emtricitabine [Emtriva] is a fluorinated derivative of lamivudine. Like lamivudine, emtricitabine is active against HIV-1 and HBV. Following uptake by cells, emtricitabine is converted to emtricitabine triphosphate, its active form, which inhibits viral DNA synthesis by (1) competing with natural substrates for binding to reverse transcriptase and (2) promoting premature termination of the growing DNA strand. Emtricitabine is a weak inhibitor of mammalian DNA polymerases, both nuclear and mitochondrial. The drug has a long intracellular half-life, and hence dosing can be done just once a day.

Pharmacokinetics. Emtricitabine undergoes rapid and nearly complete absorption, both in the presence and absence of food. Plasma levels peak 1 to 2 hours after dosing. Protein binding in blood is minimal, as is hepatic metabolism. Most of each dose is eliminated unchanged in the urine. The plasma half-life is 10 hours, and the intracellular half-life is more than 20 hours.

Adverse Effects. Emtricitabine is generally well tolerated. The most common adverse effects are headache, diarrhea, nausea, and rash. An unusual side effect—hyperpigmentation of the palms and soles—develops in some patients. Like other nucleoside analogs, emtricitabine may pose a risk of lactic acidosis and severe hepatomegaly with steatosis, usually in women. If either complication arises, emtricitabine should be withdrawn. Because emtricitabine can suppress HBV, patients co-infected with HBV may experience a severe exacerbation of hepatitis when emtricitabine is discontinued.

Drug Interactions. Emtricitabine does not induce or inhibit cytochrome P450, and hence is unlikely to interact with other drugs. No significant interactions were noted in patients taking emtricitabine with indinavir, stavudine, famciclovir, or tenofovir.

Preparations, Dosage, and Administration. Preparations. Emtricitabine [Emtriva] is supplied in 200-mg capsules and an oral solution (10 mg/mL). The drug is also available in three fixed-dose combinations: emtricitabine/tenofovir [Truvada], emtricitabine/tenofovir/efavirenz [Atripla], and emtricitabine/tenofovir/rilpivirine [Complera].

Dosage and Administration. Dosing may be done with or without food. For patients with normal kidney function, the dosage is as follows:

- Adults—200 mg once a day (using the capsules) or 240 mg once a day (using the oral solution)
- Pediatric patients 0 to 3 months old—3 mg/kg once daily
- Pediatric patients 3 months through 17 years old—6 mg/kg once daily (max 240 mg/day)

Because emtricitabine is eliminated primarily by the kidneys, the dosing interval should be increased in patients with renal impairment.

Combination Products

The availability of combination antiretroviral products has reduced simplified treatment. In fact, with two combination products—Atripla and Complera—patients can now be treated with one pill once a day.

Abacavir/Zidovudine/Lamivudine. Abacavir, lamivudine, and zidovudine are available in a single tablet under the trade name *Trizivir*. The amount of each drug in the combination is the same as in their individual formulations: abacavir, 300 mg; lamivudine, 150 mg; and zidovudine, 300 mg. Dosing is done twice a day—the same schedule employed when the drugs are taken separately. The only benefit of the combination is that patients can now take just one pill twice a day, instead of three pills twice a day. Dosing may be done with or without food. Because dosage of each component cannot be adjusted separately, the product should not be used by patients with renal or hepatic impairment.

Adverse effects are like those seen with each component taken separately. Abacavir can cause potentially fatal hypersensitivity reactions. Early manifestations include fever, rash, fatigue, GI symptoms, and respiratory symptoms. If these develop, treatment should be interrupted while an evaluation is conducted. If hypersensitivity cannot be ruled out, the drug should be discontinued permanently. Before *Trizivir* is used, patients should be screened for HLA-B*5701, a genetic variant strongly associated with hypersensitivity. Patients who test positive for HLA-B*5701 should not get the drug. Zidovudine can cause anemia and neutropenia. Hematologic status should be closely monitored. In patients co-infected with HBV, discontinuation of *Trizivir* can lead to exacerbation of hepatitis (because lamivudine had been keeping HBV in check). All nucleosides can cause lactic acidosis and severe hepatomegaly with steatosis.

Abacavir/Lamivudine. Abacavir (600 mg) and lamivudine (300 mg) are available in a single tablet, sold as *Epzicom*, for treating HIV-1 infection in adults. The dosage is 1 tablet once a day. Adverse effects are similar to those seen with each drug taken separately—although the incidence of severe hypersensitivity reactions from abacavir may be higher than usual, owing to dosing once daily rather than twice daily. Before *Epzicom* is used, patients should be screened for HLA-B*5701, a genetic variant strongly associated with hypersensitivity. Patients who test positive for HLA-B*5701 should not get the drug. Both components pose a small risk of fatal lactic acidosis and severe hepatomegaly with steatosis. In patients co-infected with HBV, discontinuation of *Epzicom* can cause exacerbation of hepatitis (because lamivudine had been keeping HBV in check). The product is contraindicated for patients with hepatic impairment or renal insufficiency (creatinine clearance [CrCl] below 50 mL/min).

Emtricitabine/Tenofovir. Emtricitabine (200 mg) and tenofovir (300 mg) are available in a single tablet, sold as *Truvada*, for treating HIV-1 infection in adults. Adverse effects are similar to those of each drug taken alone. Lactic acidosis and hepatomegaly are the greatest concerns. In patients co-infected with HBV, discontinuation of *Truvada* can lead to exacerbation of hepatitis (because both emtricitabine and lamivudine had been keeping HBV in check). The dosage for *Truvada* is 1 tablet once a day, taken with or without food. For patients with renal impairment, dosage must be adjusted as follows: CrCl 30 to 49 mL/min, 1 tablet every 48 hours; CrCl below 30 mL/min (including patients on dialysis), don't use this product.

Lamivudine/Zidovudine. Lamivudine (150 mg) and zidovudine (300 mg) are available in a single tablet under the name *Combivir*. The dosage for adults and for children at least 12 years old is 1 tablet twice a day, taken without regard to meals. Because the dosage of each component cannot be adjusted separately, the product should not be used by patients with renal or hepatic impairment. Principal adverse effects are anemia and neutropenia (caused by zidovudine) and lactic acidosis with hepatic steatosis (caused by both drugs). In patients co-infected with HBV, discontinuation of *Combivir* can lead to exacerbation of hepatitis (because lamivudine had been keeping HBV in check).

Emtricitabine/Tenofovir/Efavirenz. This fixed-dose combination, sold as *Atripla*, was the first product to contain drugs from two different antiretroviral classes: emtricitabine (200 mg) and tenofovir (300 mg) are NRTIs, whereas efavirenz (600 mg) is an NNRTI. The combination is a recommended first-line regimen for treatment-naïve patients. Dosing is done just once a day (on an empty stomach), making *Atripla* the first *one-pill once-a-day* HIV treatment. Adverse effects are like those seen with each component taken separately. Primary concerns are CNS disturbances, rash, and lactic acidosis with hepatomegaly. In patients co-infected with HBV, discontinuation of *Atripla* can lead to exacerbation of hepatitis (because both emtricitabine and tenofovir had been keeping HBV in check). Efavirenz is teratogenic, and hence the combination must be avoided during pregnancy.

Emtricitabine/Tenofovir/Rilpivirine. Like *Atripla*, this fixed-dose combination, sold as *Complera*, contains drugs from two different antiretroviral classes: emtricitabine (200 mg) and tenofovir (300 mg) are NRTIs, whereas rilpivirine (25 mg) is an NNRTI. The combination is a recommended first-line regimen for treatment-naïve patients. Dosing is done once a day with food. Adverse effects are like those seen with each component taken separately. Primary concerns are depression, insomnia, and lactic acidosis with hepatomegaly. In patients co-infected with HBV, discontinuation of *Complera* can lead to exacerbation of hepatitis (because both emtricitabine and tenofovir had been keeping HBV in check). *Complera* is subject to many drug interactions, primarily because of rilpivirine.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) differ from the NRTIs in structure and mechanism of action. As their name suggests, the NNRTIs have no structural relationship with naturally occurring nucleosides. Also, in contrast to the NRTIs, which inhibit synthesis of HIV DNA primarily by causing premature termination of the growing DNA strand, the NNRTIs bind to the active center of reverse transcriptase, and thereby cause direct inhibition. Furthermore, whereas all NRTIs must undergo intracellular conversion to their active forms, the NNRTIs are active as administered. At this time, five NNRTIs

are available: efavirenz [*Sustiva*], nevirapine [*Viramune*], delamanvir [*Rescriptor*], etravirine [*Intelence*], and rilpivirine [*Edurant*]. The principal adverse effect of these drugs is rash, which can be severe. Pharmacologic properties of the NNRTIs are summarized in Table 94-4.

Efavirenz

Efavirenz [*Sustiva*] is the only NNRTI deemed a preferred agent for treating HIV. The drug is effective and, because of its long half-life, can be administered once a day. Its principal drawbacks are teratogenicity and transient adverse CNS effects.

Mechanism of Action. Efavirenz binds directly to HIV reverse transcriptase and thereby disrupts the active center of the enzyme. As a result, enzyme activity is suppressed. Efavirenz only inhibits reverse transcriptase of HIV-1; it does not inhibit reverse transcriptase of HIV-2. In addition, efavirenz does not inhibit human DNA polymerases, and hence is harmless to us.

Therapeutic Use. Efavirenz is the only NNRTI recommended as first-line therapy for HIV infection. In clinical trials, the combination of efavirenz plus two NRTIs (zidovudine and lamivudine) was at least as effective as indinavir (a protease inhibitor) combined with the same two NRTIs. Furthermore, the efavirenz-based regimen was better tolerated. Like all other drugs for HIV infection, efavirenz should be used only in combination with other antiretroviral agents.

Pharmacokinetics. Efavirenz is administered orally and should be taken on an empty stomach. Administration with a high-fat meal can increase plasma levels by 39% (using efavirenz capsules) and by 50% (using efavirenz tablets). Plasma levels peak 3 to 5 hours after dosing. In the blood, efavirenz is highly (over 99%) protein bound. The drug crosses the blood-brain barrier and can reduce HIV levels in the CNS. Efavirenz undergoes metabolism by CYP3A4 and CYP2B6, followed by excretion in the urine and feces. The drug has a long serum half-life (40 to 55 hours), and hence can be taken just once a day.

Adverse Effects. CNS symptoms occur in over 50% of patients. The most common are dizziness, insomnia, impaired consciousness, drowsiness, vivid dreams, and nightmares. Delusions, hallucinations, and severe acute depression may also occur, primarily in patients with a history of mental illness or drug abuse. Patients who experience these severe reactions should discontinue the drug. CNS symptoms are prominent at the onset of treatment, but generally resolve within 2 to 4 weeks, despite continuous drug use.

Rash, which can be severe, occurs often. In clinical trials, rash developed in 27% of adults and 40% of children. The median time to rash onset was 11 days, and the median duration was 14 days. Rash can range in severity from mild (erythema, pruritus) to moderate (diffuse maculopapular rash, dry desquamation) to severe (vesiculation, moist desquamation, ulceration). Very rarely, rash evolves into potentially fatal Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis. Accordingly, if severe rash occurs, efavirenz should be withdrawn immediately. Mild rash may respond to antihistamines and topical glucocorticoids.

Efavirenz is *teratogenic*. In monkeys, doses equivalent to those used in humans produced a high incidence of fetal malformation. Women using the drug must avoid getting pregnant. A barrier method of birth control (eg, condom) should be used in conjunction with a hormonal method (eg, oral contracep-

ive). Pregnancy must be ruled out before efavirenz is used. Efavirenz is classified in FDA Pregnancy Risk Category D.

Like other NNRTIs, efavirenz may pose a risk of *liver damage*. Liver enzymes should be monitored, especially in patients with hepatitis B or C.

Drug Interactions. Efavirenz can compete with other drugs for metabolism by cytochrome P450, thereby causing them to accumulate, possibly to dangerous levels. To avoid harm, efavirenz should not be combined with cisapride, alprazolam, midazolam, triazolam, dihydroergotamine, or ergotamine—or with astemizole or terfenadine, which are no longer available in the United States.

Efavirenz *induces P450*, and can thereby accelerate its own metabolism and the metabolism of many other drugs. Increased metabolism of two protease inhibitors—saquinavir and indinavir—is of particular concern. If efavirenz is combined with indinavir, the dosage of indinavir should be increased. Combined use with saquinavir, a drug with low bioavailability, should be avoided.

By inducing P450, efavirenz can decrease the effects of *hormonal contraceptives*, including oral contraceptives and the etonogestrel contraceptive implant. Contraceptive failure can result. Since efavirenz is teratogenic, it is essential that women of child-bearing potential use a barrier contraceptive in addition to any hormonal contraceptive.

Combining efavirenz with ritonavir (a protease inhibitor that inhibits P450) can increase levels of both drugs. Toxicity may result.

St. John's wort—an herbal supplement taken for depression—may reduce levels of efavirenz and other NNRTIs. The principal mechanism is accelerated metabolism secondary to induction of P450 (see Chapter 108).

Preparations, Dosage, and Administration. Efavirenz [Sustiva] is available in 600-mg tablets and in capsules (50 and 200 mg). The adult dosage is 600 mg taken once daily on an empty stomach, preferably at bedtime (to reduce the impact of CNS effects).

Other NNRTIs

Nevirapine

Mechanism of Action. Like other NNRTIs, nevirapine [Viramune, Viramune XR] binds directly to HIV reverse transcriptase, causing noncompetitive inhibition of the enzyme. Nevirapine is selective for HIV-1. It does not affect HIV-2, and does not inhibit human DNA polymerase.

Pharmacokinetics. Nevirapine is well absorbed (over 90%) following oral administration, both in the presence and absence of food. The drug is very lipid soluble, and hence can cross both the placenta and blood-brain barrier, and can enter breast milk with ease. Concentrations achieved in cerebrospinal fluid are about 45% of those in plasma. Elimination results from hepatic metabolism followed by excretion in the urine (80%) and feces.

Therapeutic Use and Resistance. Nevirapine is approved only for treating infection with HIV-1; the drug is not active against HIV-2. Resistance to nevirapine develops rapidly if the drug is used alone. Accordingly, nevirapine should always be combined with other antiretroviral drugs.

Adverse Effects. The most common adverse effect is *rash*, which usually occurs early in therapy and can be severe or even life threatening. For most patients, the rash is benign and, if needed, can be managed with an antihistamine or topical glucocorticoid. However, if the patient experiences severe rash or rash associated with fever, blistering, oral lesions, conjunctivitis, muscle pain, or joint pain, nevirapine should be withdrawn. Why? Because these symptoms may indicate development of *erythema multiforme* or *Stevens-Johnson syndrome*. Rash can be minimized by using a low dosage initially and then increasing the dosage if rash does not occur.

Nevirapine can cause severe *hepatotoxicity* including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure. Fatalities have occurred. The risk is highest during the first 12 weeks of treatment, and is increased by a history of chronic hepatitis B or hepatitis C. Liver function tests should be done at baseline, prior to dosage escalation, 2 weeks after dosage

escalation, and whenever patients have symptoms (fatigue, malaise, anorexia, nausea) suggesting an early stage of liver damage. If hepatotoxicity is diagnosed, nevirapine should be withdrawn as soon as possible.

Drug Interactions. Nevirapine induces cytochrome P450, and can thereby increase the metabolism of other drugs, causing their levels to decline. The ability to decrease levels of *protease inhibitors*, *hormonal contraceptives*, and *methadone* is of particular concern.

Like nevirapine, *rifampin* can induce P450, and can thereby significantly reduce nevirapine levels. Accordingly, the combination is not recommended.

St. John's wort induces P450, and can thereby reduce levels of nevirapine. The combination should be avoided.

Preparations, Dosage, and Administration. Nevirapine is available in 200-mg immediate-release tablets and a 10-mg/mL oral suspension, both sold as Viramune, and in extended-release tablets sold as Viramune XR. Viramune XR is approved only for adults; Viramune is approved for adults and children. Dosages are as follows:

- **Adults**—Start with 200 mg once a day for 14 days and then, if no rash develops, switch to either (1) 200 mg twice daily (using the oral solution or immediate-release tablets) or (2) 400 mg once daily (using the extended-release tablets).
- **Children 15 days and older**—Start with 150 mg/m² daily for 14 days and then, if no rash develops, use 150 mg/m² twice daily thereafter.

Delavirdine

Actions, Resistance, and Use. Delavirdine [Rescriptor] is similar to efavirenz in actions and uses. Like efavirenz, delavirdine is a non-nucleoside that acts directly to inhibit reverse transcriptase, thereby suppressing HIV replication. Because resistant forms of HIV rapidly emerge when delavirdine is used alone, the drug should always be combined with other antiretroviral agents. Like efavirenz, delavirdine is active only against HIV-1.

Adverse Effects. Like efavirenz, delavirdine causes potentially serious *rash and other hypersensitivity reactions*. In clinical trials, rash developed in up to 50% of patients; erythema multiforme and Stevens-Johnson syndrome have been reported rarely. If severe rash develops, the drug should be withdrawn. Other common side effects include headache, fatigue, GI intolerance (nausea, vomiting, diarrhea), and elevation of liver enzymes.

Drug Interactions. In contrast to efavirenz and nevirapine, which induce cytochrome P450, delavirdine *inhibits* cytochrome P450. As a result, levels of drugs taken concurrently may rise. To avoid toxicity from excessive drug levels, patients should not take cisapride, alprazolam, midazolam, triazolam, lovastatin, or simvastatin—or astemizole or terfenadine, which are no longer available in the United States. Other drugs whose levels may be increased include indinavir, saquinavir, clarithromycin, dapsone, warfarin, quinidine, ergot alkaloids, phosphodiesterase type 5 (PDE5) inhibitors (eg, sildenafil [Viagra]), and the dihydropyridine-type calcium channel blockers; all of these agents should be used with caution.

Agents that induce P450 (eg, *St. John's wort*, rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine) may decrease levels of delavirdine, and may thereby reduce antiviral effects. Don't use delavirdine with these agents.

Drugs that reduce gastric acidity—antacids, histamine₂ (H₂) receptor antagonists, proton pump inhibitors, and buffered didanosine formulations—can decrease absorption of delavirdine.

Preparations, Dosage, and Administration. Delavirdine [Rescriptor] is available in 100- and 200-mg tablets. The recommended dosage is 400 mg 3 times a day, taken with or without food. Patients who are unable to swallow tablets whole can mix 4 of the 100-mg tablets with water (at least 3 ounces) and swallow the resulting suspension. The 200-mg tablets should be swallowed whole. Acidity enhances delavirdine absorption. Accordingly, patients with achlorhydria (lack of stomach acid) should administer delavirdine with an acidic beverage (eg, orange juice, cranberry juice).

Etravirine

Actions and Use. Etravirine [Intelence], approved in 2008, is similar to other NNRTIs in actions and uses. The drug is a non-nucleoside that binds to and inhibits reverse transcriptase, and thereby suppresses HIV replication. Like other NNRTIs, etravirine is active only against HIV-1. The drug does not inhibit human DNA polymerases. Etravirine is indicated for treatment-experienced adults infected with HIV-1 strains resistant to other NNRTIs and other antiretroviral drugs, and must always be combined with other effective agents. In many cases, etravirine is effective against HIV strains resistant to other NNRTIs and to PIs.

Pharmacokinetics. Etravirine is administered orally and should be taken following a meal. Why? Because food increases absorption by 50%. In the blood, the drug is 99% protein bound, primarily to albumin. Etravirine is

TABLE 94-4 ■ Properties of Non-nucleoside Reverse Transcriptase Inhibitors

	Delavirdine (DLV)	Efavirenz (EFV)	Etravirine (ETR)	Nevirapine (NVP)	Rilpivirine (RPV)
Trade Name	Rescriptor	Sustiva	Intelence	Viramune, Viramune XR	Edurant
Formulations	Tablets: 100, 200 mg	Capsules: 50, 200 mg Tablets: 600 mg	Tablets: 100, 200 mg	Tablets, IR: 200 mg Tablets, XR: 400 mg PO suspension: 100 mg/10 mL	Tablets: 25 mg
Impact of Food	Take with or without food	Take on an empty stomach. High-fat meals increase plasma levels by 39% with capsules and by 79% with tablets.	Take following a meal	Take with or without food	Take with food
Dosage	400 mg 3 times/day (can mix four 100-mg tablets in 3 or more ounces of water to produce a slurry; 200-mg tablets should be taken intact)	600 mg once daily, preferably at bedtime	200 mg twice a day	200 mg once a day for 14 days, then either 200 mg twice a day (with IR tablets or oral suspension) or 400 mg once a day (with XR tablets)	25 mg once a day
Bioavailability	85%	Data not available	Data not available	Over 90%	Data not available
Serum Half-life	5.8 hr	40–55 hr	41 hr	25–30 hr	50 hr
Elimination	Metabolized by P450, followed by excretion in urine (51%) and feces (44%)	Metabolized by CYP3A4 and CYP2B6, followed by excretion in the urine (14–34%) and feces (16–61%)	Metabolized by CYP3A4, CYP2C9, and CYP2C19, followed by excretion in urine (1.2%) and feces (93.7%)	Metabolized by P450, followed by excretion in urine (80%) and feces (10%)	Metabolized by CYP3A4, followed by excretion in the feces (85%) and urine (6.1%)
Adverse Events	<ul style="list-style-type: none"> • Rash* • Increased transaminase levels • Nausea • Headache 	<ul style="list-style-type: none"> • Rash* • Increased transaminase levels • CNS symptoms[†] • Hyperlipidemia • Teratogenic in monkeys 	<ul style="list-style-type: none"> • Rash* • Increased transaminase levels • Diarrhea • Nausea • Increased amylase • Elevated creatinine 	<ul style="list-style-type: none"> • Rash* • Increased transaminase levels • Hepatitis 	<ul style="list-style-type: none"> • Rash* • Depression • Insomnia • Headache
Drug Interactions	<ul style="list-style-type: none"> • Inhibits P450 and may thereby increase levels of other drugs. • Because of P450 inhibition, the following drugs are contraindicated: astemizole,[‡] terfenadine,[‡] alprazolam, midazolam, triazolam, simvastatin, lovastatin, and cisapride. 	<ul style="list-style-type: none"> • Efavirenz can compete with other drugs for metabolism by P450, thereby causing them to accumulate to toxic levels. Accordingly, efavirenz should not be combined with astemizole,[‡] terfenadine,[‡] cisapride, midazolam, alprazolam, triazolam, or ergot alkaloids. 	<ul style="list-style-type: none"> • The following drugs can decrease etravirine levels: anticonvulsants, darunavir/ritonavir, ritonavir, saquinavir/ritonavir, tipranavir/ritonavir, St. John's wort, and systemic dexamethasone. 	<ul style="list-style-type: none"> • Induces P450 and may thereby decrease levels of other drugs; effects on protease inhibitors, oral contraceptives, and methadone are of particular concern. 	<ul style="list-style-type: none"> • The following drugs can decrease rilpivirine levels and hence are contraindicated: anticonvulsants (eg, carbamazepine, phenytoin), rifamycins (eg, rifabutin, rifampin), proton pump inhibitors (eg, esomeprazole, pantoprazole), glucocorticoids (if more than one dose is taken), and St. John's wort.

TABLE 94-4 • Properties of Non-nucleoside Reverse Transcriptase Inhibitors—cont'd

	Delavirdine (DLV)	Efavirenz (EFV)	Etravirine (ETR)	Nevirapine (NVP)	Rilpivirine (RPV)
Drug interactions (continued)	<ul style="list-style-type: none"> Because of P450 inhibition, the following drugs should be used with caution: indinavir, saquinavir, clarithromycin, dapson, ergot alkaloids, dihydropyridine, calcium channel blockers, quinidine, warfarin, and sildenafil [Viagra]. Antacids, histamine₂ receptor blockers (eg, cimetidine), proton pump inhibitors (eg, omeprazole), and buffered formulations of didanosine can decrease absorption of delavirdine. Rifampin, rifabutin, and St. John's wort induce P450 and can thereby greatly reduce levels of delavirdine. Don't use delavirdine with these agents. 	<ul style="list-style-type: none"> Efavirenz induces P450, and can thereby decrease levels of saquinavir and indinavir. Don't combine with saquinavir. Increase indinavir dosage. By inducing P450, efavirenz can render hormonal contraceptives ineffective. Combining efavirenz with ritonavir increases levels of both drugs; toxicity can result. St. John's wort induces P450 and can thereby reduce levels of efavirenz. Don't combine efavirenz with this agent. 	<ul style="list-style-type: none"> The following drugs can increase etravirine levels: itraconazole, ketoconazole, fluconazole, posaconazole, and diazepam. 	<ul style="list-style-type: none"> Rifampin and St. John's wort induce P450, and may thereby decrease levels of nevirapine. Don't use nevirapine with these agents. 	<ul style="list-style-type: none"> Antacids and histamine₂ receptor blockers (eg, cimetidine) can decrease absorption of rilpivirine. Azole antifungal drugs (eg, ketoconazole, itraconazole) and macrolide antibiotics (eg, erythromycin, clarithromycin) induce P450, and therefore can lower rilpivirine levels.

IR = immediate release, XR = extended release.

*Rarely, rash evolves into Stevens-Johnson syndrome, which can be fatal.

[†]CNS symptoms, including dizziness, somnolence, insomnia, abnormal dreams, abnormal thinking, confusion, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria, occur in about 50% of patients.

[‡]No longer available in the United States.

Adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, prepared by the Panel on Clinical Practices for Treatment of HIV Infection, convened by the DHHS, as updated on October 14, 2011.

metabolized by cytochrome P450 isozymes (primarily CYP3A4, CYP2C9, and CYP2C19) and then excreted in the urine and feces. The serum half-life is 41 hours.

Adverse Effects. Etravirine is generally well tolerated. However, like other NNRTIs, etravirine can cause *rash and other hypersensitivity reactions*, some of which can be fatal. In clinical trials, mild to moderate rash developed in up to 9% of patients, but the incidence of severe skin reactions—Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme—was low: less than 1%. Etravirine should be discontinued immediately if a severe hypersensitivity reaction develops. Signs and symptoms include severe rash, or rash accompanied by fever, malaise, fatigue, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, muscle aches, or joint aches.

Other adverse effects include nausea (4.7%), vomiting (2.3%), diarrhea (5.2%), abdominal pain (3%), fatigue (3.3%), headache (2.7%), peripheral neuropathy (2.8%), and hypertension (2.8%).

Use in Pregnancy and Lactation. No adequate studies have been conducted in pregnant women. Etravirine is classified in FDA Pregnancy Risk Category B. However, even though etravirine may be safe, mothers with HIV should not breast-feed, owing to the risk of transmitting HIV to the infant.

Drug Interactions. Etravirine is subject to many drug interactions. As noted, etravirine is a substrate for CYP3A4, CYP2C9, and CYP2C19. In addition, it can induce 3A4 and inhibit 2C9 and 2C19. Accordingly, the following generalities apply:

- Drugs that inhibit CYP3A4, CYP2C9, or CYP2C19 may raise etravirine levels.
- Drugs that induce CYP3A4, CYP2C9, or CYP2C19 may reduce etravirine levels.
- Etravirine can reduce levels of drugs that are substrates for 3A4.
- Etravirine can raise levels of drugs that are substrates for 2C9 and 2C19.

Some specific interacting drugs are listed in Table 94-4.

Preparations, Dosage, and Administration. Etravirine [Intelence] is available in 100- and 200-mg tablets. The adult dosage is 200 mg twice taken daily following a meal.

Rilpivirine

Actions and Use. Rilpivirine [Edurant], approved in 2011, is similar to other NNRTIs in actions and uses. The drug binds to and inhibits reverse transcriptase, and thereby suppresses HIV replication. Like other NNRTIs, rilpivirine is active only against HIV-1. The drug is indicated for use with other antiretroviral drugs to treat HIV-1 infection in treatment-naïve adults. Compared with efavirenz, rilpivirine is just as effective and possibly better tolerated—but carries a greater risk of resistance and virologic failure, especially in patients with a high viral load (>100,000 virions/mL).

Pharmacokinetics. Rilpivirine is administered by mouth and should be taken with food. Why? Because food increases absorption by 50%. In the blood, the drug is 99.7% protein bound, primarily to albumin. Rilpivirine un-

dergoes hepatic metabolism (primarily by CYP3A4), followed by excretion in the feces (85%) and urine (6.1%). The serum half-life is about 50 hours.

Adverse Effects. Rilpivirine is generally well tolerated. The most common adverse effects are depression (4%), insomnia (3%), headache (3%), and mild to moderate rash (3%). Discontinuation owing to serious rash was very low (<0.1%). Rilpivirine can prolong the QT interval, but only at doses 3 to 12 times greater than recommended.

Use in Pregnancy and Lactation. No adequate studies have been conducted in pregnant women. However, animal studies have shown no evidence of fetal harm. Accordingly, rilpivirine is classified in FDA Pregnancy Risk Category B. Owing to the risk of HIV transmission and possible drug toxicity, breast-feeding should be avoided.

Drug Interactions. Levels of rilpivirine can be increased or reduced by other drugs. Three major mechanisms are involved: inhibition of P450, induction of P450, and elevation of gastric pH.

All of the following drugs, which reduce rilpivirine levels, are contraindicated:

- **Antiseizure drugs**—Carbamazepine, oxcarbazepine, phenobarbital, phenytoin (these drugs induce P450, and thereby increase rilpivirine metabolism)
- **Rifamycins**—Rifabutin, rifampin, rifapentine (these drugs induce P450, and thereby increase rilpivirine metabolism)
- **St. John's wort** (this herb induces P450, and thereby increases rilpivirine metabolism)
- **Proton pump inhibitors**—Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole (these drugs increase gastric pH, and thereby reduce rilpivirine absorption)
- **Dexamethasone and other glucocorticoids** (when given in repeated doses, glucocorticoids can decrease rilpivirine levels)

The following drugs, which either reduce or elevate rilpivirine levels, should be used with caution:

- **Antacids** (eg, aluminum hydroxide, magnesium hydroxide, calcium carbonate) increase gastric pH, and can thereby reduce rilpivirine absorption. Advise patients to take antacids at least 2 hours before rilpivirine or 4 hours after.
- **Histamine₂-receptor blockers** (eg, cimetidine, famotidine, ranitidine) increase gastric pH, and can thereby reduce rilpivirine absorption. Advise patients to take H₂ blockers at least 12 hours before rilpivirine or 4 hours after.
- **Azole antifungal drugs** (eg, ketoconazole, itraconazole, fluconazole) inhibit P450, and can thereby increase rilpivirine levels
- **Macrolide antibiotics** (eg, erythromycin, clarithromycin, troleanomycin) inhibit P450, and can thereby increase rilpivirine levels

Preparations, Dosage, and Administration. Rilpivirine, by itself, is available in 25-mg tablets marketed as *Edurant*. The usual adult dosage is 25 mg taken once daily with food.

Rilpivirine is also available in fixed-dose combination tablets—25 mg rilpivirine/200 mg emtricitabine/300 mg tenofovir—marketed as *Complera*. The usual dosage is one tablet taken once daily with food.

PROTEASE INHIBITORS

The protease inhibitors (PIs) are among the most effective antiretroviral drugs available. When used in combination with NRTIs, they can reduce viral load to a level that is undetectable with current assays.

In early trials, PIs were generally well tolerated, although they did cause GI disturbances. However, widespread use of these drugs has revealed additional side effects: fat maldistribution, hyperglycemia and diabetes, reduced bone mineral density, increased bleeding in hemophiliacs, and elevation of triglyceride and transaminase levels.

All of the PIs can inhibit cytochrome P450 enzymes, and can thereby increase levels of other drugs. Because of this mechanism and others, PIs are subject to a bewildering array of drug interactions.

As with other antiretroviral drugs, HIV resistance can be a significant problem. Mutant strains of HIV that are resistant to one PI are likely to be cross-resistant to other PIs. In contrast, since PIs do not share the same mechanism as the reverse trans-

criptase inhibitors, fusion inhibitors, integrase strand transfer inhibitors, or CCR5 antagonists, cross-resistance between PIs and these other antiretroviral drugs does not occur. To reduce the risk of resistance, PIs should never be used alone; rather, they should always be combined with at least one reverse transcriptase inhibitor, and preferably two.

Nine PIs are available. Unfortunately, data on comparative efficacy of these drugs are limited. Accordingly, until such data become available, selection among them must be based on other factors, mainly side effect profile, drug interactions, and patient acceptance. The major properties of the PIs are summarized in Tables 94-5 and 94-6.

Group Properties

Adverse Effects

Hyperglycemia/Diabetes. Protease inhibitors have been associated with hyperglycemia, new-onset diabetes, abrupt exacerbation of existing diabetes, and diabetic ketoacidosis. Onset typically occurs after 2 months of drug use, but can also develop much earlier. Hyperglycemia can be managed with insulin and oral antidiabetic agents (eg, metformin). Because of the possible risk of diabetes, patients should be instructed to report signs of the disease, such as polydipsia (increased fluid intake), polyphagia (increased food intake), and polyuria (frequent urination). In patients with existing diabetes, blood glucose should be monitored closely. In others, blood glucose should be measured at baseline, every 3 to 4 months during the first year of treatment, and less frequently thereafter. Although withdrawing PIs may restore normal glucose metabolism, discontinuation is not recommended.

Fat Maldistribution. Use of PIs has been associated with maldistribution of body fat, sometimes referred to as *lipodystrophy syndrome* or *pseudo-Cushing's syndrome*. Fat accumulates in the abdomen ("protease paunch"), in the breasts of men and women, and between the shoulder blades ("buffalo hump"). Fat is lost from the face, arms, buttocks, and legs. Leg and arm veins become prominent. Muscle mass and strength are unaffected. The underlying mechanism has not been determined. Although these fat changes resemble those of Cushing's syndrome, which is caused by excessive cortisol, elevated cortisol has not been observed. Health risks of the syndrome are unknown, although it can be psychologically distressing. Drug withdrawal may cause symptoms to resolve, but is not recommended.

In 2004, a product called *Sculptra* was approved for restoring and/or correcting loss of facial fat in people with HIV infection. *Sculptra* is an injectable form of poly-L-lactic acid, a biodegradable synthetic polymer that has been widely used in dissolvable stitches, bone screws, and facial implants. Administration is by direct injection into the deep dermis or subcutaneous tissue using a 26-gauge needle. After the initial series of injections, repeat treatments may be needed to maintain the correction. Principal adverse effects are local reactions, including redness, swelling, bruising, and development of nodules.

In 2010, *tesamorelin* [Egrifta] was approved for reducing excess visceral abdominal fat in patients with lipodystrophy associated with HIV infection. The drug is a synthetic analog of growth hormone-releasing hormone (GH-RH), a hypothalamic peptide that promotes release of growth hormone (GH) from the pituitary. Benefits derive at least in part from the lipolytic and anabolic actions of GH. In clinical trials, *tesamorelin* reduced visceral abdominal adipose tissue by 14% to 18%—

about the same reduction that can be achieved with diet and exercise. The most common adverse effects are hypersensitivity and injection-site reactions. More importantly, tesamorelin increases the risk of diabetes by more than threefold. Tesamorelin is teratogenic, and hence must not be used during pregnancy (FDA Pregnancy Risk Category X). The recommended dosage is 2 mg injected subQ in the abdomen once daily.

Hyperlipidemia. All PIs can elevate plasma levels of cholesterol and triglycerides. These effects may occur with or without redistribution of fat. Elevation of cholesterol can lead to atherosclerosis and associated cardiovascular events. Elevation of triglycerides can lead to pancreatitis. Changes in plasma lipids can be detected by monitoring lipid levels every 3 to 4 months. Potential interventions for hyperlipidemia include diet, exercise, and lipid-lowering drugs. However, benefits of these interventions have not been established. If lipid-lowering drugs are employed, lovastatin and simvastatin should be avoided. Why? Because inhibition of cytochrome P450 by PIs can cause lovastatin and simvastatin to accumulate to dangerous levels.

Increased Bleeding in People with Hemophilia. Protease inhibitors may increase the risk of bleeding in patients with hemophilia. Bleeding typically occurs in the joints and soft tissues, where danger is low. However, serious bleeds in the brain and GI tract have also occurred. The mean time to increased bleeding is 22 days after the onset of treatment. Patients may need to increase their dosage of coagulation factors.

Reduced Bone Mineral Density. Protease inhibitors can accelerate bone loss. In some patients, bone loss is severe enough to meet the definition of osteoporosis. In a study conducted at Washington University, involving 122 patients on ART, 21% of those taking PIs had osteoporosis. In an Australian study involving 74 patients taking PIs, 28% of patients had low bone mineral density and 10% had osteoporosis. To help protect against bone loss, patients should ensure adequate intake of calcium and vitamin D. If significant bone loss develops, bisphosphonates, raloxifene, calcitonin, teriparatide, or denosumab may be indicated (see Chapter 75).

Elevation of Serum Transaminases. Protease inhibitors can increase serum levels of transaminases, indicating injury to the liver. Exercise caution in patients with chronic liver disease (eg, hepatitis B or C, cirrhosis). Serum transaminases should be measured at baseline and periodically thereafter.

Drug Interactions

All PIs are metabolized by cytochrome P450 enzymes, and all PIs can inhibit cytochrome P450 enzymes. As a result, PIs can interact with drugs that inhibit or induce P450 enzymes, and with drugs that are substrates for P450 enzymes. Drug interactions of the PIs are summarized in Table 94-6.

P450 Inhibitors. Agents that inhibit P450 can retard metabolism of the PIs, thereby increasing their levels. Important inhibitors include *ketoconazole* (an antifungal drug), *clarithromycin* (an antibacterial drug), and *grapefruit juice*. If inhibition of metabolism is substantial, dosage of the PI should be reduced.

P450 Inducers. Drugs that induce P450 can accelerate the metabolism of PIs, and can thereby reduce their levels. Important inducers include *rifampin* and *rifabutin* (used for mycobacterial infections), and three antiseizure drugs: *phenobarbital*, *phenytoin*, and *carbamazepine*. If induction of P450 is substantial, loss of therapeutic effects can result. For example,

when rifampin is combined with the PI indinavir, total body content of indinavir is reduced by 92%. Similar reductions occur with other PIs. Accordingly, combined use of rifampin and PIs should be avoided.

P450 Substrates. By inhibiting P450, PIs can slow the metabolism of other drugs, thereby causing their levels to rise. Serious toxicity can result. To avoid toxicity, PIs should not be combined with the following P450 substrates: *astemizole* and *terfenadine* (nonsedating antihistamines; no longer available in the United States); *cisapride* (a drug for heartburn; available in the United States, but with limited access); *alprazolam*, *triazolam*, and *midazolam* (benzodiazepine sedative-hypnotics); *ergotamine* and *dihydroergotamine* (drugs that promote vasoconstriction and relieve migraine); and *lovastatin* and *simvastatin* (drugs that lower cholesterol).

By inhibiting P450, PIs can intensify and prolong the effects of three PDE5 inhibitors used for erectile dysfunction: *sildenafil* [Viagra], *tadalafil* [Cialis], and *varafenafil* [Levitra]. Although this might seem beneficial, it's potentially dangerous. Accordingly, dosages of these drugs should be reduced: sildenafil should not exceed 25 mg in 48 hours; tadalafil should not exceed 10 mg every 72 hours; and varafenafil should not exceed 2.5 mg in 72 hours.

Protease Inhibitor Combinations: Ritonavir Boosting. By inhibiting P450, one PI can increase the level of another PI, and can thereby intensify therapeutic effects (as well as adverse effects). One PI—*ritonavir* [Norvir]—is routinely combined with other PIs with the specific purpose of increasing the other PIs' effects. In this technique, known as *ritonavir boosting*, the dose of ritonavir is low: 100 to 400 mg/day. This dosage is too low to contribute significant antiviral effects, but still high enough to inhibit P450.

Herb Interactions

St. John's Wort. St. John's wort, an herbal supplement taken for depression, can decrease levels of all PIs. The principal mechanism is accelerated metabolism owing to induction of P450 (see Chapter 108). To avoid loss of efficacy, patients using PIs must not use St. John's wort.

Garlic. Garlic supplements can decrease levels of *saquinavir*, and probably levels of other PIs. Scientists at the National Institutes of Health reported that garlic supplements can produce a dramatic (50%) decrease in blood levels of saquinavir. Not only is this effect profound, it persists: 10 days after stopping garlic intake, saquinavir levels remained 30% to 40% below baseline. These observations are significant. Why? Because many patients with HIV infection take garlic supplements on the belief (albeit unfounded) that garlic can suppress HIV replication and stimulate immune function. Although we don't know how garlic lowers saquinavir levels, induction of P450 is suspected. If this is correct, garlic supplements are likely to reduce levels of other drugs, including other PIs and NNRTIs. Accordingly, it would seem prudent for patients taking PIs or NNRTIs to avoid garlic supplements. The small amount of garlic in prepared foods is probably of no concern. Garlic is discussed further in Chapter 108.

Lopinavir/Ritonavir

Description and Use. Lopinavir and ritonavir are available in a fixed-dose combination under the trade name *Kaletra*. The combination is approved for HIV infection in adults

Text continued on p. 1190.

TABLE 94-5 ■ Properties of Protease Inhibitors (PIs)

	Atazanavir (ATV)	Darunavir (DRV)	Fosamprenavir (FPV)	Indinavir (IDV)
Trade Name	Reyataz	Prezista	Lexiva, Telzir*	Crixivan
Formulations	Capsules: 100, 150, 200, 300 mg	Tablets: 75, 150, 300, 400, and 600 mg	Tablets: 700 mg Suspension: 50 mg/mL	Capsules: 100, 200, and 400 mg
Dosage	400 mg once daily <i>or</i> 300 mg once daily boosted with 100 mg ritonavir once daily Dosage for combined use with efavirenz or tenofovir: see text.	Must be boosted with ritonavir. <i>ART-naïve patients:</i> 800 mg once daily, boosted with 100 mg ritonavir once daily <i>ART-experienced patients:</i> 600 mg twice daily, boosted with 100 mg ritonavir twice daily	Dosage depends on treatment history, liver function, and use of ritonavir (see text).	800 mg every 8 hr, or 800 mg every 12 hr boosted with ritonavir (100 or 200 mg)
Impact of Food	Food increases bioavailability. Take with food. Avoid taking with antacids.	Food increases bioavailability. Take with food.	<i>Tablets:</i> Take with or without food. <i>Suspension:</i> Take without food.	Food decreases levels by 77%. Take 1 hr before meals or 2 hr after; may take with skim milk or a low-fat meal. If boosted with ritonavir, may take without regard to meals.
Storage	Room temperature	Room temperature	Room temperature	Room temperature, but protect from moisture
Bioavailability	Not determined	82% (with ritonavir)	Not determined	65%
Serum Half-life	7 hr	15 hr (with ritonavir)	7.7 hr	1.5–2 hr
Adverse Effects Common to All PIs	<ul style="list-style-type: none"> • Fat maldistribution • Hyperlipidemia • Hyperglycemia—PIs may exacerbate hyperglycemia in patients with existing diabetes, and may cause new-onset diabetes • Possible increased risk of bleeding in patients with hemophilia • Bone loss • Elevation of serum transaminases 			
Adverse Effects of Individual PIs	<ul style="list-style-type: none"> • Indirect hyperbilirubinemia • Prolongs PR interval, posing a risk of atrioventricular block • Nephrolithiasis 	<ul style="list-style-type: none"> • GI: nausea, diarrhea • Rash • Headache • Stevens-Johnson syndrome • Hepatotoxicity 	<ul style="list-style-type: none"> • GI: nausea, vomiting, diarrhea • Rash • Headache • Nephrolithiasis 	<ul style="list-style-type: none"> • GI: nausea • Nephrolithiasis • Indirect hyperbilirubinemia • Miscellaneous: headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia
Drug Interactions	Drug interactions for the PIs are summarized in Table 94-6.			

Adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, prepared by the Panel on Clinical Practices for Treatment of HIV Infection, convened by the DHHS, as updated on October 14, 2011.

Lopinavir/Ritonavir (LPV/r)	Nelfinavir (NFV)	Ritonavir (RTV)	Saquinavir (SQV)	Tipranavir (TPV)
<p>Kaletra</p> <p>Tablets: 200 mg LPV/50 mg RTV, 100 mg LPV/25 mg RTV</p> <p>PO soln: Each 5 mL has 400 mg LPV/100 mg RTV</p>	<p>Viracept</p> <p>Tablets: 250 and 625 mg</p> <p>PO powder: 50 mg/gm</p>	<p>Norvir</p> <p>Tablets: 100 mg</p> <p>Soft-gel capsules: 100 mg</p> <p>PO soln: 80 mg/mL</p>	<p>Invirase</p> <p>Hard-gel capsules: 200 mg</p> <p>Tablets: 500 mg</p>	<p>Aptivus</p> <p>Capsules: 250 mg</p> <p>PO soln: 100 mg/mL</p>
<p>400 mg lopinavir/100 mg ritonavir twice daily</p> <p>or</p> <p>800 mg lopinavir/200 mg ritonavir once daily</p> <p>or</p> <p>When used with efavirenz or nevirapine: Either 533 mg lopinavir/133 mg ritonavir twice daily or 500 mg lopinavir/125 mg ritonavir twice daily</p>	<p>750 mg 3 times/day or 1250 mg 2 times/day</p>	<p>As pharmacokinetic booster for other PIs: 100–400 mg/day in 1 or 2 doses</p>	<p>Must be used boosted with ritonavir. Dosage is 1000 mg SQV/100 mg ritonavir twice daily.</p>	<p>Must be boosted with ritonavir. Dosage is 500 mg twice daily/200 mg ritonavir twice daily.</p>
<p>Tablets: Take with or without food.</p> <p>PO soln: Take with food.</p>	<p>Food increases levels 2- to 3-fold. Take with a meal or a snack.</p>	<p>Tablets: Take with food.</p> <p>Capsules and PO soln: Take with food, if possible, to improve tolerability.</p>	<p>Take with meals or within 2 hr after a meal.</p>	<p>When combined with ritonavir tablets, take with meals.</p> <p>When combined with ritonavir capsules or solution, take with or without food.</p>
<p>Tablets: Stable at room temperature</p> <p>PO soln: Can store at room temperature up to 2 months; refrigerate for long-term storage</p>	<p>Room temperature</p>	<p>Tablets: Room temperature</p> <p>Capsules: Store unopened bottle refrigerated. Open bottle can be kept at room temperature, but must be used in 30 days.</p> <p>PO soln: Do not refrigerate.</p>	<p>Room temperature</p>	<p>Capsules: Store unopened bottle refrigerated. Open bottle can be kept at room temperature, but must be used in 60 days.</p> <p>PO soln: Do not refrigerate; use within 60 days after opening.</p>
<p>Not determined</p> <p>5–6 hr</p>	<p>20%–80%</p> <p>3.5–5 hr</p>	<p>Adequate</p> <p>3–5 hr</p>	<p>Low (4%) and erratic</p> <p>1–2 hr</p>	<p>Not determined</p> <p>6 hr</p>

- GI: nausea, vomiting, diarrhea (higher incidence with once-daily dosing)
- Asthenia
- Pancreatitis
- Prolongs PR interval, posing a risk of atrioventricular block
- Prolongs QT interval, posing a risk of torsades de pointes

- GI: diarrhea

- GI: nausea, vomiting, diarrhea
- Paresthesias (circumoral and peripheral)
- Asthenia
- Taste perversion

- GI: nausea, diarrhea
- Headache
- Prolongs PR interval, posing a risk of atrioventricular block
- Prolongs QT interval, posing a risk of torsades de pointes

- Hepatotoxicity
- Rash
- Rarely, intracranial hemorrhage

TABLE 94-6 • Drug Interactions of Protease Inhibitors (PIs)

Atazanavir (ATV) [Reyataz]	Darunavir (DRV) [Prezista]	Fosamprenavir (FPV) [Lexiva, Telzir*]	Indinavir (IDV) [Crixivan]
Interactions Shared by All PIs			
<ul style="list-style-type: none"> All PIs inhibit P450 (ritonavir inhibits the most) and hence can cause other drugs to accumulate to dangerous levels. Accordingly, <i>patients must not take the following drugs</i>: astemizole,* terfenadine,* cisapride, alprazolam, triazolam, midazolam, ergotamine, dihydroergotamine, lovastatin, and simvastatin. By inhibiting P450, PIs can increase levels of sildenafil [Viagra], tadalafil [Cialis], and vardenafil [Levitra]; dosages of all three should be reduced. St. John's wort induces P450 and thereby decreases levels of PIs. Combined use of <i>St. John's wort and protease inhibitors must be avoided</i>. Certain antiseizure drugs—phenobarbital, phenytoin, and carbamazepine—induce P450, and may thereby decrease levels of PIs substantially. 			
Interactions of Individual PIs			
<ul style="list-style-type: none"> Because of P450 inhibition, <i>patients must avoid</i> bepridil and pimozone (in addition to the drugs listed for all PIs). Use clarithromycin, atorvastatin, and diltiazem in reduced dosage, and use cyclosporine, sirolimus, and tacrolimus with caution. Drugs that raise gastric pH can decrease the solubility of atazanavir, and thereby decrease its absorption. Atazanavir should be taken 2 hr before or 1 hr after antacids or buffered medications, and 12 hr apart from H₂-receptor blockers. Proton pump inhibitors should be avoided. Rifampin reduces levels of atazanavir; don't combine these drugs. Atazanavir greatly increases levels of irinotecan (by inhibiting UDP glucuronyltransferase); don't combine these drugs. 	<ul style="list-style-type: none"> Always combine with ritonavir to boost darunavir levels. Rifampin can greatly reduce darunavir levels, and hence should be avoided. Ketoconazole can increase darunavir levels by 42%. Use with caution. Darunavir can reduce levels of two antidepressants: paroxetine and sertraline. Titrate antidepressant dosage based on clinical response. 	<ul style="list-style-type: none"> Fosamprenavir undergoes conversion to <i>amprenavir</i> in the body, and hence the interactions of fosamprenavir are the same as those for amprenavir (which has been withdrawn). Amprenavir increases rifabutin levels by 193%; reduce rifabutin dosage. Rifampin reduces amprenavir levels by 90%; avoid the combination. Amprenavir may reduce efficacy of oral contraceptives; use a different method of birth control. Disulfiram and metronidazole increase the risk of toxicity from propylene glycol in amprenavir oral solution; avoid these drugs. Don't take within 1 hr of antacids or buffered didanosine. 	<ul style="list-style-type: none"> Rifampin reduces indinavir levels by 89%; avoid the combination. Indinavir increases rifabutin levels twofold; reduce rifabutin dosage. Ketoconazole increases indinavir levels by 68%; reduce indinavir dosage. Buffered formulations of didanosine reduce indinavir absorption; take at least 1 hr apart.

Adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, prepared by the Panel on Clinical Practices for Treatment of HIV Infection, convened by the DHHS, as updated on October 14, 2011.

*No longer available in the United States.

Lopinavir/Ritonavir
(LPV/r) [Kaletra]Nelfinavir (NFV)
[Viracept]Ritonavir (RTV)
[Norvir]Saquinavir (SQV)
[Invirase]Tipranavir (TPV)
[Aptivus]

- Because of P450 inhibition, *patients must avoid the following drugs* (in addition to those listed for all PIs): flecainide, propafenone, ergonovine, methyl-ergonovine, and pimozone.
- Rifampin, efavirenz, and nevirapine greatly reduce levels of lopinavir, and hence should be avoided.
- Because of P450 inhibition, dosages of the following drugs must be *greatly reduced*: clarithromycin, ketoconazole, itraconazole, and rifabutin.
- Lopinavir/ritonavir decreases levels of ethinyl estradiol found in oral contraceptives; use a different form of birth control.
- Lopinavir/ritonavir decreases methadone availability by 53%; monitor methadone efficacy and increase dose as needed.
- Owing to its alcohol content, the PO solution of lopinavir/ritonavir should not be combined with disulfiram or metronidazole.
- Rifampin reduces nelfinavir levels by 82%; avoid the combination.
- Rifabutin reduces nelfinavir levels by 32%; increase nelfinavir dosage.
- Nelfinavir decreases levels of ethinyl estradiol and norethindrone found in oral contraceptives; use a different method of birth control.
- Nelfinavir increases levels of ketoconazole.
- Because of P450 inhibition, *patients must avoid the following drugs* (in addition to those listed for all PIs): amiodarone, bepridil, bupropion, clorazepate, clozapine, diazepam, encainide, estazolam, flecainide, flurazepam, meperidine, piroxicam, propoxyphene, propafenone, quinidine, and zolpidem.
- Ritonavir decreases levels of ethinyl estradiol found in oral contraceptives; use a different method of birth control.
- Ritonavir increases levels of rifabutin (fourfold), ketoconazole (threefold), clarithromycin (77%), and desipramine (145%); reduce dosages of these drugs.
- Buffered formulations of didanosine reduce ritonavir absorption; take at least 2 hr apart.
- Always combine with ritonavir to boost saquinavir levels.
- Rifampin and rifabutin reduce levels of saquinavir; don't use these drugs.
- Saquinavir levels are increased by ritonavir, ketoconazole, clarithromycin, and grapefruit juice.
- Always combine with ritonavir to boost tipranavir levels.
- Because of P450 inhibition, *patients must avoid* amiodarone, flecainide, and pimozone (in addition to the drugs listed for all PIs).
- By inducing P-glycoprotein, tipranavir/ritonavir can greatly decrease levels of amprenavir, fosamprenavir, lopinavir, and saquinavir, and hence should not be used with these other PIs.
- Tipranavir/ritonavir decreases levels of ethinyl estradiol in oral contraceptives; use a different form of contraception.

and children over 6 months old. Lopinavir is the active antiretroviral component. Ritonavir is present only to boost lopinavir's effects: By inhibiting P450, ritonavir raises lopinavir levels substantially, and thereby enhances antiviral actions. The amount of ritonavir, although large enough to inhibit P450, is too small to exert significant antiretroviral effects. Hence, therapeutic responses to the combination are due solely to lopinavir. In clinical trials, lopinavir/ritonavir was highly effective, and even worked against some HIV strains that had become resistant to other PIs. Lopinavir/ritonavir is a preferred component for multidrug antiretroviral regimens.

Mechanism of Action. To understand the effects of lopinavir and the other PIs, we must first understand the function of HIV protease. As discussed above, protease catalyzes the final step in HIV maturation. When the various enzymes and structural proteins of HIV are synthesized, they are not produced as separate entities; rather, they are strung together in large polyproteins. The role of protease is to cleave bonds in the polyproteins, thereby freeing the individual enzymes and structural proteins. Once these components have been freed, HIV can complete its maturation.

Protease inhibitors bind to the active site of HIV protease and thereby prevent the enzyme from cleaving HIV polyproteins. As a result, the structural proteins and enzymes of HIV are unable to function, and hence the virus remains immature and noninfectious.

Pharmacokinetics. Discussion here is limited to lopinavir. The pharmacokinetics of ritonavir are discussed below.

Lopinavir is administered PO, and absorption is enhanced by food. In blood, the drug is highly (99%) bound to plasma proteins. Lopinavir undergoes extensive metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450), followed by excretion in the urine (10%) and feces (83%). The drug's half-life is 5 to 6 hours.

Two observations tell us that the antiretroviral effects of lopinavir/ritonavir are due entirely to lopinavir. First, when patients take lopinavir/ritonavir, steady-state levels of lopinavir are 15- to 20-fold *higher* than those of ritonavir. Second, in the test tube, the concentration of lopinavir required to suppress HIV replication is 10-fold *lower* than that of ritonavir. Therefore, since lopinavir achieves much higher concentrations than ritonavir, and yet works at much lower concentrations than ritonavir, it is clear that virtually all of the antiviral effects of the combination are due to lopinavir.

Adverse Effects. Lopinavir/ritonavir is generally well tolerated. The most common adverse effects are diarrhea (13.8%), nausea (6.4%), headache (2.5%), and weakness or tiredness (3.4%). Like all other PIs, lopinavir/ritonavir poses a risk of hyperglycemia, new-onset diabetes, exacerbation of existing diabetes, fat maldistribution, hyperlipidemia, bone loss, elevation of transaminases, and increased bleeding in patients with hemophilia. Rash may occur in children.

Cardiac Effects. Lopinavir/ritonavir prolongs both the PR and QT intervals. By prolonging the PR interval, the drug increases the risk of second- or third-degree atrioventricular (AV) block. Accordingly, it should be used with caution in patients with structural heart disease, pre-existing cardiac conduction disturbances, or ischemic heart disease, and in those taking other drugs that prolong the PR interval.

By prolonging the QT interval, lopinavir/ritonavir increases the risk of torsades de pointes and other severe dysrhythmias. Accordingly, the drug should be avoided in pa-

tients with congenital long QT syndrome, and in those taking other drugs that prolong the QT interval.

Toxicity in Newborns. When given to preterm and full-term infants, lopinavir/ritonavir *oral solution* can cause serious cardiac, renal, and respiratory problems. Deaths have occurred. What's the cause? The solution contains both 42% alcohol and 15% propylene glycol. Toxicity is due mainly to accumulation of propylene glycol, which infants are unable to metabolize. Accordingly, the oral solution should be avoided in full-term infants (for the first 14 days after birth) and in preterm infants (until 14 days after their predicted due date).

Drug Interactions. Lopinavir/ritonavir *inhibits* two drug-metabolizing enzymes—CYP3A4 and CYP2D6—and can thereby raise levels of drugs that are substrates for these enzymes. Serious toxicity can result. To avoid toxicity, certain drugs must be used in greatly reduced dosage, and others must not be used at all. Drugs that require a large reduction in dosage include clarithromycin, ketoconazole, itraconazole, rifabutin, and PDE5 inhibitors used for erectile dysfunction (eg, sildenafil [Viagra]). Drugs that must be avoided entirely include cisapride, flecainide, propafenone, dihydroergotamine, ergonovine, ergotamine, methylethergonovine, pimozone, midazolam, triazolam, lovastatin, and simvastatin—and astemizole and terfenadine, which are no longer available in the United States.

Paradoxically, lopinavir/ritonavir can *induce* metabolism of some drugs, including methadone and ethinyl estradiol, a component of many oral contraceptives. Methadone efficacy should be monitored and dosage increased as needed. Women using ethinyl estradiol-based oral contraceptives should switch to a different form of birth control.

Agents that induce CYP3A4 can accelerate metabolism of lopinavir/ritonavir, and can thereby decrease antiretroviral effects. Known inducers include rifampin, efavirenz, nevirapine, phenobarbital, phenytoin, carbamazepine, and St. John's wort. Concurrent use of these agents should be avoided.

Because of its alcohol content, the oral solution of lopinavir/ritonavir should not be combined with disulfiram [Antabuse] or metronidazole. Why? Because both drugs will cause accumulation of acetaldehyde, a toxic metabolite of alcohol.

Preparations, Dosage, and Administration. Lopinavir/ritonavir [Kaletra] is available in tablets (200 mg lopinavir/50 mg ritonavir, 100 mg lopinavir/25 mg ritonavir) and an oral solution (400 mg lopinavir/100 mg ritonavir in 5 mL of liquid containing 42% alcohol and 15% propylene glycol). The solution should be taken with food. The tablets may be taken with or without food.

The *adult dosage* for patients not taking efavirenz or nevirapine is either (1) 400 mg lopinavir/100 mg ritonavir twice daily or (2) 800 mg lopinavir/200 mg ritonavir once daily. For patients taking efavirenz or nevirapine, the dosage is either (1) 533 mg lopinavir/133 mg ritonavir twice daily or (2) 500 mg lopinavir/125 mg ritonavir twice daily.

Other Protease Inhibitors

Ritonavir

Actions and Uses. Ritonavir [Norvir] inhibits HIV protease, and thereby prevents maturation of HIV. The drug is active against HIV-1 and HIV-2, and indicated to treat HIV infection in adults and children. To reduce emergence of resistance, ritonavir should always be combined with at least one reverse transcriptase inhibitor. Because of its ability to inhibit P450, ritonavir is often combined with other PIs to boost their effects. Nearly one-third of HIV patients use this drug.

Pharmacokinetics. Ritonavir is well absorbed following oral dosing. Dilution of the oral solution in chocolate milk, Ensure, or Advera has no impact on absorption, but does improve its taste (which is otherwise unpleasant). Ritonavir undergoes metabolism by P450 enzymes, followed by excretion in the feces (84%) and urine (11%). The plasma half-life is 3 to 5 hours.

Adverse Effects. Adverse effects are common during the initial weeks of therapy and then tend to fade. The effects seen most often are nausea (25%), diarrhea (16%), vomiting (14%), muscle weakness (12%), altered taste (8%), and paresthesias (tingling or numbness) around the mouth and in the extremities. These effects can be reduced by initiating therapy at a low dosage and then gradually titrating up to the maintenance dosage. Like other PIs, ritonavir may pose a risk of hyperglycemia, new-onset diabetes, exacerbation of existing diabetes, fat maldistribution, hyperlipidemia, bone loss, elevation of transaminase levels, and increased bleeding in patients with hemophilia.

Drug Interactions. Ritonavir is a powerful inhibitor of P450 drug-metabolizing enzymes, and can thereby decrease the metabolism of other drugs, causing their levels to rise. Because drug accumulation can result in serious adverse effects, ritonavir is contraindicated for use with a large number of agents, including terfenadine and astemizole (no longer available in the United States), which can cause fatal dysrhythmias when present at excessive levels. A list of contraindicated drugs is given in Table 94-6.

Although ritonavir inhibits P450, it appears to induce other drug-metabolizing enzymes, and can thereby decrease levels of certain drugs. Among these are ethinyl estradiol (a component of many oral contraceptives), zidovudine, clarithromycin, sulfamethoxazole, and theophylline. Care must be taken to ensure that concentrations of these drugs do not fall to subtherapeutic levels.

Ritonavir is often used with other PIs to boost their effects. Benefits derive from inhibiting P450.

St. John's wort induces cytochrome P450, and can thereby decrease levels of ritonavir. Accordingly, the combination should be avoided.

Preparations, Dosage, and Administration. **Preparations.** Ritonavir [Norvir] is available in 100-mg tablets, 100-mg soft-gel capsules, and an oral solution (80 mg/mL). In addition, the drug is available in a fixed-dose combination with lopinavir under the trade name Kaletra (see above).

Dosage and Administration. The maintenance dosage for adults is 600 mg every 12 hours. The maintenance dosage for children is 350 to 400 mg/m² every 12 hours. Adverse effects can be minimized by starting therapy with a low dosage and then titrating up to the maintenance dosage. If possible, ritonavir should be administered with food (to minimize GI effects). Palatability of the oral solution can be improved by mixing it with chocolate milk, Ensure, or Advera within 1 hour of administration.

Storage. Storage conditions depend on the formulation:

- **Tablets**—Store at room temperature.
- **Oral solution**—Store at room temperature. Do not refrigerate.
- **Capsules**—Store the unopened bottle refrigerated and protected from light. After opening, the bottle can be kept at room temperature for 30 days.

Indinavir

Actions and Use. Indinavir [Crixivan] inhibits HIV protease and thereby prevents the cleavage of large HIV polyproteins into their smaller, functional forms. As a result, HIV particles remain immature and noninfectious. Indinavir is approved only for HIV infection. To reduce the risk of resistance, indinavir is usually combined with two NRTIs.

Pharmacokinetics. When administered on an empty stomach, indinavir has good (65%) bioavailability. Administration with a meal high in fat, protein, or calories can decrease absorption by 70%. Indinavir undergoes metabolism by hepatic cytochrome P450 followed by excretion in the feces (83%) and urine (19%). The plasma half-life is 1.5 to 2 hours. In patients with liver dysfunction, indinavir levels may increase and the half-life may be prolonged.

Adverse Effects. Indinavir is generally well tolerated. The major adverse effect of note is nephrolithiasis (kidney stones), manifested by flank pain with or without hematuria. As a rule, indinavir-induced nephrolithiasis does not compromise kidney function, and resolves following hydration and interruption of indinavir for 1 to 3 days. To decrease the risk of nephrolithiasis, patients should consume at least 48 ounces (1.5 L) of water daily. Like other PIs, indinavir may pose a risk of hyperglycemia, new-onset diabetes, exacerbation of existing diabetes, fat maldistribution, hyperlipidemia, bone loss, elevation of transaminase levels, and increased bleeding in patients with hemophilia. Other side effects include GI intolerance, headache, asthenia (weakness), blurred vision, dizziness, rash, metallic taste, thrombocytopenia, and indirect hyperbilirubinemia.

Drug Interactions. Indinavir inhibits cytochrome P450, and can thereby decrease the metabolism of other drugs. As a result, drugs may accumulate to dangerous or even life-threatening levels. Agents that can produce serious toxicity because of this interaction include cisapride, alprazolam, triazolam, midazolam, ergot alkaloids, simvastatin, and lovastatin—as well as astemizole and terfenadine, which are no longer available in the United States. Accordingly, patients taking indinavir must not be given these drugs.

Buffered formulations of didanosine can decrease absorption of indinavir. The mechanism is reduction of acidity. Let me explain. Didanosine and indi-

navir differ in their acidity requirements: whereas indinavir needs acidity for absorption, acidity decreases absorption of didanosine. Because acidity decreases absorption of didanosine, some formulations contain a buffering agent to neutralize gastric acid (other formulations are enteric coated). Hence, if buffered didanosine and indinavir are administered together, the buffering agent in didanosine will reduce absorption of indinavir. To prevent this interaction, indinavir and buffered didanosine should be administered at least 1 hour apart.

Rifampin, rifabutin, and *St. John's wort* can induce P450. As a result, these agents can accelerate metabolism of indinavir, thereby decreasing its levels. In contrast, levels of indinavir can be increased by *ketocanazole*, a drug that inhibits P450.

Preparations, Dosage, Administration, and Storage. Indinavir [Crixivan] is available in capsules (100, 200, and 400 mg) for oral dosing. The recommended dosage is 800 mg every 8 hours or 800 mg every 12 hours boosted with 100 or 200 mg of ritonavir. To maximize absorption, administer either (1) with water but on an empty stomach (ie, 1 hour before a meal or 2 hours after); or (2) with skim milk, coffee, tea, or a low-fat meal (eg, corn flakes with skim milk and sugar). Do not administer with a large meal. If indinavir is boosted with ritonavir, it may be taken without regard to meals. If the regimen includes buffered didanosine, indinavir and didanosine should be administered at least 1 hour apart.

Indinavir should be stored at room temperature and protected from moisture, which can degrade the drug. To protect indinavir from moisture, store tightly sealed in the vesicant-containing package supplied by the manufacturer.

Saquinavir

Saquinavir was the first PI to receive FDA approval. In the test tube, the drug appears more potent than other PIs.

Formulations. Saquinavir is available in two formulations: *tablets* and *hard-gelatin capsules*, both sold under the trade name *Invirase*. A third formulation—soft-gelatin capsules sold as *Fortovase*—has been voluntarily withdrawn. To ensure adequate saquinavir levels, Invirase tablets and capsules must be boosted with ritonavir.

Actions and Therapeutic Use. Saquinavir inhibits HIV protease and thereby prevents the cleavage of large HIV polyproteins into their smaller, functional forms. As a result, HIV particles remain immature and noninfectious. The drug is approved only for HIV infection. To reduce emergence of resistance, it should always be combined with at least one inhibitor of reverse transcriptase.

Pharmacokinetics. Saquinavir is administered orally, always in combination with ritonavir. With this combination, food has no effect on blood levels. Saquinavir undergoes metabolism by P450, followed by excretion in the feces. The plasma half-life is 1 to 2 hours.

Adverse Effects. Saquinavir is generally well tolerated. The most common side effects are GI reactions: nausea, diarrhea, dyspepsia, and abdominal pain. As discussed above, saquinavir and all other PIs may pose a risk of hyperglycemia, new-onset diabetes, exacerbation of existing diabetes, fat maldistribution, hyperlipidemia, bone loss, elevation of transaminase levels, and increased bleeding in patients with hemophilia.

Cardiac Effects. Like lopinavir/ritonavir, saquinavir prolongs the PR and QT intervals. By prolonging the PR interval, saquinavir can cause AV block, and hence should be used with caution in patients with structural heart disease, pre-existing cardiac conduction disturbances, or ischemic heart disease, and in those taking other drugs that prolong the PR interval. By prolonging the QT interval, saquinavir increases the risk of severe dysrhythmias, and hence should be avoided in patients with congenital long QT syndrome, and in those taking other drugs that prolong the QT interval.

Drug and Food Interactions. Agents that inhibit P450 (eg, ketocanazole, clarithromycin, grapefruit juice) can raise levels of saquinavir. Conversely, agents that induce P450 (eg, rifampin, rifabutin, phenobarbital, *St. John's wort*) can reduce levels of saquinavir.

Because saquinavir inhibits P450, it can raise levels of other drugs. To avoid toxicity from excessive levels, saquinavir should not be combined with cisapride, alprazolam, triazolam, midazolam, bepridil, ergot alkaloids, simvastatin, and lovastatin—or with astemizole or terfenadine, which are no longer available in the United States.

Preparations, Dosage, and Administration. Saquinavir [Invirase] is available in 500-mg tablets and 200-mg hard-gelatin capsules. Both formulations must be boosted with ritonavir. The dosage is 1000 mg saquinavir/100 mg ritonavir taken twice daily, either with a meal or within 2 hours after.

Nelfinavir

Actions and Uses. Nelfinavir [Viracept] inhibits HIV protease, and thereby prevents maturation of HIV. The drug is approved for treating HIV infection in adults and in children as young as 2 years old. To reduce emer-

gence of resistance, nelfinavir should always be combined with at least one reverse transcriptase inhibitor.

Pharmacokinetics. Nelfinavir is administered orally, and food increases absorption greatly (two- to threefold). In the blood, more than 98% of the drug is protein bound. Nelfinavir undergoes extensive hepatic metabolism followed by excretion in the feces. Only 1% of the drug is excreted in the urine. The plasma half-life is 3.5 to 5 hours.

Adverse Effects. Diarrhea can be dose limiting. During clinical trials, 20% to 32% of patients developed moderate to severe diarrhea. In most cases, diarrhea can be managed with an over-the-counter antidiarrheal drug (eg, loperamide).

Like other PIs, nelfinavir may pose a risk of hyperglycemia, new-onset diabetes, exacerbation of existing diabetes, fat maldistribution, hyperlipidemia, bone loss, elevation of transaminase levels, and increased bleeding in patients with hemophilia.

Drug Interactions. Like all other PIs, nelfinavir *inhibits P450*, and can thereby decrease the metabolism of other drugs, causing their levels to rise. Accumulation of several drugs, including astemizole and terfenadine (no longer available in the United States), cisapride, midazolam, and ergot alkaloids, can result in serious adverse effects. Accordingly, these agents are contraindicated for patients taking nelfinavir.

Like ritonavir, nelfinavir can *decrease levels of ethinyl estradiol and norethindrone*, a combination found in many oral contraceptives. Women taking oral contraceptives should be advised to use an alternative or additional form of contraception.

Rifampin, *rifabutin*, and *St. John's wort* induce hepatic drug-metabolizing enzymes, and can thereby decrease levels of nelfinavir. Accordingly, patients receiving nelfinavir should avoid these agents.

Preparations, Dosage, and Administration. Nelfinavir [Viracept] is available in tablets (250 and 625 mg) and a powder (50 mg/gm) for oral dosing. The powder should be mixed with a small amount of water, milk, formula, soy formula, soy milk, or dietary supplement—but *not* with acidic foods or juices (eg, applesauce, apple juice, orange juice) because the resulting combination may have a bitter taste. The recommended adult dosage is 750 mg every 8 hours or 1250 mg every 12 hours. The pediatric dosage is 20 to 30 mg/kg every 8 hours. Nelfinavir should be administered with food to enhance absorption.

Fosamprenavir

Fosamprenavir [Lexiva, Telzir[®]] is a prodrug that undergoes rapid conversion to amprenavir, its active form. Accordingly, fosamprenavir is nearly identical to amprenavir with regard to actions, uses, adverse effects, drug interactions, precautions, and contraindications. However, there are differences that make fosamprenavir more attractive. Most importantly, fosamprenavir is better tolerated: the incidence of nausea and vomiting is much lower with fosamprenavir (about 5% vs. 73%), as is the incidence of rash (8% vs. 25%). Following the introduction of fosamprenavir, amprenavir [Agenerase] was withdrawn.

Actions and Use. Fosamprenavir, in the form of amprenavir, inhibits HIV protease, and thereby prevents maturation of HIV. The drug is approved for use in combination with other antiretroviral agents to treat HIV-infected adults and children.

Pharmacokinetics. Following ingestion, fosamprenavir undergoes rapid conversion to amprenavir by enzymes in the GI epithelium. Amprenavir has a relatively long half-life, and hence can be dosed just 2 times a day. The drug undergoes metabolism by hepatic P450 followed by excretion in the urine (14%) and feces (75%).

Adverse Effects. The most common adverse effects are nausea, vomiting, diarrhea, headache, and rash. Rash is generally mild or moderate, and does not preclude continuing therapy. Rarely, severe rash develops, including potentially fatal Stevens-Johnson syndrome. Like other PIs, fosamprenavir may pose a risk of hyperglycemia, new-onset diabetes, exacerbation of existing diabetes, fat maldistribution, hyperlipidemia, bone loss, elevation of transaminase levels, and increased bleeding in patients with hemophilia.

Rarely, patients develop *nephrolithiasis* (kidney stones). Patients should be informed about symptoms—pain in the abdomen, groin, testicles, or side of the back—and instructed to report these if they develop. If nephrolithiasis is diagnosed, interruption or discontinuation of fosamprenavir should be considered.

Amprenavir is a chemical relative of the sulfonamide antibiotics. At this time, we do not know if people with sulfonamide hypersensitivity will also experience hypersensitivity to amprenavir. Until more is known, fosamprenavir should be avoided in patients with a history of sulfonamide reactions.

Drug Interactions. Like all other PIs, fosamprenavir *inhibits P450*, and can thereby cause other drugs to accumulate to dangerous levels. Accord-

ingly, patients must not be given the following agents: astemizole and terfenadine (no longer available in the United States) or cisapride, alprazolam, triazolam, midazolam, bepridil, ergot alkaloids, simvastatin, and lovastatin.

Rifampin reduces fosamprenavir levels by 90%. The combination should be avoided.

St. John's wort induces P450, and can thereby reduce fosamprenavir levels. The combination should be avoided.

Like ritonavir and nelfinavir, fosamprenavir may reduce the efficacy of oral contraceptives. An alternative form of contraception should be used.

Preparations, Dosage, and Administration. Fosamprenavir [Lexiva, Telzir[®]] is available in 700-mg tablets and a 50-mg/mL suspension. The suspension should be taken with food. The tablets may be taken with or without food. Dosage depends on treatment history, liver function, and concurrent use of ritonavir for boosting. Specific dosages for adults are as follows:

Adults who are treatment naïve

- 1400 mg twice daily *or*
- 1400 mg once daily plus 100 or 200 mg ritonavir once daily *or*
- 700 mg twice daily plus 100 mg ritonavir twice daily

Adults who have used PIs before

- 700 mg twice daily plus 100 mg ritonavir twice daily

Adults with hepatic impairment

- If hepatic impairment is mild to moderate, use with caution at a dosage of 700 mg twice daily, and don't combine with ritonavir.
- If hepatic impairment is more severe, do not use fosamprenavir.

Atazanavir

Actions and Uses. Atazanavir [Reyataz] inhibits HIV protease and thereby prevents maturation of HIV. The drug is approved for combination use with other antiretroviral agents to treat HIV-infected patients. Dosing is done just once a day, with or without boosting with ritonavir.

Pharmacokinetics. Atazanavir is taken orally, and plasma levels peak 2.5 hours after dosing. Food increases the amount absorbed, and decreases absorption variability. Atazanavir undergoes extensive hepatic metabolism, mainly by CYP3A enzymes, followed by excretion in the feces (79%) and urine (13%). Hepatic impairment increases blood levels of atazanavir, and slows elimination. The half-life is 7 hours in patients with normal liver function, and increases to 12 hours in those with significant impairment.

Adverse Effects. The most common adverse effects are nausea, infection, headache, vomiting, diarrhea, drowsiness, insomnia, fever, and rash. Like other PIs, atazanavir may cause hyperglycemia, new-onset diabetes, exacerbation of existing diabetes, and increased bleeding in patients with hemophilia. Atazanavir causes less hyperlipidemia than other PIs, but we don't yet know if long-term use will cause less lipodystrophy.

Atazanavir prolongs the PR interval, causing asymptomatic first-degree atrioventricular (AV) block in 5% to 9% of patients. Accordingly, the drug should be used with caution in patients with structural heart disease, pre-existing cardiac conduction disturbances, or ischemic heart disease, and in those taking other drugs that prolong the PR interval.

Atazanavir interferes with normal processing of bilirubin, and thereby raises levels of unconjugated bilirubin in plasma (indirect hyperbilirubinemia). As a result, about 11% of patients develop jaundice (yellowing of the skin) and scleral icterus (yellowing of the eyes), which reverse following drug withdrawal.

Drug Interactions. Atazanavir is subject to numerous interactions with other drugs. It can raise levels of other drugs, and other drugs can raise or lower levels of atazanavir.

Because atazanavir is a substrate for CYP3A, drugs that inhibit CYP3A can raise atazanavir levels, and drugs that induce CYP3A can lower atazanavir levels.

St. John's wort, which induces P450, can lower atazanavir levels, thereby posing a risk of therapeutic failure. Accordingly, the combination must be avoided.

Atazanavir inhibits CYP3A4, and can thereby intensify and prolong the effects of many drugs. Toxicity can result. Because of toxicity concerns, certain drugs are contraindicated for use with atazanavir. Among these are ergotamine, ergonovine, methylergonovine, bepridil, cisapride, lovastatin, simvastatin, midazolam, triazolam, and pimozone—as well as astemizole and terfenadine, which are no longer available in the United States. Inhibitors of PDE5—sildenafil, vardenafil, and tadalafil—should be used in reduced dosage, and certain immunosuppressants—cyclosporine, sirolimus, and tacrolimus—should be used with caution. Atazanavir can also inhibit the metabolism of minocycline; combined use should be avoided.

Drugs that raise gastric pH—antacids, buffered medications, H₂-receptor blockers, and proton pump inhibitors—can decrease the solubility of atazanavir, and can thereby decrease its absorption. Atazanavir should be taken 2 hours before or 1 hour after antacids or buffered medications, and should be taken 12 hours apart from H₂-receptor blockers. Atazanavir should not be used with proton pump inhibitors.

Atazanavir has the potential to interact with many additional drugs, including antidysrhythmics (amiodarone, lidocaine, quinidine), calcium channel blockers (diltiazem, verapamil, felodipine, nifedipine, nicardipine), other PIs (efavirenz, saquinavir, ritonavir), warfarin, rifabutin, clarithromycin, tricyclic antidepressants, and oral contraceptives. Details can be found in product literature.

Preparations, Dosage, and Administration. Atazanavir [Reyataz] is supplied in capsules (100, 150, 200, and 300 mg) for dosing with food. Dosages are as follows:

- For treatment-naïve adults—400 mg once daily or 300 mg once daily boosted with 100 mg ritonavir once daily
- For treatment-experienced adults taking tenofovir—300 mg once daily boosted with 100 mg ritonavir once daily
- For treatment-naïve adults taking efavirenz—400 mg once daily boosted with 100 mg ritonavir once daily

If atazanavir is combined with a buffered formulation of didanosine, atazanavir should be taken 2 hours before didanosine or 1 hour after.

In patients with moderate hepatic insufficiency, a reduction in atazanavir dosage should be considered (eg, to 300 mg once daily). In patients with severe hepatic insufficiency, atazanavir should not be used.

Tipranavir (Plus Ritonavir)

Therapeutic Use. Tipranavir [Aptivus], boosted with ritonavir, is indicated for use with other antiretroviral drugs to treat HIV-infected adults who have evidence of ongoing viral replication and who either (1) have taken antiretroviral drugs for a long time or (2) are infected with HIV strains known to be resistant to multiple PIs. Tipranavir should not be used in the absence of ritonavir boosting.

Mechanism of Action. Tipranavir inhibits HIV protease, and thereby prevents maturation of HIV. However, in contrast to all other PIs, which are rigid peptides, tipranavir is a flexible nonpeptide. Because of its flexibility, tipranavir can adapt to conformational changes in HIV protease that render the enzyme resistant to other PIs. As a result, some HIV strains that have become resistant to other PIs can still be suppressed with tipranavir.

Pharmacokinetics. Absorption from the GI tract is limited, but can be enhanced by a high-fat meal. In the blood, tipranavir is extensively protein bound (more than 99.9%). Tipranavir is a substrate for CYP3A4. However, when the drug is coadministered with ritonavir, conversion to metabolites is minimal. As a result, tipranavir is excreted largely unchanged, primarily in the feces. The plasma half-life is 6 hours.

Adverse Effects. Hepatotoxicity. Liver damage is the greatest concern. Tipranavir may cause severe hepatitis. Some patients have died. To reduce risk, liver function should be assessed at baseline and frequently thereafter. Patients with chronic hepatitis B or C are especially vulnerable, and hence should be followed closely.

Intracranial Hemorrhage. There have been reports of fatal and nonfatal intracranial hemorrhage. However, a causal relationship has not been established.

Other Adverse Effects. The most common adverse effects are nausea, vomiting, diarrhea, headache, and fatigue. Tipranavir contains a sulfonamide group, and hence should be used with caution in patients allergic to sulfonamides. Like other PIs, tipranavir may pose a risk of hyperglycemia, new-onset diabetes, exacerbation of existing diabetes, fat maldistribution, and increased bleeding in patients with hemophilia. Increases in plasma cholesterol and triglycerides with tipranavir are larger than with other PIs.

Drug Interactions. Tipranavir/ritonavir is subject to numerous drug interactions. The combination can inhibit the metabolism of some drugs and accelerate the excretion of others. Also, other drugs can alter the kinetics of tipranavir.

The tipranavir/ritonavir combination is a net inhibitor of CYP3A and CYP2D6, and hence can intensify the effects of drugs metabolized by these enzymes. To avoid toxicity, patients using tipranavir/ritonavir should not take enzymes. To avoid toxicity, patients using tipranavir/ritonavir should not take enzymes. To avoid toxicity, patients using tipranavir/ritonavir should not take enzymes. To avoid toxicity, patients using tipranavir/ritonavir should not take enzymes.

The tipranavir/ritonavir combination is a net inducer of P-glycoprotein, a transport molecule that pumps drugs into the bile, urine, and gut. Hence, by inducing P-glycoprotein, the combination can hasten the excretion of certain drugs. In particular, tipranavir/ritonavir can greatly decrease levels of fosam-

prenavir (amprenavir), lopinavir, and saquinavir, and hence should not be combined with these PIs. Whether tipranavir/ritonavir decreases levels of other PIs has not been determined.

Tipranavir/ritonavir can decrease levels of ethinyl estradiol, a component of many oral contraceptives. Women taking oral contraceptives should be advised to use an alternative or additional form of contraception.

Tipranavir itself is a substrate for CYP3A and P-glycoprotein. Accordingly, agents such as rifampin and St. John's wort, which induce these pathways, can decrease tipranavir levels, and might thereby cause treatment failure.

Preparations, Dosage, Administration, and Storage. Tipranavir [Aptivus] is supplied in solution (100 mg/mL) and 250-mg, soft-gelatin capsules. The adult dosage is 500 mg tipranavir plus 200 mg ritonavir twice daily. When tipranavir is combined with ritonavir tablets, it should be taken with food. However, when tipranavir is combined with ritonavir capsules or solution, it may be taken with or without food.

Unopened bottles of tipranavir capsules should be refrigerated. After opening, the bottles may be kept at room temperature, but capsules must be used within 60 days.

Tipranavir oral solution should be stored at room temperature—never refrigerated—and used within 60 days after opening.

Darunavir (Plus Ritonavir)

Darunavir [Prezista] is a second-generation PI with activity against HIV strains that are resistant to other PIs. Strains resistant to darunavir are generally cross-resistant with all other PIs, except possibly tipranavir. Darunavir, boosted with ritonavir (and combined with other antiretroviral drugs), is indicated for HIV-infected adults and children. The combination can be especially useful in treatment-experienced patients infected with HIV strains that are resistant to one or more other PIs.

Darunavir is administered PO, and should be taken with food to increase absorption. In blood, the drug is 95% protein bound. When taken alone, darunavir is rapidly inactivated in the liver, primarily by CYP3A. Accordingly, it should always be combined with ritonavir, a PI that inhibits CYP3A. In one study, ritonavir increased darunavir levels 14-fold. When darunavir is combined with ritonavir, its half-life is 15 hours.

Adverse effects are similar to those of other PIs. The most common reactions are diarrhea, nausea, and headache. The incidence of rash is 7%. Some patients experience elevations in serum lipids and aminotransferase activity. Like tipranavir and fosamprenavir, darunavir has a sulfonamide component, and hence should be used with caution in patients with sulfonamide allergy. Of note, signs of glucose dysregulation—new-onset diabetes, worsening of existing diabetes, and hyperglycemia—that occur with other PIs have not been reported with darunavir.

Both darunavir and ritonavir inhibit CYP3A, and hence will increase levels of drugs that depend on CYP3A for their clearance. Because elevated levels of certain drugs can be especially dangerous, they are contraindicated for use with darunavir/ritonavir. In this group are ergot derivatives (ergonovine, ergotamine, dihydroergotamine, methylergonovine), two benzodiazepines (midazolam and triazolam), cisapride (a GI motility agent), and pimozide (a neuroleptic).

Darunavir [Prezista] is supplied in film-coated tablets (75, 150, 300, 400, and 600 mg) for oral dosing with food. For treatment-naïve adults, the dosage is 800 mg once daily boosted with 100 mg ritonavir once daily. For treatment-experienced adults, the dosage is 600 mg twice daily boosted with 100 mg ritonavir twice daily.

RALTEGRAVIR, AN INTEGRASE STRAND TRANSFER INHIBITOR

Actions and Use. Raltegravir [Isentress], approved in 2007, is our first and only HIV integrase strand transfer inhibitor (INSTI), or simply *integrase inhibitor*. As discussed above, integrase is one of three viral enzymes needed for HIV replication. The other two enzymes—reverse transcriptase and protease—are inhibited by older drugs. As its name implies, integrase inserts HIV genetic material into the DNA of CD4 cells. By inhibiting integrase, raltegravir prevents insertion of HIV DNA, and thereby stops HIV replication. Raltegravir is active against HIV strains resistant to other drugs. Another INSTI—*elvitegravir*—is in the advanced stages of development.

Raltegravir is indicated for combined use with other antiretroviral agents to treat adults infected with HIV-1. The drug was originally approved only for treatment-experienced patients, but is now approved for treatment-naïve patients as well. In current guidelines, raltegravir (in combination with tenofovir plus either emtricitabine or lamivudine) is considered a first-choice drug for HIV treatment.

Pharmacokinetics. Raltegravir is administered orally, and plasma levels peak about 3 hours after dosing. In the blood, about 83% is protein bound. The drug is metabolized by an enzyme known as uridine diphosphate glucuronosyltransferase (UGT). Metabolites are excreted in the feces and urine. The serum half-life is approximately 9 hours.

Adverse Effects. Raltegravir is generally well tolerated. The most common side effects are insomnia and headache. In clinical trials, some patients experienced myopathy and rhabdomyolysis, but a causal relationship has not been established.

Rarely, patients have developed *severe hypersensitivity reactions*. Skin reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis, which can be fatal. Organ dysfunction, including liver failure, may also develop. Patients who develop signs of a hypersensitivity reaction (eg, severe rash, or rash associated with blisters, fever, malaise, fatigue, oral lesions, facial edema, hepatitis, angioedema, muscle or joint aches) should discontinue raltegravir immediately.

Use During Pregnancy and Lactation. Raltegravir is classified in FDA Pregnancy Risk Category C. No adequate or well-controlled studies have been done in pregnant women. Breast-feeding is not recommended.

Drug Interactions. Atazanavir and other inhibitors of UGT can increase levels of raltegravir. Conversely, rifampin and other inducers of UGT can lower raltegravir levels.

Preparations, Dosage, and Administration. Raltegravir [Isentress] is supplied in 400-mg tablets for oral dosing, with or without food. The recommended dosage is 400 mg twice daily. During coadministration with rifampin, the dosage is 800 mg twice daily. Raltegravir can be stored at room temperature.

ENFUVIRTIDE, AN HIV FUSION INHIBITOR

Enfuvirtide [Fuzeon], widely known as T-20, is the first and only HIV fusion inhibitor. Unlike most other drugs for HIV, which inhibit essential viral enzymes—either reverse transcriptase, integrase, or protease—enfuvirtide blocks entry of HIV into CD4 T cells. Unfortunately, although enfuvirtide is effective, it is also inconvenient (treatment requires twice-daily subQ injections) and very expensive (treatment costs about \$20,000 a year). Furthermore, injection-site reactions occur in nearly all patients. Significant interactions with other drugs have not been observed. Enfuvirtide received FDA approval in 2003.

Chemistry

Enfuvirtide is a synthetic peptide that contains 36 amino acids. Its molecular weight is 4492. Laboratory synthesis of enfuvirtide is complex: 106 steps are involved, compared with 8 to 12 steps for traditional antiretroviral drugs. As a result, enfuvirtide is expensive to make, which largely explains its high cost.

Mechanism of Action

Enfuvirtide prevents the HIV envelope from fusing with the cell membrane of CD4 cells (Fig. 94-2, step 2), and thereby blocks viral entry and replication. Fusion inhibition results

from binding of enfuvirtide to gp41, a subunit of the glycoproteins embedded in the HIV envelope (see Fig. 94-1). As a result of enfuvirtide binding, the glycoprotein becomes rigid, and hence cannot undergo the configurational change needed to permit fusion of HIV with the cell membrane.

Resistance

Resistance to enfuvirtide has developed in cultured cells and in patients. The cause is a structural change in gp41. In clinical trials, reductions in drug susceptibility have ranged from 4- to 422-fold. Fortunately, the HIV mutations that confer resistance to enfuvirtide do not confer cross-resistance to NRTIs, NNRTIs, PIs, INSTIs, or CCR5 antagonists. Conversely, resistance to NRTIs, NNRTIs, PIs, INSTIs, or CCR5 antagonists does not confer cross-resistance to enfuvirtide.

The rate at which resistance develops depends on the efficacy of the drugs used concurrently. When the patient's other antiretroviral drugs are still effective, resistance to enfuvirtide develops relatively slowly. However, when there is significant resistance to the other drugs, resistance to enfuvirtide develops rapidly.

Pharmacokinetics

Enfuvirtide is administered subQ, and plasma levels peak in 3 to 12 hours. Bioavailability is about 84%, regardless of the site of injection (upper arm, thigh, abdomen). In the blood, enfuvirtide is 92% protein bound, mainly to albumin. Because enfuvirtide is a peptide, we presume it undergoes breakdown to its constituent amino acids—although studies to identify specific metabolic pathways have not been conducted. The elimination half-life is 3.8 hours.

Therapeutic Use

Enfuvirtide is reserved for treating HIV-1 infection that has become resistant to other antiretroviral agents. Specifically, the drug is indicated for HIV-1 infection in patients age 6 years and older who are treatment experienced and have evidence of HIV replication despite ongoing antiretroviral therapy. To delay emergence of resistance, enfuvirtide should always be combined with other antiretroviral drugs.

In clinical trials, enfuvirtide was given to patients with measurable plasma HIV RNA despite use of an optimized antiretroviral regimen (OAR). The result? Compared with patients receiving the OAR alone, those receiving the OAR plus enfuvirtide showed a significant reduction in plasma HIV RNA and an increase in circulating CD4 T cells. Benefits were sustained for at least 24 weeks.

Adverse Effects

Injection-Site Reactions. In clinical trials, injection-site reactions (ISRs) developed in 98% of patients, usually within the first week of treatment. Principal manifestations are pain and tenderness (95%), erythema and induration (89%), nodules or cysts (76%), pruritus (62%), and ecchymosis (small hemorrhagic spots; 48%). Although generally mild to moderate, symptoms can also be severe. In 17% of patients, individual ISRs persisted more than 7 days. Because ISRs are both common and long lasting, 23% of patients had six or more ongoing ISRs at any given time. The intensity of ISRs can be reduced by rotating the injection site, avoiding sites with an active ISR, and avoiding unnecessarily deep injections. If a severe ISR occurs, or if local infection develops, patients should seek immediate medical attention.

Pneumonia. Enfuvirtide appears to increase the risk of bacterial pneumonia. Patients should be informed about signs

of pneumonia (cough, fever, breathing difficulties), and instructed to report them immediately. Enfuvirtide should be used with caution in patients who have pneumonia risk factors: low initial CD4 cell counts, high initial viral load, IV drug use, smoking, and a history of lung disease.

Hypersensitivity Reactions. Because enfuvirtide is a foreign peptide, it can trigger hypersensitivity reactions. Typical symptoms, which may occur individually and in combination, are rash, fever, nausea, vomiting, chills, rigors, hypotension, and elevated serum transaminases. Enfuvirtide has also been associated with respiratory distress, glomerulonephritis, Guillain-Barré syndrome, and primary immune complex reaction, all of which may be immune mediated. If a systemic hypersensitivity reaction occurs, enfuvirtide should be discontinued immediately and never used again.

Effects During Pregnancy and Lactation. In animal studies, enfuvirtide failed to cause fetal harm. Studies in pregnant humans have not been conducted. Until more is known, the drug should be used during pregnancy only if clearly indicated. Enfuvirtide is classified in FDA Pregnancy Risk Category B.

Women with HIV infection should not breast-feed, owing to the risk of HIV transmission. Whether enfuvirtide enters breast milk is unknown.

Drug Interactions

Enfuvirtide appears devoid of significant drug interactions. There are no interactions with other antiretroviral drugs that would require a dosage adjustment for either enfuvirtide or the other agent.

Preparations, Dosage, Administration, and Storage

Preparations and Storage. Enfuvirtide [Fuzeon] is supplied in single-use vials that contain 108 mg of powdered drug, which must be reconstituted to a 90-mg/mL solution by adding 1.1 mL of sterile water for injection. The solution can be used immediately or stored cold (2°C to 8°C; 36°F to 46°F) for up to 24 hours. Before injection, stored solutions should be brought to room temperature and inspected to ensure they are still clear, colorless, and free of bubbles and particulate matter. Powdered enfuvirtide can be stored at room temperature.

Dosage and Administration. Administration is by subQ injection. The dosage for adults is 90 mg (1 mL) twice daily. The dosage for children ages 6 through 16 years is 2 mg/kg twice daily, but not more than 90 mg twice daily. Injections are made into the upper arm, anterior thigh, or abdomen (but not the navel), using aseptic technique to avoid infection. The site should be moved for each injection. Injections should not be made into tissue that is scarred or bruised, or into sites where there is an ongoing reaction to a previous dose.

MARAVIROC, A CCR5 ANTAGONIST

Actions. Maraviroc [Selzentry, Celsentri[®]], approved in 2007, is the first representative of a new class of antiretroviral drugs: the *chemokine receptor 5 (CCR5) antagonists*. As discussed above, CCR5 is a co-receptor that some strains of HIV must bind with in order to enter CD4 cells. Maraviroc binds with CCR5, and thereby blocks viral entry. HIV strains that require CCR5 for entry are referred to as being *CCR5 tropic*. Between 50% and 60% of patients are infected with this type of HIV. Maraviroc and enfuvirtide (a fusion inhibitor) are the only antiretroviral drugs that block HIV entry. All other agents inhibit HIV enzymes, either reverse transcriptase, integrase, or protease.

Therapeutic Use. Maraviroc is indicated for combined use with other antiretroviral agents to treat patients age

16 years and older who are infected with CCR5-tropic HIV-1 strains. The drug was originally approved only for treatment-experienced patients, but is now approved for treatment-naïve patients as well. However, although the target population has been expanded, use of the drug is likely to remain low. Why? Because (1) dosing is complex (maraviroc must be taken twice daily, and dosage must be adjusted on the basis of other drugs being used) and (2) before maraviroc is used, a relatively expensive test must be performed to confirm that the infecting HIV strain is indeed CCR5 tropic.

Pharmacokinetics. Maraviroc is administered PO, and plasma levels peak in 0.5 to 4 hours. With a 300-mg dose, bioavailability is 33%. In the blood, the drug is 70% protein bound. Maraviroc undergoes hepatic conversion to inactive metabolites, primarily by CYP3A4. The serum half-life is 14 to 18 hours.

Adverse Effects. The most common side effects are cough, dizziness, pyrexia, rash, abdominal pain, musculoskeletal symptoms, and upper respiratory tract infections. Intensity is generally mild to moderate.

Liver injury has been seen in some patients, and may be preceded by signs of an allergic reaction (eg, eosinophilia, pruritic rash, elevated immunoglobulin E). Patients should be informed about signs of an evolving reaction (itchy rash, jaundice, vomiting and/or abdominal pain), and instructed to stop maraviroc and seek medical attention.

During clinical trials, a few patients experienced *cardiovascular events*, including myocardial ischemia and myocardial infarction. Maraviroc should be used with caution in patients with cardiovascular risk factors.

Effects During Pregnancy and Lactation. There are no adequate and well-controlled studies in pregnant women. Maraviroc is classified in FDA Pregnancy Risk Category B. Women with HIV infections should not breast-feed, owing to the risk of HIV transmission. Whether maraviroc enters breast milk is unknown.

Drug Interactions. Because maraviroc is metabolized by CYP3A4, drugs that inhibit or induce this enzyme will affect maraviroc levels. Levels will be raised by strong CYP3A4 inhibitors, including protease inhibitors (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazodone, and telithromycin. Conversely, maraviroc levels will be lowered by strong CYP3A4 inducers, including rifampin, efavirenz, carbamazepine, phenobarbital, phenytoin, and St. John's wort.

Preparations, Dosage, and Administration. Maraviroc [Selzentry, Celsentri[®]] is supplied in 150- and 300-mg tablets, for dosing with or without food. Dosage depends on other drugs being used as follows:

- Strong CYP3A4 inhibitors—150 mg twice daily
- Strong CYP3A4 inducers—600 mg twice daily
- All other medications—300 mg twice daily

Specific CYP3A4 inhibitors and inducers are indicated above under *Drug Interactions*.

MANAGEMENT OF HIV INFECTION

Thanks to the drugs we have today, HIV infection has been transformed from a near-certain death sentence to a manageable chronic disease. Most patients take several antiretroviral drugs—typically two NRTIs combined with either a PI or NNRTI. These highly effective regimens can reduce plasma

HIV to undetectable levels, causing CD4 T-cell counts to return toward normal, thereby restoring some immune function. However, despite these advances, treatment cannot cure HIV. In all cases, discontinuation of antiretroviral drugs has led to a rebound in plasma HIV.

Therapy of HIV disease is often complex. Patients take a combination of drugs for HIV itself—and may take additional drugs to manage treatment side effects (eg, hyperlipidemia, lipodystrophy, depression) along with drugs to prevent or treat opportunistic infections. As a result, the potential for adverse effects and drug interactions is large. Also, among the drugs used for HIV, emergence of resistance is common. Furthermore, adverse effects and pill burden make adherence difficult. Because of these complexities, management is best done by a clinician with extensive experience in treating HIV.

Much of the discussion that follows is based on treatment guidelines for adult patients developed by the Panel on Clinical Practices for Treatment of HIV Infection, convened by the U.S. Department of Health and Human Services (DHHS). This document—*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*—undergoes periodic updates. The version cited here was updated on October 14, 2011. This guideline is available online at aidsinfo.nih.gov, along with companion guidelines for treating pediatric and pregnant patients, and for prophylaxis following HIV exposure.

Screening and Diagnosis

Several tests are used to screen for HIV. They all detect anti-HIV antibodies. If an initial screen produces a positive result, it must be confirmed by a follow-up test.

It should be noted that antibody testing has one important limitation: It can't detect infection immediately following HIV exposure. Why? Because for days to weeks after initial exposure, antibody levels are too low to be measured. Hence, if early diagnosis is needed, a different type of test must be used—specifically, measurement of plasma HIV RNA (see below). If the test for HIV RNA is positive, it should be confirmed with an antibody-based test 2 to 4 months later.

Initial Screening. Prior to 2003, only one type of test was used for HIV screening: an *enzyme-linked immunosorbent assay* (ELISA). ELISAs measure HIV antibodies in blood, and take at least 48 hours to conduct. In reality, however, results are usually not ready for 1 to 2 weeks. Because of this delay, testees must make a return visit. Unfortunately, many don't bother.

Seven rapid HIV tests are now available. One of them—the *INSTI HIV-1 Antibody Test*—gives results in as little as 60 seconds. The others give results in 10 to 20 minutes. Because these tests are so rapid, testees needn't return to learn their HIV status.

Follow-up Confirmation. Positive results from an initial screening test are considered preliminary, and must be confirmed with a second test, usually a Western blot assay. Unlike the initial screening procedures, which test for all types of anti-HIV antibodies, the Western blot measures individual antibody classes. To be considered positive, the Western blot must detect antibodies against at least two of the following three proteins: p24 (a core protein of HIV), and gp41 and gp120/161 (HIV proteins needed for attachment to CD4 T cells).

Laboratory Tests

The principal laboratory tests employed to monitor HIV infection and guide therapy are *CD4 T-cell counts* and *plasma HIV RNA (viral load) assays*. Measurement of viral load indicates the magnitude of HIV replication and predicts the rate of CD4 T-cell destruction. In contrast, CD4 T-cell counts indicate how much damage the immune system has already suffered. In addition to these tests, evaluation of *HIV drug resistance* is now done routinely. Some patients will also need tests for *HLA-B*5701* (a genetic variant linked to abacavir hypersensitivity) and for *HIV CCR5 tropism* (a determinant of responsiveness to maraviroc).

CD4 T-Cell Counts

The CD4 T-cell count is the principal indicator of how much immunocompetence remains. Accordingly, the CD4 count is a major factor in deciding *when to initiate* antiretroviral therapy, and *when to change drugs* if the regimen is failing. Also, by telling us about immune status, the assay can help guide initiation, discontinuation, and resumption of drugs for opportunistic infections.

As antiretroviral therapy takes effect, CD4 T-cell counts will begin to rise, indicating some return of immune function. With ART, increases of 100 to 250 cells/mm³ have been observed. Although restoration of CD4 T-cell counts may not produce *complete* immunocompetence, it is often sufficient to permit discontinuation of prophylactic therapy against some opportunistic infections.

Measurement of CD4 T cells should be obtained when HIV infection is diagnosed and every 3 to 6 months thereafter. A healthy range for CD4 T cells is 800 to 1200 cells/mm³. A 30% reduction is considered significant. Among people with HIV infection, a CD4 T-cell count above 500 cells/mm³ is considered relatively high. In contrast, a count below 200 cells/mm³ indicates clear immunodeficiency.

Viral Load (Plasma HIV RNA)

Ongoing treatment of HIV infection is guided primarily by monitoring *viral load*, which is determined by measuring *HIV RNA in plasma*. The source of the RNA is intact HIV virions (virus particles), each of which has two copies of HIV RNA. Guidelines regarding when to measure HIV RNA are summarized in Table 94-7.

Several assays are approved for measuring HIV RNA. With all of these tests, results are expressed as number of copies of HIV RNA per milliliter. In order to obtain reliable results, blood for HIV RNA determinations must be collected and preserved according to recommended procedures. However, because these tests use different technologies, results will differ depending on the test employed. In order to interpret the results, the clinician must know which test was used.

Given that the vast majority of HIV in the body is present in lymphoid tissues rather than in the blood, you might ask whether measurement of HIV RNA in *plasma* is a true reflection of the *total body* load of HIV. The answer is "Yes." Why? Because, when HIV in lymphoid tissues replicates, many of the new virions are released into the blood. As a result, levels of HIV in blood parallel levels in lymphoid tissues. Accordingly, measurement of HIV RNA in blood gives an accurate picture of the total HIV load.

Plasma HIV RNA is the best measurement available for predicting clinical outcome. If HIV RNA is high (eg, 100,000 cop-

TABLE 94-7 • Times When Plasma HIV RNA Should Be Measured

When to Measure Plasma HIV RNA	Information Obtained	Use of the Information
When a patient presents with a syndrome consistent with acute HIV infection	Establishes presence of HIV when HIV antibody test is negative or indeterminate	Diagnosis of HIV infection
Following initial diagnosis of HIV infection	Establishes baseline viral load	Use in conjunction with CD4 T-cell count for decision to start or defer therapy
Every 3–6 months in HIV patients not on ART	Extent to which viral load has increased	Use in conjunction with CD4 T-cell count for decision to initiate therapy
2–8 weeks after starting or changing ART (preferably within 2–4 weeks)	Virologic impact of therapy	Decision to continue or change therapy
Every 3–6 months in patients on ART (every 6 months in adherent/stable patients with suppressed HIV RNA for greater than 2–3 years)	Durability of drug effects	Decision to continue or change therapy
When a clinical event or a decline in CD4 T cells occurs	Establishes if the clinical event or decline in CD4 T cells occurred in association with an increase in viral load	Decision to initiate, continue, or change therapy

ART = antiretroviral therapy.

Adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, prepared by the Panel on Clinical Practices for Treatment of HIV Infection, convened by the DHHS, as updated on October 14, 2011.

ies/mL), the prognosis is poor. Conversely, if HIV RNA is low (eg, 500 copies/mL), the risk of disease progression and death is greatly reduced. Accordingly, the goal of therapy is to decrease plasma HIV RNA as much as possible—preferably to a level that is undetectable with current assays (ie, below 20 to 75 copies/mL of plasma, depending on the test employed). It is important to appreciate, however, that even when plasma HIV RNA is undetectable, the patient may still be able to transmit HIV to others—although the risk of transmission is greatly reduced.

When patients are treated with ART, levels of HIV RNA should decline to 10% of baseline within 2 to 8 weeks. After 16 to 20 weeks of treatment, plasma HIV RNA should reach its minimum. With optimal therapy, the minimum reached should be below the limit of detection.

HIV Drug Resistance

Resistance is a significant concern in HIV therapy. In most cases, resistance emerges over the course of treatment as a result of nonadherence to the prescribed regimen. Rarely, resistance results from primary infection with a drug-resistant HIV variant. Resistance tests can be used to guide drug selection, especially when changing a regimen that has failed.

Two major types of resistance assays are employed: *phenotypic assays* and *genotypic assays*. Phenotypic assays measure the ability of HIV to grow in the presence of increasing concentrations of antiretroviral drugs. (The ability to grow in high concentrations indicates resistance.) Genotypic assays are designed to detect resistance-conferring mutations in HIV genes that code for the targets that drugs attack (eg, reverse transcriptase and protease). Unfortunately, assays for resistance have multiple drawbacks: they are expensive (\$400 to \$1000); turnaround is slow (2 to 4 weeks); sensitivity is low;

phenotypic assays can produce false-negative results; and genotypic assays are difficult to interpret. There are no prospective data showing that one type of assay (genotypic or phenotypic) is superior to the other.

When should resistance be tested? According to the 2011 guideline updates, the following recommendations apply:

- Test all patients entering HIV care, even if drug therapy will not start immediately. (If drugs are delayed, consider repeating the test.) For these treatment-naïve patients, a genotypic assay is generally preferred.
- Test to aid selection of new drugs when there is virologic failure and HIV RNA levels exceed 1000 copies/mL. (In persons with more than 500 but less than 1000 copies/mL, testing should still be considered.)
- Test when managing suboptimal viral load reduction.
- Test all pregnant women who have not started therapy, and test women who become pregnant while on therapy if they have detectable levels of HIV RNA. In both cases, use a genotypic assay.

HLA-B*5701 Screening

As discussed above, the risk of having a hypersensitivity reaction to abacavir is determined largely by a genetic variation, known as HLA-B*5701. Accordingly, patients should be screened for HLA-B*5701 before starting abacavir. If the test is positive, abacavir should not be used, and the patient's positive status should be recorded as an abacavir allergy in his or her medical record. If HLA-B*5701 testing is not available, abacavir may still be used, provided the patient is counseled about possible risk, and monitored for signs of hypersensitivity.

CCR5 Tropism

As discussed above, CCR5 is a co-receptor that many strains of HIV must bind with in order to enter CD4 cells. Strains of HIV that use this co-receptor are referred to as being CCR5 tropic. Currently, we have one drug—maraviroc—that can inhibit CCR5 and thereby block HIV entry, but only if the strain is CCR5 tropic. Accordingly, when therapy with maraviroc is under consideration, a CCR5 tropism assay should be performed. Two commercial assays are available: *Trofile* and *Phenoscript*. *Trofile* takes 2 weeks to perform and requires a plasma HIV RNA level of 1000 copies/mL or more.

Therapeutic Drug Monitoring

The term *therapeutic drug monitoring* (TDM) refers to the measurement of plasma drug levels to help guide treatment. For antiretroviral therapy, routine TDM is *not* recommended.

Ideally, by knowing drug levels, we can adjust dosages to maximize antiviral effects and minimize toxicity. However, for TDM to be clinically useful, we must first know a drug's therapeutic range. That is, we need to know the minimal plasma level required for therapeutic effects, and the maximal level we can achieve before toxicity begins. For the antiretroviral drugs, we have some of this information, but not all of it. Specifically, for the PIs, NNRTIs, and maraviroc (a CCR5 antagonist), we know how low drug levels can fall and still be effective—but we don't know how high levels can rise before toxicity sets in. For the NRTIs, enfuvirtide (a fusion inhibitor), and raltegravir (an integrase strand transfer inhibitor), we have no information that could help guide treatment. Hence, at this time, monitoring plasma levels of PIs, NNRTIs, and maraviroc might be clinically useful, but monitoring levels of other drugs would not.

Why is TDM needed? Because there is considerable variation in drug levels among patients taking the same dose of the same drug. Important sources of variation include differences in drug absorption, and alterations in drug metabolism owing to concurrent use of inducers and/or inhibitors of cytochrome P450. Specific conditions under which TDM might be useful include

- Concurrent use of an interacting drug
- Pathologic changes in GI, hepatic, or renal function that could alter drug absorption or elimination
- Pregnancy, which can lower drug concentrations
- Treatment of patients who have partially resistant HIV
- Use of a dosing regimen whose efficacy has not been established in clinical trials
- Suspected concentration-dependent drug toxicity
- Lack of expected virologic response in medication-adherent patients.

Are there limitations to TDM? Yes. First, and most important, we lack prospective studies showing that TDM actually improves clinical outcomes. Second, laboratories that can measure plasma levels of antiretroviral drugs are not widely available. Third, as noted already, information on target drug levels—both therapeutic and toxic—is very limited. Because of these factors, routine TDM is generally not recommended.

Treatment of Adult and Adolescent Patients

As discussed above, HIV disease has three phases: an initial acute phase, followed by a prolonged asymptomatic phase, followed by a late symptomatic phase during which AIDS oc-

curs. In the discussion below, we consider drug therapy for each phase separately. However, to facilitate discussion, the phases are discussed in reverse sequence. That is, we discuss asymptomatic HIV disease first, then asymptomatic HIV disease, and then acute HIV disease. For patients with symptomatic or acute HIV disease, the benefits of treatment clearly outweigh the risks; hence, immediate and aggressive treatment is recommended. In contrast, for patients with asymptomatic HIV disease, the benefits of immediate treatment may not outweigh the risks; hence, in some cases, it may be appropriate to delay treatment. During all phases of HIV disease, treatment has six basic goals:

- Maximal and durable suppression of viral load
- Restoration or preservation of immune function
- Improved quality of life
- Reduction of HIV-related morbidity and mortality
- Reduction of sexual HIV transmission
- Prevention of vertical HIV transmission (ie, transmission from mother to child, either during pregnancy, delivery, or breast-feeding)

Symptomatic HIV Disease

All patients with symptomatic (advanced) HIV disease should receive maximally effective antiretroviral therapy, regardless of CD4 counts. The virologic goal is to produce maximal and sustained suppression of HIV replication, as evidenced by reduction of plasma HIV RNA to an undetectable level. The treatments employed are referred to as ART, formerly known as HAART (highly active antiretroviral therapy).

ART regimens typically contain *three drugs*. Regimens that contain only two drugs are not generally recommended, and monotherapy should always be avoided, except possibly during pregnancy.

Recommended regimens are summarized in Table 94-8. As indicated, all regimens contain drugs from *two different classes*. Preferred regimens consist of either (1) an NNRTI combined with two NRTIs, (2) a PI combined with two NRTIs, or (3) raltegravir (an INSTI) combined with two NRTIs. By using drugs from different classes, we can attack HIV in two different ways (eg, inhibition of reverse transcriptase and inhibition of protease), and can thereby enhance antiviral effects.

In addition to enhancing antiviral effects, *use of multiple drugs reduces the risk of resistance*. Why? Because the probability that HIV will undergo a mutation that confers simultaneous resistance to three or four drugs is much smaller than the probability of undergoing a mutation that confers resistance to just one drug. For example, if our patient is taking three drugs—efavirenz, tenofovir, and emtricitabine—and a virion mutates to a form that is resistant to efavirenz, the other two drugs—tenofovir and emtricitabine—will still be effective against the resistant virion, and hence suppression of replication is more likely to be sustained. On the other hand, if our patient were only taking efavirenz, then treatment would most likely fail. Because of concerns about resistance, when a patient who began treatment with monotherapy is switched to multidrug therapy, we should employ drugs that (1) the patient has not used before and (2) are not cross-resistant with drugs the patient has used before.

Most regimens employ drugs from only two of the six available classes of antiretroviral agents. Because four classes

TABLE 94-8 ■ Preferred and Alternative Antiretroviral Regimens for Initial Therapy of Established HIV Infection

All regimens contain three antiretroviral drugs: NNRTI-based regimens contain an NNRTI combined with 2 NRTIs, PI-based regimens contain a PI combined with 2 NRTIs, and INSTI-based regimens contain raltegravir combined with 2 NRTIs.

PREFERRED REGIMENS

NNRTI-Based Regimen

Efavirenz* + tenofovir + emtricitabine

PI-Based Regimens

Atazanavir/ritonavir[†] + tenofovir + emtricitabine *or* lamivudine

Darunavir/ritonavir[†] + tenofovir + emtricitabine *or* lamivudine

INSTI-Based Regimen

Raltegravir + tenofovir + emtricitabine *or* lamivudine

Preferred Regimen for Pregnant Women

Lopinavir/ritonavir[†] + zidovudine + emtricitabine *or* lamivudine

ALTERNATIVE REGIMENS

NNRTI-Based Regimens

Efavirenz* + abacavir + emtricitabine *or* lamivudine

Rilpivirine + tenofovir + emtricitabine *or* lamivudine

Rilpivirine + abacavir + emtricitabine *or* lamivudine

PI-Based Regimens

Atazanavir/ritonavir[†] + abacavir + emtricitabine *or* lamivudine

Darunavir/ritonavir[†] + abacavir + emtricitabine *or* lamivudine

Fosamprenavir/ritonavir[†] + abacavir *or* tenofovir + emtricitabine *or* lamivudine

Lopinavir/ritonavir[†] + abacavir *or* tenofovir + emtricitabine *or* lamivudine

INSTI-Based Regimen

Raltegravir + abacavir + emtricitabine *or* lamivudine

HIV RNA. Accordingly, patients must understand that reducing HIV RNA to undetectable levels does not mean that HIV has been eradicated, and does not mean they have been cured. It only means that the amount of HIV in plasma is too low to measure. Patients with undetectable HIV RNA should be told that they are still infectious, and hence must avoid behaviors that can transmit HIV to others. Because patients still harbor HIV, treatment should continue indefinitely.

A combination of factors—complex regimens, multiple adverse effects, drug-drug and drug-food interactions, life-long treatment—make safe and effective ART difficult. These same factors make patient adherence difficult too. If treatment is to succeed, patients must be fully informed about the importance of strict adherence to the regimen, timing of dosing with regard to meals, and the potential for adverse effects and interactions. Specific measures to promote adherence are discussed below.

Chronic Asymptomatic HIV Disease

Making the decision to treat during the chronic asymptomatic phase of HIV disease is more difficult than during the symptomatic phase. Why? Because we lack strong clinical data to guide the decision. For patients in the symptomatic phase, we have solid evidence that the benefits of treatment outweigh the risks, and hence all patients should be given the option of treatment. However, for most patients in the asymptomatic phase, we simply don't know if the benefits will outweigh the risks, and hence the optimal time to initiate therapy is uncertain. Given this lack of certainty, patients and their prescribers must weigh multiple factors when deciding whether to initiate ART. Specifically, they must consider the potential benefits and risks of treatment, as well as factors unique to each patient, especially viral load and the existing degree of immunodeficiency. Table 94-9 summarizes these factors.

Early intervention offers several benefits, the most obvious being reduction of viral load. As a result, progression of immunodeficiency is slowed, progression to AIDS is delayed, life may be prolonged, and the risk of transmitting HIV is reduced. In addition, suppression of replication decreases the rate of HIV mutation, and can thereby decrease emergence of drug-resistant mutants. Finally, early treatment decreases the risk of multiple disorders associated with HIV infection, including tuberculosis, Kaposi's sarcoma, and disease of the kidneys, liver, and heart.

Unfortunately, early intervention does have drawbacks. Drug therapy can decrease quality of life. How? By exposing an otherwise symptom-free person to the adverse effects of drugs, including long-term toxicities that may not yet be known. In addition, although it is true that decreasing viral load and replication will decrease spontaneous production of resistant mutants, if resistant mutants *are* produced, the presence of drugs will create selection pressure favoring their emergence. Hence, it is possible that drug therapy will allow resistance to develop sooner than it would have in the absence of drugs. This is especially true if the patient fails to adhere to the regimen. Furthermore, if resistance does develop, drug options for future therapy will be limited, and the risk of transmitting resistance will be increased.

In addition to balancing benefits versus risks, factors unique to the patient must be considered before initiating therapy. Obviously, the patient must be ready to initiate treatment. Also, the patient must be prepared to carefully follow

INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside/nucleotide reverse transcriptase inhibitor, PI = protease inhibitor.

*Efavirenz is not recommended for use in the first trimester of pregnancy or by women with a high pregnancy potential.

[†]The purpose of ritonavir in these combinations is to boost the effects of the other PI by inhibiting its metabolism.

Adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, prepared by the Panel on Clinical Practices for Treatment of HIV Infection, convened by the DHHS, as updated on October 14, 2011.

of antiretroviral drugs are *not* used, these regimens are considered *class-sparing*. For example, a regimen that employs a PI plus NRTIs would spare the use of NNRTIs, fusion inhibitors, INSTIs, and CCR5 antagonists. A major benefit of class-sparing regimens is that they postpone development of resistance to the unused drug classes, and thereby increase the likelihood that the unused classes will be effective for the patient in the future.

Plasma HIV RNA should be monitored to assess the impact of treatment. With ART, plasma HIV RNA should show a 10-fold decrease by 8 weeks, and should be undetectable (ie, below 20 to 75 copies/mL) by 4 to 6 months.

ART cannot cure HIV. Why? Because some HIV virions remain dormant in memory CD4 T cells, and hence escape harm. In all cases, discontinuation of ART has led to a rise in

the dosing schedule. Finally, the patient's HIV status must be considered. Specifically, we must consider (1) the degree of immunodeficiency, as indicated by CD4 T-cell counts; and (2) the risk of disease progression, as indicated by plasma HIV RNA level.

So, who should be treated? According to current guidelines, the following persons should definitely receive ART, *regardless of absolute CD4 count*:

- Patients with symptomatic disease
- Patients with a history of an AIDS-defining illness
- Pregnant women
- Patients with HIV-associated nephropathy
- Patients with active hepatitis B virus co-infection
- Patients with active or high-risk cardiovascular disease
- Patients with a high viral load (more than 100,000 copies of HIV RNA/mL)
- Patients undergoing a rapid decline in CD4 count (more than 100/mm³/yr)

Regarding CD4 counts, the threshold for initiating treatment has been raised—from 350 cells/mm³ in earlier guidelines to 500 cells/mm³ in current guidelines. As a result, ART is now started *sooner* than in the past. That is, rather than waiting for CD4 counts to drop to 350 cells/mm³, we now start treatment when CD4 counts have only dropped to 500 cells/mm³. What about patients with CD4 counts *above* 500 cells/mm³? Opinion is mixed: Among panel members who created the current guidelines, 50% recommended starting ART immediately, and 50% viewed ART as being optional.

For patients with a high viral load (more than 100,000 copies of HIV RNA/mL) but with reasonable immunologic status (more than 350 CD4 T cells/mL), experts disagree about what to do: Some would start ART immediately; others would defer treatment. When treatment is deferred, immunologic status (CD4 counts) and virologic status (plasma HIV RNA) should be assessed at least every 3 months. For patients at lowest risk (more than 350 CD4 T cells/mm³ and less than 100,000 copies of HIV RNA/mL), treatment may be deferred.

If the patient and physician agree to initiate treatment, the goal is the same as with symptomatic patients: reduction of HIV RNA to levels that are undetectable with sensitive assays. As with symptomatic patients, the preferred regimens consist of three or four drugs (see Table 94–8).

Acute HIV Disease

All patients with primary acute HIV disease should receive maximally effective antiretroviral therapy. As with symptomatic HIV disease, the preferred regimens consist of three or four drugs (see Table 94–8).

Early and aggressive intervention offers multiple potential benefits. Of greatest interest is the possibility of eradicating HIV before it gets firmly established, although eradication has not yet been demonstrated. However, even if we can't clear HIV from the body, early treatment still offers the following benefits:

- By suppressing the initial burst of viral replication, treatment may decrease the extent to which HIV disseminates throughout the body.
- By reducing viral load, treatment can preserve immune function, and may also slow the progression of HIV disease.

TABLE 94–9 • Factors to Consider When Deciding to Initiate Antiretroviral Therapy During the Asymptomatic Phase of HIV Disease (with CD4 T-Cell Counts Above 350 cells/mm³)

Potential Benefits

- Prevention of potentially irreversible injury to the immune system, and maintenance of a higher CD4 count
- Control of viral replication decreases rate of mutation, and can thereby decrease emergence of drug-resistant mutants
- Decreased risk of developing cardiovascular, renal, and liver diseases, and non-AIDS-associated malignancies and infections
- Decreased risk of developing HIV-associated complications that can still occur at higher CD4 counts (>350 cells/mm³), including tuberculosis, non-Hodgkin's lymphoma, Kaposi's sarcoma, peripheral neuropathy, HPV-associated malignancies, and HIV-associated cognitive impairment
- Decreased risk of transmitting HIV to others

Potential Risks

- Development of treatment-associated adverse effects and toxicities
- Exposure of HIV to antiretroviral drugs can lead to earlier emergence of drug-resistant mutants
- If resistance develops, drug options for future therapy will be limited
- If resistance develops, the risk of transmitting resistant mutants will be increased
- Premature use of therapy before the development of more effective, less toxic, and/or better studied drug combinations
- Increased length of treatment, with an increased risk of treatment fatigue
- Long-term toxicity of certain antiretroviral drugs is not yet known

Factors Unique to the Patient

- Willingness to start therapy
- Likelihood of adhering to the regimen
- Degree of immunodeficiency, as indicated by CD4 T-cell count
- Risk of disease progression, as indicated by plasma HIV RNA

- By reducing viral load and the rate of replication, treatment can decrease the rate of mutation, and hence can decrease the risk that a drug-resistant virion will emerge.
- By reducing viral load, treatment can decrease the severity of acute illness, and can reduce the risk of viral transmission.

As with asymptomatic HIV disease, treatment of acute HIV infection does have potential drawbacks. Among these are

- Reduction in quality of life because of drug toxicity
- Possible blunting of the early immune response to HIV because of reduced viral presence
- Emergence of drug-resistant HIV if treatment fails

Nonetheless, given the potential benefits of treatment, these drawbacks do not constitute a compelling reason to postpone therapy.

Changing the Regimen

There are two basic reasons for changing antiretroviral therapy: treatment failure and drug toxicity. Guidelines for altering the regimen because of these factors are discussed below.

Treatment Failure. Treatment failure is arguably the most compelling reason for changing the regimen. Failure is indicated if

- Plasma HIV RNA remains above 200 copies/mL after 24 weeks
- Plasma HIV RNA remains above 50 copies/mL after 48 weeks
- Plasma HIV RNA rebounds after falling to an undetectable level
- CD4 T-cell counts continue to drop despite antiretroviral treatment
- Clinical disease progresses despite antiretroviral treatment

Of these five signs of failure, the first three are the most meaningful, in that they represent a direct measurement of antiretroviral efficacy.

When treatment failure occurs, the reason must be determined. Possibilities include patient nonadherence, poor drug absorption, accelerated drug metabolism (owing to drug interactions), and viral resistance. If nonadherence is the cause, several measures may help (see below). If poor absorption is the cause, changing the timing of administration with respect to meals or increasing the dosage may help. If accelerated metabolism is the cause, increasing the dosage may help. Alternatively, it may be appropriate to substitute a different drug for the one that is causing metabolism to increase. For PIs, accelerated metabolism can be suppressed by adding low-dose ritonavir.

When failure is the result of viral resistance, the preferred response is to change *all* drugs in the regimen. This makes sense in that failure means that HIV is replicating despite current treatment, indicating the presence of at least one HIV strain that is resistant to all drugs in the regimen. If we were to add or change just one drug, resistance would quickly develop to that agent, and failure would recur. The risk of renewed resistance is substantially lower if we change at least two drugs, and even lower if we change three. When we change the regimen, the new drugs should be agents that (1) the patient has not taken previously and (2) are not cross-resistant with drugs the patient has taken previously. Whenever possible, selection of replacement drugs should be guided by resistance testing.

Unfortunately, some patients are already resistant to nearly all available drugs, and hence their options are limited. In such cases, it is rational to continue with the current regimen, which may at least provide partial suppression. To date, there is limited experience with regimens that consist of either two PIs or a PI plus an NNRTI. Nonetheless, for patients who have no other choice, these combinations are potential options. Because cross-resistance is common between ritonavir and indinavir (two PIs), these drugs should not be substituted for each other. Although there is cross-resistance among NNRTIs, a newer NNRTI—etravirine—may be active against HIV strains that are resistant to older NNRTIs.

Three drugs—*enfuvirtide*, *maraviroc*, and *raltegravir*—may be especially valuable for managing treatment failure. As discussed above, all three have unique mechanisms: enfuvirtide is a fusion inhibitor, maraviroc is a CCR5 inhibitor, and raltegravir is an integrase strand transfer inhibitor (INSTI). Because these drugs work differently from the older agents—PIs, NRTIs, and NNRTIs—cross-resistance does not exist. Furthermore, since these three drugs are relatively new, patients are unlikely to harbor HIV strains resistant to them.

Drug Toxicity. If a patient experiences toxicity typical of a particular drug in the regimen, that drug should be withdrawn and replaced with a drug that is (1) from the same class and (2) of equal efficacy. For example, if a patient taking zidovudine were to develop anemia and neutropenia, zidovudine should be discontinued and replaced with another NRTI (eg, stavudine). Note that, when toxicity is the reason for altering the regimen, changing just one drug is proper, whereas when resistance or suboptimal treatment is the reason, at least two of the drugs should be changed.

Promoting Patient Adherence

In order to achieve treatment goals and delay emergence of resistance, strict adherence to the prescribed regimen is critical. Unfortunately, several factors—duration of treatment, pill burden, adverse drug effects, drug-drug interactions, and drug-food interactions—make adhering to antiretroviral therapy unusually hard. The DHHS guidelines identify factors that predict *poor* adherence (eg, poor clinician-patient relationship, active use of alcohol or street drugs, depression and other mental illnesses) as well as factors that predict *good* adherence (eg, availability of emotional and practical support, ability to fit dosing into the daily routine, appreciation that poor adherence will cause treatment failure). Strategies for promoting adherence are summarized below.

Patient- and Medication-Related Strategies

- Thoroughly educate the patient, using multiple sessions, about the goals of therapy and the importance of adherence.
- Ensure that the patient is motivated to take medication *before* the first prescription is written.
- Negotiate a treatment plan that the patient understands and will commit to.
- Devise a regimen that minimizes pill burden and dosing frequency, and that integrates the dosing schedule with meals and the patient's daily routine. (Many patients can now be treated with just one pill taken once a day.)
- Inform the patient about side effects; anticipate side effects and treat them.
- Avoid adverse drug interactions.
- Recruit family and friends to support the treatment plan.
- Organize an adherence support group, or add adherence issues to the agenda of an existing group.

Clinician- and Healthcare Team-Related Strategies

- Establish trust.
- Serve as educator and information resource.
- Provide ongoing support and monitoring.
- Be available between scheduled visits for questions or problems; provide access via pager when away (including on vacation and at conferences).
- Monitor adherence and, when it's low, intensify management (ie, schedule more frequent visits, recruit family and friends, deploy other team members, provide referral to mental health or chemical dependence services).
- Utilize the healthcare team for all patients, and especially for difficult patients and those with special needs (eg, provide peer educators for adolescents or injection-drug users).
- Consider the impact of new diagnoses (eg, depression, liver disease, wasting, recurrent chemical dependency) on adherence, and include adherence intervention in management.

- Utilize all concerned people—pharmacists, peer educators, volunteers, case managers, drug counselors, physician assistants, and all nurses, including nurse practitioners and research nurses—to reinforce the adherence message.
- Educate the support team about antiretroviral therapy and adherence.

Treatment of Infants and Young Children

Pediatric HIV infection is common and increasing in developing countries, but rare and declining in the United States. Worldwide in 2009, an estimated 2.5 million children under the age of 15 were living with HIV/AIDS (90% in sub-Saharan Africa), another 400,000 became newly infected, and 260,000 died due to AIDS. In stark contrast, only 71 new pediatric HIV/AIDS cases were diagnosed in the United States in 2009, down from 954 new AIDS cases in 1992. In almost all cases, pediatric HIV infection is the result of mother-to-child transmission.

In young children, the course of HIV infection is accelerated. Whereas adults generally remain symptom free for a decade or more, many children develop symptoms by their first birthday. Death usually ensues by age 5—even with ART. Why do young children succumb so quickly? Primarily because their immune systems are immature, and hence less able to fend off the virus. Because immune function is limited, levels of HIV RNA climb higher in toddlers than in adults, and then decline at a much slower rate.

In very young patients, diagnosis and monitoring of HIV infection employs different methods than those used in adolescents and adults. In particular, for infants under 18 months of age, diagnosis should be based on viral load assays, not on antibody tests. For children under 5 years of age, monitoring of immune status should be based on the *percentage* of CD4 cells, not on absolute CD4 counts.

Like older patients, young patients should be treated with a combination of antiretroviral drugs, with the goals of (1) reducing plasma viral HIV to an undetectable level and (2) stabilizing or improving immune status. Two preferred regimens are

- *PI-based ART*: lopinavir/ritonavir *plus* two NRTIs (eg, abacavir or zidovudine plus lamivudine or emtricitabine)
- *NNRTI-based ART*: efavirenz or nevirapine (the choice may depend on the child's age) *plus* two NRTIs (eg, abacavir or zidovudine plus lamivudine or emtricitabine)

Recommended alternatives include

- Two NRTIs *plus* a PI (nelfinavir, atazanavir, or fosamprenavir)
- Three NRTIs (zidovudine plus lamivudine plus abacavir). This combination is recommended only if a PI- or NNRTI-based regimen cannot be used.

Unfortunately, therapy in young patients is confounded by limited information on dosing, pharmacokinetics, and safety, and by the limited availability of pediatric formulations. The information we do have on dosage, formulations, monitoring, and other aspects of therapy can be found in the document titled *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, prepared by the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. The guidelines, which undergo periodic updates, are available online at www.aidsinfo.nih.gov/guidelines/.

Treatment of Pregnant Patients

Basic Principles

In general, *management of HIV infection in pregnant women should follow the same guidelines for managing HIV infection in nonpregnant adults*. Accordingly, current guidelines recommend ART for all pregnant HIV-infected women. ART is recommended for pregnant women who require therapy now for their own health. And ART is recommended for pregnant women who do not yet require therapy for their own health. Why? Because, even when ART is not needed for maternal health, it will still reduce the risk of perinatal HIV transmission. Our discussion on the role of ART in pregnancy is based on a recent clinical guideline: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*, as updated on September 14, 2011.

When treating HIV infection in pregnant women, the goal is to balance the benefits of treatment—reducing viral load, thereby promoting the health of the mother and decreasing the risk of vertical HIV transmission (ie, transmission to the fetus)—against the risks of drug-induced fetal harm (eg, teratogenesis, lactic acidosis, death). As a rule, the benefits of treatment outweigh the risks. The primary determinants of therapy are the clinical, virologic, and immunologic status of the mother; pregnancy is a secondary consideration. Nonetheless, pregnancy should not be ignored. Because the risk of teratogenesis is greatest during the first 10 to 12 weeks of pregnancy, it might be appropriate to interrupt therapy until the first trimester is over, especially if maternal risk is low (ie, CD4 T-cell count exceeds 350 cells/mm³ and plasma HIV RNA is below 1000 copies/mL). The drawback, of course, is that the viral load will increase, and may thereby intensify HIV disease in the mother and enhance transmission to the fetus. Many experts recommend continuation of maximally effective treatment even during the first trimester. If the mother *does* decide to interrupt treatment, *all* antiretroviral drugs should be stopped. Continuing treatment with just one or two drugs increases the risk of resistance, thereby rendering those drugs ineffective for current or future use by the patient. When treatment resumes, the full regimen should be reinstated.

Drug selection is challenging in that information on pharmacokinetics and safety during pregnancy is limited. The combination of *didanosine plus stavudine* should be avoided, owing to a risk of lactic acidosis and maternal/neonatal mortality. *Efavirenz* should be avoided during the first trimester, owing to a risk of teratogenesis. All of the *protease inhibitors* increase the risk of gestational diabetes, and hence blood sugar should be monitored closely.

Use of IV zidovudine during labor is discussed below under *Preventing Perinatal HIV Transmission*.

Mitochondrial Toxicity from NRTIs

As discussed above, NRTIs can disrupt synthesis of mitochondrial DNA, and can thereby impair mitochondrial function. The major clinical consequence is *lactic acidosis associated with hepatic steatosis* (fatty degeneration of the liver). Clinicians and patients should be alert for signs and symptoms of lactic acidosis (nausea, vomiting, abdominal pain, malaise, fatigue, anorexia, hyperventilation). If these develop,

a thorough evaluation should be conducted. During the third trimester, measurement of electrolytes and hepatic enzymes should be done more frequently. In addition to causing lactic acidosis, mitochondrial injury may result in neuropathy, myopathy, cardiomyopathy, and pancreatitis.

One combination of NRTIs—*didanosine plus stavudine*—should be avoided. Why? Because some pregnant women taking the combination have died, as have some infants who were exposed to the combination *in utero*. Although other NRTIs may pose some risk to the infant, that risk is extremely low—and must be compared with the known benefit of using an NRTI (usually zidovudine) during pregnancy.

Preconception Counseling and Care

In women with HIV, as in all other women, preconception interventions are directed at optimizing maternal and fetal health. We need to identify risk factors for adverse maternal and fetal outcomes, stabilize existing medical conditions prior to conception, and provide education and counseling targeted at needs of the individual. Specific recommendations for HIV-infected women include the following:

- Selection of effective contraceptive methods to reduce the risk of unintended pregnancy
- Education and counseling about potential effects of both HIV infection and antiretroviral therapy on pregnancy course and outcomes
- Education and counseling regarding perinatal HIV transmission risk and strategies to reduce that risk
- Initiation or modification of antiretroviral therapy prior to conception in order to
 - Avoid fetotoxic agents (eg, efavirenz, delavirdine)
 - Choose agents known to reduce perinatal HIV transmission
 - Attain maximal and stable suppression of maternal viral load
 - Evaluate and manage side effects that can harm the fetus or mother (eg, hyperglycemia, anemia, hepatotoxicity)
- Evaluation for opportunistic infections and initiation of appropriate prophylaxis
- Immunization (eg, for influenza, hepatitis B) as indicated
- Optimization of maternal nutritional status
- Implementation of standard recommendations for preconceptional evaluation and management (eg, assessment of reproductive history and family genetic history; starting folic acid supplementation; screening for infectious disease, including sexually transmitted diseases)
- Screening for maternal psychologic disorders and substance abuse
- Planning for perinatal consultation if desired or indicated

PREVENTING HIV INFECTION WITH DRUGS

When given to HIV-positive or HIV-negative persons, antiretroviral drugs can greatly reduce the risk of HIV transmission. As discussed below, these drugs can reduce the risk of sexual HIV transmission, mother-to-infant HIV transmission, and transmission from accidental HIV exposure.

Treatment as Prevention

In 2010, a randomized trial—the *HIV Prevention Trials Network Study 052*—provided definitive proof of a long-held belief: Treatment of HIV-positive people with ART greatly reduces the risk of transmitting HIV to their sexual partners. The study enrolled 1763 couples in which only one partner was HIV positive. Nearly all couples were heterosexual, and most were married. Half the infected partners were male; half were female. The couples were divided into two groups. In one group, the infected partner started ART *immediately*. In the other group, ART was *delayed* until CD4 counts dropped substantially or until an HIV-related event occurred. The result? Among the 886 couples who received *immediate* ART, there was only 1 case of HIV transmission, compared with 27 cases of HIV transmission among the 877 couples who received *delayed* ART. That is, institution of early ART reduced the risk of HIV transmission by 96%. Among the couples who received delayed ART, 9 cases of HIV transmission were man-to-woman, and 18 cases were woman-to-man.

Pre-exposure Prophylaxis

The term *pre-exposure prophylaxis* (PrEP) refers to the use of antiretroviral drugs to *prevent* HIV infection, rather than treat it. As discussed above, antiretroviral drugs can dramatically reduce HIV *transmission* when given to an HIV-*positive* person. In this section, we consider the ability of antiretroviral drugs to reduce HIV *acquisition* when given to an HIV-*negative* person. Our discussion focuses on three recent trials, one using oral PrEP and two using topical PrEP.

Oral Pre-exposure Prophylaxis. In 2010, results of the *Pre-Exposure Prophylaxis Initiative* study, also known as iPrEx, demonstrated that oral drugs can help protect high-risk homosexual men from acquiring HIV. In this trial, 1224 HIV-negative men received antiretroviral drugs—tenofovir/emtricitabine [Truvada] once daily—and 1217 received placebo. The result? Among the men who received placebo, 64 became infected, compared with only 36 who received the two drugs. On average, PrEP reduced infection risk by 44%. However, among men who adhered most closely to the regimen, risk reduction was much higher: 73%. These results led the CDC to recommend use of tenofovir/emtricitabine for PrEP—but only in men who have sex with men, and only in those considered at high risk of HIV acquisition.

Topical (Vaginal) Pre-exposure Prophylaxis. Two recent trials have studied the use of intravaginal tenofovir gel for PrEP. In one trial, the gel was highly effective. In the other, the gel offered no protection, probably because the dosing schedule was not optimal.

In 2010, results of the *Centre for AIDS Programme for Research in South Africa (CAPRISA)* trial indicated that topical tenofovir can help protect heterosexual women from acquiring HIV. The trial enrolled nearly 900 HIV-negative, sexually active women in sub-Saharan Africa, and randomized half to placebo treatment and half to intravaginal therapy with a 1% tenofovir gel, applied before and after intercourse. After 2 years, the overall rate of HIV acquisition in the tenofovir group was 39% lower than in the placebo group. Furthermore, among women who adhered most closely to the protocol, risk reduction was even higher: 54%.

In 2011, the National Institutes of Health discontinued part of the *Vaginal and Oral Interventions to Control the Epidemic*

(VOICE) study because an interim analysis showed that daily vaginal application of 1% tenofovir gel did not protect against HIV acquisition. This study enrolled over 5000 HIV-negative women in South Africa, Uganda, and Zimbabwe. Why did 1% tenofovir gel protect women in the CAPRISA trial, but not in the VOICE trial? Probably because, in CAPRISA, dosing was done immediately before and after intercourse, thereby ensuring high levels of tenofovir at the time of HIV exposure. In VOICE, dosing was done once a day (assuming no doses were missed) without regard to time of intercourse. As a result, vaginal levels of tenofovir at the time of HIV exposure would be lower than in CAPRISA.

Postexposure Prophylaxis

One-time exposure to HIV carries a small, but nonetheless real, risk of infection. Sources of exposure include unprotected vaginal or anal intercourse, receptive oral intercourse, sharing a contaminated needle, accidental needle sticks, and being splashed with blood and other body fluids. Risk is especially high following exposure to a large quantity of infected blood or blood with a high virus titer, and following deep percutaneous penetration with a needle recently removed from the vein of an infected person.

The risk of developing HIV disease after a single exposure can be reduced—but not eliminated—with prophylactic antiretroviral drugs. Presumably, protection results from preventing initial cellular infection and local propagation of HIV, thereby allowing host immune defenses to eliminate the virus before it can become established. To be effective, postexposure prophylaxis (PEP) should be initiated as soon as possible after HIV exposure—preferably within 1 or 2 hours, and no later than 72 hours—and should continue for 28 days. All patients should undergo testing for antibodies against HIV, preferably at the time of exposure, and then 6 weeks, 12 weeks, and 6 months after exposure.

Recommendations for PEP are based on whether the exposure was nonoccupational or occupational, defined as exposure of healthcare personnel while on the job.

Nonoccupational Postexposure Prophylaxis

For nonoccupational PEP, current guidelines recommend ART regimens much like those employed for initial therapy of established HIV infection (see Table 94–8). Two three-drug regimens are preferred:

- *NNRTI-based*: efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir)
- *PI-based*: lopinavir/ritonavir + (lamivudine or emtricitabine) + zidovudine

Detailed information on nonoccupational PEP is available in a document titled *Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States* (revised January 21, 2005), which can be found online at aidsinfo.nih.gov.

Occupational Postexposure Prophylaxis

Recommendations for occupational PEP are based on the risk of acquiring HIV, which is determined by multiple factors, including (1) the nature of the exposure (skin penetration vs. body fluid splashed onto nonintact skin or mucous mem-

brane); (2) the severity of the exposure (eg, shallow skin penetration with a solid probe, deep skin penetration with a large-bore hollow needle, surface exposure to small volume of sputum, surface exposure to a large volume of blood); and (3) the HIV status of the exposure source (eg, asymptomatic with a low viral load, symptomatic with a high viral load). Preferred regimens, based on risk of transmission, may involve one of the following options:

- No PEP
- 2 NRTIs (eg, emtricitabine plus tenofovir)
- PI-based regimen (eg, lopinavir/ritonavir plus emtricitabine plus tenofovir)

Please note that our discussion of this important topic is greatly simplified. For detailed information, you can refer to a document titled *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis* (revised September 30, 2005), which is available online at aidsinfo.nih.gov. Another valuable resource for recommendations on managing PEP (occupational, nonoccupational, or perinatal) is a 24-hour National HIV/AIDS Clinicians' Consultative Center through the University of California, San Francisco. Information is available by calling the PEP hotline at 1-888-448-4911.

Preventing Perinatal HIV Transmission

Most mother-to-child transmission of HIV occurs during the perinatal period, primarily during delivery. Among American children, perinatal transmission accounts for nearly all new HIV infections. In the absence of antiretroviral drugs, the rate of perinatal transmission in the United States is 25%. A high viral load increases risk. The risk for vertical transmission can be reduced by giving antiretroviral drugs to the mother during gestation and labor, and to the infant for 6 weeks postpartum. Delivery by cesarean section is recommended for patients with a viral load above 1000 copies/mL.

Zidovudine is the drug of choice for reducing perinatal HIV transmission—regardless of whether ART had been used during gestation. Zidovudine is given IV to the mother during labor and delivery, and then IV or PO to the infant. When this protocol is followed, the rate of HIV transmission is essentially zero. Dosages for mother and neonate are shown in Table 94–10. As indicated, neonatal dosage is based on gestational age.

PROPHYLAXIS AND TREATMENT OF OPPORTUNISTIC INFECTIONS

Individuals with advanced HIV disease are vulnerable to infections caused by opportunistic organisms (ie, organisms that rarely cause serious disease, except when host defenses are compromised). Vulnerability to opportunistic infections (OIs) is caused by immunodeficiency resulting from loss of CD4 T cells. The risk of OIs is greatest in patients with fewer than 200 CD4 T cells/mL. Because of the risk of OIs, patients with low CD4 counts must take antibiotics as prophylaxis. Prior to the advent of ART, prophylaxis was required lifelong. Since the introduction of ART, the incidence of new OIs has declined dramatically. For example, the incidences of cy-

TABLE 94-10 ■ Intrapartum Maternal and Neonatal Zidovudine for Prevention of Mother-to-Child HIV Transmission*

Zidovudine Recipient	Onset and Duration of Treatment	Dosage
Mother	Start when labor begins and continue until delivery of the infant	2 mg/kg infused IV over 1 hr, then 1 mg/kg/hr by continuous infusion
Infant	Start as soon as possible after birth (preferably within 6–12 hr) and continue through 6 wk of age	<p><30 weeks' gestation: 2 mg/kg PO (or 1.5 mg/kg IV) every 12 hr initially, then every 8 hr at age 4 wk</p> <p>≥30 to <35 weeks' gestation: 2 mg/kg PO (or 1.5 mg/kg IV) every 12 hr initially, then every 8 hr at age 2 wk</p> <p>≥35 weeks' gestation: 4 mg/kg PO every 12 hr or 1.5 mg/kg IV every 6 hr</p>

*Based on Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission: Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health, and Interventions to Reduce Perinatal HIV Transmission in the United States, September 14, 2011.

tomegalovirus retinitis and disseminated mycobacterial infection have fallen by as much as 75% to 80%. In many patients with low CD4 T-cell counts, ART has caused CD4 counts to rise, thereby restoring some immunocompetence and permitting withdrawal of prophylactic drugs. Unfortunately, ART cannot help all patients. In the discussion below, we consider prophylaxis and treatment of OIs in these people. Additional details on the management of OIs can be found in *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*, released in April 2009, and *Guidelines for Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children*, released in September 2009. These documents are available online at aidsinfo.nih.gov.

Pneumocystis Pneumonia (PCP)

Pneumocystis pneumonia—known as PCP (for *Pneumocystis pneumonia*)—is a potentially fatal infection caused by *Pneumocystis jirovecii*, a fungus formerly misidentified as *Pneumocystis carinii*. Before the use of ART and prophylactic drugs, PCP was the leading cause of death among people with AIDS. At one time, PCP developed in 70% to 80% of HIV-infected people, and killed about 20% to 40%. Following control of an initial bout of PCP, the rate of recurrence was 60% within the first year. In patients receiving ART, PCP is rare, and prophylaxis is often unnecessary.

Clinical manifestations of PCP are generally nonspecific. Early symptoms include fever, cough, dyspnea, chest discomfort, pallor, and cyanosis. In advanced infection, lung morphology is altered. Left untreated, PCP has a mortality rate of 90%.

Treatment of Active PCP. The treatment of choice for PCP is *trimethoprim plus sulfamethoxazole* (TMP/SMZ), marketed as Bactrim and Septra. TMP/SMZ is effective in

90% of patients. Nothing works better. As a rule, clinical improvement is seen in 4 to 8 days. For patients who are severely immunocompromised, *IV pentamidine* [Pentam 300] may be preferred. Alternatives to TMP/SMZ or pentamidine include *atovaquone* [Mepron], *trimethoprim plus dapsone* and *primaquine plus clindamycin*. All of these regimens are less effective than TMP/SMZ or pentamidine, but may be better tolerated. Atovaquone is noteworthy for its cost (over \$11,000 wholesale for a year's supply). Dosages are summarized in Table 94-11.

Prophylaxis of PCP. Prophylactic therapy is recommended for all patients with a CD4 T-cell count below 200 cells/mm³. If ART raises CD4 counts above 200 cells/mm³ for at least 3 months, prophylaxis can be discontinued.

The preferred medication for prophylaxis is *trimethoprim plus sulfamethoxazole*, given as 1 double-strength tablet each day. For patients who cannot tolerate TMP/SMZ, *aerosolized pentamidine* [NebuPent] may be used instead. Unfortunately, although aerosolized pentamidine is better tolerated than TMP/SMZ, it is less effective. Dosages for TMP/SMZ, pentamidine, and other drugs for prophylaxis are summarized in Table 94-11.

Cytomegalovirus Retinitis

Cytomegalovirus (CMV) retinitis is the leading cause of vision loss in people with AIDS. Prior to availability of ART, the incidence of CMV retinitis was about 40%. Individuals with CD4 T-cell counts below 50 cells/mm³ are most vulnerable. Left untreated, CMV retinitis invariably leads to retinal necrosis and blindness.

Drug therapy of CMV retinitis proceeds in two stages: induction followed by maintenance. The induction phase reduces CMV load and greatly slows the rate of disease progression. However, induction does not eliminate CMV.

TABLE 94-11 • Drugs for *Pneumocystis Pneumonia*

Drugs	Dosage	
	Adults and Adolescents	Infants and Young Children
Treatment of Active Infection		
Drugs of Choice		
Trimethoprim (TMP) + sulfamethoxazole (SMZ)	TMP: 15–20 mg/kg/day in 3 or 4 divided doses SMZ: 75–100 mg/kg/day in 3 or 4 divided doses Administer both drugs together, PO or IV, for 21 days.	Same as adult
Alternatives		
Pentamidine (IV)	4 mg/kg IV once daily for 21 days	Same as adult
Primaquine (PRM) + clindamycin (CLN)	PRM: 15–30 mg base PO daily for 21 days CLN: 600–900 mg IV every 6–8 hr for 21 days or 300–450 mg PO every 6–8 hr for 21 days	PRM: 0.3 mg/kg PO once daily (max. 30 mg/day) for 21 days CLN: 10 mg/kg PO or IV (max. 350–400 mg PO or 600 mg IV) every 6 hr for 21 days
Trimethoprim (TMP) + dapsone (DAP)	TMP: 5 mg/kg PO 3 times daily for 21 days DAP: 100 mg PO daily for 21 days	TMP: 5 mg/kg PO 3 times daily for 21 days DAP: 2 mg/kg PO once daily (max. 100 mg/day) for 21 days
Atovaquone	750 mg PO twice daily for 21 days	4–24 months: 22.5 mg/kg PO twice daily for 21 days 1–3 months and over 24 months: 15–20 mg/kg PO twice daily (max. 1500 mg/day) for 21 days
Prophylaxis (Primary or Secondary)		
Drugs of Choice		
Trimethoprim + sulfamethoxazole	1 single-strength tablet* PO daily or 1 double-strength tablet* PO daily	TMP: 150 mg/m ² /day (320 mg max.) in 2 divided doses SMZ: 750 mg/m ² /day (1600 mg max.) in 2 divided doses Administer PO together on 3 consecutive days each week
Alternatives		
Pentamidine (inhaled)	300 mg inhaled once a month	5 yr and older: Same as adult
Dapsone	50 mg PO twice daily or 100 mg PO once daily	2 mg/kg (max. of 100 mg) PO daily or 4 mg/kg (max. of 200 mg) PO once a week
Atovaquone	1500 mg PO daily	4–24 months: 22.5 mg/kg PO twice daily 1–3 months and over 24 months: 15 mg/kg PO twice daily
Atovaquone (ATOV) + pyrimethamine (PYR) + leucovorin (LEU)	ATOV 1500 mg + PYR 25 mg PO + LEU 10 mg, all taken PO once daily	Not recommended

*Single-strength tablet = 80 mg TMP + 400 mg SMZ, double-strength tablet = 160 mg TMP + 800 mg SMZ.

Data for adults and adolescents from Centers for Disease Control and Prevention: Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. MMWR Recomm Rep 58(RR-4), 2009.

Data for infants and children from Centers for Disease Control and Prevention: Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children. MMWR Recomm Rep 58(RR-11), 2009.

Accordingly, maintenance therapy is given to reduce the risk of relapse. Before ART was available, maintenance therapy was required lifelong. However, when ART is able to restore sufficient immune function (by raising CD4 T-cell counts above 100 cells/mm³ for 3 to 6 months), maintenance therapy can be discontinued.

CMV retinitis can be treated with four agents: ganciclovir, valganciclovir, cidofovir, and foscarnet. The basic pharmacology of these drugs is discussed in Chapter 93. Three agents—ganciclovir, foscarnet, and cidofovir—may be given intravenously. One of these—ganciclovir—may also be given orally

and by intraocular implant. Valganciclovir is administered only by mouth.

Ganciclovir. Ganciclovir [Cytovene, Vitrasert] is a drug of choice for CMV retinitis. For induction, IV administration is traditional, although intraocular implants or direct intraocular injections may also be used. For maintenance, intraocular implants or daily IV infusions via a central venous catheter are preferred. The implants are more effective than the infusions and cause fewer side effects. To reduce the risk of systemic CMV infection, patients with ocular implants can also take oral valganciclovir. Dose-limiting toxicities of IV ganci-

clovir are neutropenia and thrombocytopenia secondary to bone marrow suppression. In addition, there is a risk of infection in the central venous catheter.

Valganciclovir. Valganciclovir [Valcyte] is a prodrug version of ganciclovir, but has greater oral bioavailability. Adverse effects are the same as those of ganciclovir. The principal concerns are blood dyscrasias—granulocytopenia, anemia, and thrombocytopenia—secondary to bone marrow suppression.

Foscarnet. Foscarnet, formerly available as *Foscavir*, is less well tolerated than ganciclovir and much more expensive. As a rule, the drug is administered by IV infusion—twice daily for induction and once daily for maintenance. To receive infusions daily, patients require an indwelling central venous catheter, and hence face a risk of catheter-related infection. Dose-limiting toxicities are nephrotoxicity, electrolyte imbalance (especially hypocalcemia), genital ulceration, and fluid overload.

Cidofovir. Cidofovir [Vistide] is an IV drug for CMV retinitis. This agent has a longer effective half-life than ganciclovir or foscarnet, and hence can be administered less often. Specifically, whereas ganciclovir and foscarnet must be infused daily for maintenance therapy, cidofovir is infused just once every 2 weeks. Because cidofovir infusions are infrequent, patients do not require an indwelling central catheter, and hence do not face a risk of catheter-related infection. The major dose-limiting toxicities are kidney damage and neutropenia. To reduce the risk of kidney injury, all patients must receive probenecid and IV hydration therapy with each infusion.

***Mycobacterium tuberculosis* and *Mycobacterium avium* Complex**

Mycobacterium tuberculosis and *Mycobacterium avium* complex (MAC) are slow-growing microbes that require prolonged drug exposure for eradication. Because therapy is prolonged, emergence of resistance is a significant concern. To reduce emergence of resistance, these infections are always treated with multiple drugs—just like HIV itself. Mycobacterial infections and their treatment are discussed at length in Chapter 90. A brief summary of treatment is presented here.

Mycobacterium tuberculosis. Tuberculosis is the leading cause of death among patients with AIDS. If the infection is caused by drug-sensitive mycobacteria, treatment is relatively simple. In one protocol, treatment is initiated with a four-drug regimen—isoniazid, rifabutin, pyrazinamide, and ethambutol—and then switched to a two-drug regimen—isoniazid plus rifabutin—2 months later. Treatment should last for at least 9 months, and for at least 3 months after sputum tests for *M. tuberculosis* become negative. Treatment of drug-resistant infections can be very difficult, sometimes requiring as many as seven drugs. Specific regimens for drug-sensitive and drug-resistant tuberculosis are summarized in Table 90-1.

HIV-infected patients with a positive skin test or blood test for tuberculosis should take prophylactic drugs to prevent active *M. tuberculosis* infection. The preferred regimen consists of isoniazid for 9 months.

***Mycobacterium avium* Complex.** MAC consists of two nearly identical microbes: *Mycobacterium avium* and *Mycobacterium intracellulare*. Infection with MAC begins in the lungs or GI tract, but may later disseminate to the blood, bone marrow, liver, spleen, lymph nodes, brain, kidneys, and skin. Among people with AIDS, disseminated infection is common, being present in 50% at autopsy. Signs and symptoms of disseminated MAC infection include fever, night sweats, weight loss, lethargy, anemia, and abnormal liver function tests.

Primary prophylaxis against MAC is indicated for patients with fewer than 50 CD4 T cells/mm³. Either azithromycin or

clarithromycin should be used. If ART produces a 3-month increase in CD4 counts to 100 cells/mm³ or more, prophylaxis may be discontinued.

If disseminated infection develops, the preferred treatment is clarithromycin plus ethambutol, with or without rifabutin. If needed, azithromycin can be substituted for clarithromycin. In the absence of immune recovery, treatment should continue lifelong. However, if the patient (1) has been treated for at least 12 months and is free of MAC symptoms, and (2) has had a 6-month sustained CD4 elevation (above 100 cells/mm³) following ART, discontinuing treatment for MAC is reasonable.

***Toxoplasma* Encephalitis**

Toxoplasma gondii is a protozoan of the Sporozoa class. In the immunocompetent host, infection with *T. gondii* is generally benign. However, in the immunocompromised host, infection can be lethal. Among patients with AIDS, toxoplasmosis usually manifests as encephalitis (inflammation of the brain or brainstem). Symptoms include fever, headache, seizures, aphasia (loss of speech), lethargy, confusion, dementia, focal neurologic deficits, and progression to coma. *Toxoplasma* encephalitis is most likely late in HIV disease, usually after CD4 T-cell counts fall below 100 cells/mm³. In the United States, the incidence of *Toxoplasma* encephalitis among AIDS patients is 3% to 10%, making this the most common opportunistic infection of the CNS in these people.

Patients who are seropositive for *T. gondii* and have low CD4 T-cell counts (below 100 cells/mm³) should take drugs to prevent active infection. The preferred regimen is 1 double-strength tablet of TMP/SMZ daily (the same regimen used to prevent PCP). Prophylaxis can be discontinued if ART produces a sustained (3 months or longer) increase in CD4 T cells (above 200 cells/mm³).

If active infection develops, the treatment of choice is pyrimethamine plus sulfadiazine plus leucovorin. The sulfadiazine component can cause rash and crystalluria. For patients who cannot tolerate sulfadiazine, pyrimethamine plus clindamycin plus leucovorin is an alternative.

Once toxoplasmosis has been controlled, lifelong suppressive therapy is needed. The preferred regimen is pyrimethamine plus sulfadiazine plus leucovorin. Pyrimethamine plus clindamycin is an alternative. However, clinical experience indicates that discontinuing prophylaxis is reasonable in patients who (1) have remained free of encephalitis symptoms and (2) have had a 6-month sustained increase in CD4 T-cell counts (above 200 cells/mm³) following ART.

Cryptococcal Meningitis

Cryptococcus neoformans is a fungus that infects 9% to 13% of patients with AIDS. In 80% of these patients, cryptococcosis manifests as meningitis (inflammation of the meninges). The most common symptoms are fever and headache. Other symptoms include nausea, vomiting, photophobia, and altered mental status. Cryptococcal meningitis typically occurs late in HIV disease, usually after CD4 T-cell counts fall below 100 cells/mm³. In addition to infecting the meninges, *C. neoformans* can infect the blood, lungs, skin, and prostate.

The treatment of choice for cryptococcal meningitis is amphotericin B plus flucytosine, infused daily for 2 weeks or

longer. The major adverse effect of amphotericin is kidney damage, and the major concern with flucytosine is bone marrow suppression (neutropenia, thrombocytopenia). Compared with amphotericin B alone, the combination of amphotericin plus flucytosine decreases rates of treatment failure and relapse. However, mortality rates with both treatments are similar. Because bone marrow suppression is a significant concern for patients with AIDS, those taking flucytosine should be monitored closely.

After the initial infection has been controlled, patients should continue maintenance therapy indefinitely. The treatment of choice is oral *fluconazole* daily. In the absence of maintenance therapy, patients are at increased risk of relapse and death. However, limited experience suggests that discontinuing maintenance therapy may be reasonable in patients who (1) have no signs or symptoms of cryptococcosis and (2) have developed a 6-month sustained increase in CD4 T-cell counts (200 cells/mm³ or higher) following ART.

The basic pharmacology of amphotericin B, flucytosine, and fluconazole is discussed in Chapter 92.

Varicella-Zoster Virus Infection

Varicella-zoster virus (VZV) can cause *chickenpox* and *herpes zoster*, also known as *shingles* or simply *zoster*. Among adults with AIDS, VZV infection usually manifests as shingles, which results from reactivation of latent VZV infection. Preferred treatments are oral therapy with *acyclovir* (20 mg/kg [800 mg max.] 5 times a day for 7 to 10 days), *valacyclovir* (1 gm 3 times a day), or *famciclovir* (500 mg 3 times a day for 5 to 7 days). For patients with disseminated VZV infection, the preferred treatment is IV *acyclovir* (10 to 15 mg/kg every 8 hours until clinical improvement is seen); IV *foscarnet* is an alternative. The basic pharmacology of acyclovir, famciclovir, and foscarnet is discussed in Chapter 93.

Herpes Simplex Virus Infection

Infection with herpes simplex virus (HSV) is common among patients with HIV disease. Lesions may occur at multiple sites, including the lips, tongue, oral cavity, genitals, and perianal region. In patients with advanced HIV disease, HSV may infect the esophagus, colon, lungs, eyes, and CNS. For infection at all sites, *acyclovir* is the drug of choice. Administration may be oral or IV. Responses usually occur within 3 to 10 days. Duration of treatment ranges from 7 to 21 days. For patients with acyclovir-resistant HSV, IV *foscarnet* can be used. Patients who experience frequent or severe recurrences can take oral *acyclovir*, *famciclovir*, or *valacyclovir* for prophylaxis.

Candidiasis

HIV-infected patients frequently develop infection with *Candida* species, usually *Candida albicans*. The most common sites are the oropharynx and esophagus. Up to 75% of patients experience oral candidiasis (thrush), which often responds to topical therapy, such as "swishing and swallowing" a *nystatin suspension* or sucking *clotrimazole troches*. Systemic therapy with an oral azole—*fluconazole*, *itraconazole*, or *posaconazole*—is an alternative. Oral azoles are more convenient than topical therapy and probably more effective. However, they are also more expensive. Prophylaxis of recurrent oral candidiasis is not always needed. However, if recur-

rence is frequent or severe, chronic intermittent therapy with an oral azole may be considered.

For esophageal candidiasis, systemic therapy is required. Options include oral *itraconazole*, oral *fluconazole*, and IV *amphotericin B*. All patients with a documented history of esophageal candidiasis should be considered for chronic suppressive therapy with oral *fluconazole*.

HIV VACCINES

Development of an HIV vaccine is critical to controlling the AIDS epidemic worldwide. Although HIV infection can now be managed with ART, treatment is expensive and potentially dangerous, and must continue lifelong. Furthermore, ART is largely unavailable in developing countries, where most AIDS cases occur. Accordingly, vaccine development has been assigned high priority.

Obstacles to Vaccine Development

Making a safe and effective vaccine against HIV has proved exceedingly and unexpectedly difficult. Obstacles include the wide global variation in HIV strains, lack of information on natural immunity to HIV, multiple modes of HIV transmission, and lack of an ideal animal model for studying vaccine efficacy. Also, scientists are concerned that the vaccine may need to (1) *prevent* HIV infection, rather than minimize it, and may need to (2) stimulate cell-mediated immunity in addition to humoral immunity. These two concerns are discussed below.

Vaccines do not prevent infection—they only attenuate it. By priming the immune system, vaccines reduce microbial replication and accelerate microbial kill. As a result, infection does not spread as far as it would in an unvaccinated person, and does not injure as many cells. Unfortunately, HIV is different from all other pathogens: HIV kills the very cells that are meant to attack it and that vaccination is meant to stimulate. Given the nature of HIV, we must ask, "Will a vaccine that permits HIV to infect even a small number of immune cells be able to contain the infection—or will HIV eventually break through?" The answer is unknown.

Vaccines elicit two kinds of immune responses: *humoral immunity* (production of antibodies) and *cell-mediated immunity* (activation of cytotoxic T lymphocytes, also known as killer T cells). Most authorities agree that, to be effective, an HIV vaccine should elicit both types of responses. Why? The answer is simple: We already know that HIV-positive people produce billions of antibodies against HIV, and yet the infection progresses relentlessly; hence, a vaccine that only stimulates humoral immunity would seem likely to fail. Unfortunately, although it's relatively easy to make a safe vaccine that stimulates humoral immunity, it's much harder to make a safe vaccine that stimulates cellular immunity. Why? Because the best way to stimulate cellular immunity is with a *live virus* vaccine—in this case, a vaccine made from HIV that has been attenuated by removing some of its genes, but has not been killed. The problem is that live virus vaccines pose a risk of infection—a risk that is unacceptable with HIV. The potential danger of this approach was underscored when monkeys were given a simian version of such a vaccine and subsequently developed simian AIDS, presumably from the vaccine itself.

Current Status of Vaccine Development

Although HIV vaccines have undergone intensive study, the number of promising candidates has dropped substantially. In 2005, 34 candidate HIV vaccines were in early phases of human clinical trials. Today, only a handful are being tested in humans.

To date, only one vaccine—AIDSVAX—has undergone a Phase III trial. AIDSVAX is a bivalent vaccine composed of gp120 proteins, which are found in the outer envelope of HIV. The vaccine activates the antibody-producing arm of the immune system, but does not activate killer T cells. The Phase III trial enrolled 5095 HIV-negative men and 308 HIV-negative women, all considered at high risk of acquiring HIV. One-third of participants received placebo, and two-thirds were injected with vaccine. The result? HIV infection developed in 5.8% of placebo recipients and 5.7% of those given the vaccine. Clearly, AIDSVAX didn't work. These results were especially disappointing in that, in an earlier trial, the vaccine elicited production of neutralizing antibodies in 99% of vaccinees. Apparently, although antibodies were made, they were unable to prevent infection.

The current best hope for protection is to combine a vaccine similar to AIDSVAX (ie, a purified HIV envelope protein) with a "vectored" vaccine, consisting of a harmless virus, such as canarypox, that has been genetically engineered to produce HIV proteins. In Phase I and II clinical trials, this approach appeared safe, and elicited both antibody production and activation of killer T cells.

KEEPING CURRENT

Drug therapy of HIV infection is continuously evolving. New drugs are being developed, knowledge of existing drugs is expanding, and new drug combinations are being studied. The following web sites are good sources of very current information:

- **AIDSinfo** (aidsinfo.nih.gov). This site, maintained by the U.S. Department of Health and Human Services, has information on treatment guidelines, drugs, vaccines, and clinical trials. Links to other HIV/AIDS-related sites are there too. Content is presented in English and Spanish. You can sign up for e-mail notification of updates.
- **HIV and AIDS Activities** (www.fda.gov/oashi/aids/hiv.html). This page on the FDA web site offers the latest information on approved drugs, drug development, and drugs in clinical trials.
- **AIDS Education Global Information System** (www.aegis.com). Perhaps the best single web site for information on HIV and AIDS information. The site contains the world's largest HIV/AIDS information base, is continuously updated, and offers chat facilities.

KEY POINTS

- HIV is a retrovirus that, like all other retroviruses, has RNA as its genetic material.
- To infect our cells, HIV must first bind to a cell-surface receptor (CD4) as well as a co-receptor (most often CCR5), and then fuse with the cell membrane.
- HIV uses *reverse transcriptase* to convert its RNA into DNA, and *integrase* to insert its DNA into ours.
- HIV uses *protease* to break large HIV polyproteins into their smaller, functional forms.
- The principal targets of HIV are CD4 T cells (helper T lymphocytes). These cells are attacked by HIV because they carry CD4 proteins on their surface, thereby providing HIV a required point of attachment.
- Because of errors made by reverse transcriptase, HIV can mutate rapidly from a drug-sensitive form into a drug-resistant form.
- HIV infection has three phases: initial, middle, and late. During the initial phase, many patients experience a flu-like acute retroviral syndrome. During the prolonged middle phase, patients are asymptomatic, although CD4 T cell counts undergo progressive decline. During the late phase, CD4 T cell counts drop below a critical level (200 cells/mL), rendering the patient vulnerable to opportunistic infections and certain neoplasms.
- HIV replicates rapidly during all phases of HIV infection, including the prolonged phase of clinical latency.
- We have six classes of antiretroviral drugs. Four classes—nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and protease inhibitors (PIs)—inhibit HIV enzymes. The other two classes—HIV fusion inhibitors and CCR5 antagonists—work outside CD4 cells to block HIV entry.
- NRTIs suppress HIV replication in two ways: (1) they become incorporated into the growing strand of viral DNA (through the actions of reverse transcriptase), and thereby prevent further strand growth; and (2) they compete with natural nucleoside triphosphates for binding to the active center of reverse transcriptase, and thereby competitively inhibit the enzyme.
- In order to interact with reverse transcriptase, NRTIs must first undergo intracellular conversion to their active (triphosphate) forms.
- All NRTIs can cause lactic acidosis and severe hepatomegaly with steatosis, which can be fatal.
- Zidovudine (an NRTI) can cause severe anemia and neutropenia.
- Didanosine and stavudine (both NRTIs) can cause peripheral neuropathy.
- Didanosine (an NRTI) can cause pancreatitis.
- Abacavir (an NRTI) can cause potentially fatal hypersensitivity reactions, and hence must not be given to patients

- with the HLA-B*5701 mutation, which predisposes them to abacavir hypersensitivity.
- NNRTIs (eg, efavirenz) differ from NRTIs in that they are not analogs of natural nucleosides, are active as administered, and cause direct noncompetitive inhibition of reverse transcriptase by binding to its active center.
 - NNRTIs frequently cause rash and other hypersensitivity reactions, which can be severe and even life threatening. If a severe reaction occurs, the NNRTI should be stopped immediately.
 - Efavirenz is the only NNRTI recommended for first-line therapy of HIV infection.
 - Efavirenz frequently causes adverse CNS effects.
 - Efavirenz is teratogenic, and must not be used during pregnancy.
 - PIs (eg, lopinavir/ritonavir) are among our most effective antiretroviral drugs.
 - PIs bind to HIV protease and thereby prevent the enzyme from cleaving HIV polyproteins. As a result, enzymes and structural proteins of HIV remain nonfunctional, and hence the virus remains immature and noninfectious.
 - All PIs pose a risk of hyperglycemia, new-onset diabetes, exacerbation of existing diabetes, fat maldistribution, hyperlipidemia, bone loss, elevation of transaminase levels, and increased bleeding in patients with hemophilia.
 - All PIs inhibit cytochrome P450, and can thereby decrease metabolism of other drugs, causing their levels to rise. Accordingly, patients should avoid drugs whose accumulation could lead to serious toxicity. Among these are cisapride, alprazolam, triazolam, midazolam, ergot alkaloids, lovastatin, and simvastatin.
 - Ritonavir—a PI that strongly inhibits P450—is often combined with other PIs to raise their plasma levels, and thereby boost antiviral effects.
 - Raltegravir, our first HIV integrase strand transfer inhibitor (INSTI), prevents insertion of HIV-derived DNA into DNA of CD4 cells, and thereby blocks HIV replication.
 - Raltegravir can cause severe hypersensitivity reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, which can be fatal.
 - Enfuvirtide, an HIV fusion inhibitor, binds with gp41 on the viral envelope, and thereby blocks entry of HIV into CD4 T cells.
 - Enfuvirtide is indicated for HIV infection that is resistant to other antiretroviral drugs.
 - The major adverse effects of enfuvirtide are injection-site reactions, which develop in nearly all patients.
 - Maraviroc—the first CCR5 antagonist—blocks HIV entry into CD4 cells. Effects are limited to HIV strains that are CCR5 tropic (ie, strains that use the CCR5 co-receptor for cellular entry). Accordingly, before maraviroc is used, testing must confirm that the infecting strain is indeed CCR5 tropic.
 - Treatment has six goals: maximal and durable suppression of viral load, restoration and/or preservation of immune function, improvement of quality of life, reduction of HIV-related morbidity and mortality, reduction of HIV sexual transmission, and prevention of vertical HIV transmission.
 - Resistance to antiretroviral drugs is a major problem. To reduce emergence of resistance, these drugs should never be used alone. Rather, they should always be combined with at least one other antiretroviral drug, and preferably two or even three.
 - The principal laboratory tests employed to monitor HIV infection and guide therapy are plasma HIV RNA (viral load) and CD4 T-cell counts. Plasma HIV RNA levels indicate the magnitude of HIV replication and predict the rate of CD4 T-cell destruction, whereas CD4 T-cell counts indicate how much damage the immune system has already suffered.
 - Plasma HIV RNA is the best measurement for predicting clinical outcome: if HIV RNA is high, the prognosis is poor; if HIV RNA is low, the risk of disease progression and death is greatly reduced. Accordingly, the goal of antiretroviral therapy is to decrease plasma HIV RNA to levels that are undetectable (20 to 75 copies/mL, depending on the assay employed).
 - Reducing plasma HIV RNA to undetectable levels does not mean that HIV has been eradicated. It only means there is too little HIV to measure. Nonetheless, patients still harbor HIV and are still infectious. Accordingly, treatment should continue indefinitely, and patients should be warned to avoid behaviors that can transmit HIV to others.
 - All patients with acute primary HIV disease or advanced (symptomatic) HIV disease should receive maximally effective antiretroviral therapy.
 - For patients with chronic asymptomatic HIV disease, antiretroviral therapy is now recommended when the CD4 count drops below 500 cells/mm³, rather than 350 cells/mm³ as in the past. As a result, ART is now initiated earlier in the course of the infection.
 - In general, the principles that guide antiretroviral therapy in adults also apply to children.
 - In general, the principles that guide antiretroviral therapy in nonpregnant adults also apply during pregnancy. Put another way, women should receive optimal antiretroviral therapy, regardless of their pregnancy status.
 - Mother-to-child transmission of HIV occurs primarily during labor and delivery. The risk of transmission can be greatly reduced by (1) using ART during gestation to minimize maternal viral load, (2) giving IV zidovudine to the mother during labor and delivery, and (3) giving oral or IV zidovudine to the infant for 6 weeks following delivery.
 - An important reason for changing an antiretroviral regimen is treatment failure, indicated by failure of plasma HIV RNA to drop to an undetectable level; a rebound in plasma HIV RNA after falling to an undetectable level; CD4 T-cell counts failing to rise (or continuing to decline); and progression of clinical disease despite antiretroviral treatment.
 - When treatment failure is the result of drug resistance, the preferred response is to change *all* drugs in the regimen. Furthermore, the new drugs should be agents the

patient has not taken before and are not cross-resistant with drugs the patient has taken before.

- Sexual transmission of HIV can be reduced by (1) treating the HIV-infected partner with antiretroviral drugs and (2) giving an HIV-negative person antiretroviral drugs as pre-exposure prophylaxis (PrEP).
- Prophylactic drugs can reduce the risk of infection following accidental exposure to HIV (eg, from a needle stick). Prophylaxis is most effective when initiated within 1 or 2 hours, and may be ineffective if initiated after 72 hours.
- Because of declining CD4 T-cell counts, individuals with advanced HIV disease are at risk for opportunistic infections (OIs), and hence may need prophylactic antibiotics.

- By elevating CD4 T-cell counts, ART can restore immune function, and can thereby reduce both the risk of OIs and the need for prophylactic antibiotics.
- Among people with AIDS, *Pneumocystis pneumonia* (PCP) is the most common opportunistic infection.
- The preferred regimen for prophylaxis and treatment of PCP is trimethoprim plus sulfamethoxazole.
- Ganciclovir is the drug of choice for cytomegalovirus retinitis, an OI.

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Summary of Major Nursing Implications*

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Abacavir
Didanosine
Emtricitabine
Lamivudine
Stavudine
Tenofovir
Zidovudine

Preadministration Assessment

Therapeutic Goals

Treatment has six goals: maximal and durable suppression of viral load, restoration and/or preservation of immune function, improvement of quality of life, reduction of HIV-related morbidity and mortality, reduction of HIV sexual transmission, and prevention of vertical HIV transmission.

Baseline Data

All NRTIs. Assess the patient's clinical status and obtain a plasma HIV RNA level and CD4 T-cell count.

Zidovudine. Obtain a hemoglobin value and granulocyte count.

Abacavir. Screen for HLA-B*5701, which indicates abacavir hypersensitivity.

Identifying High-Risk Patients

Didanosine. The risk of pancreatitis is increased by a history of alcoholism or pancreatitis and by use of IV pen-tamidine.

Zidovudine. The risk of hematologic toxicity is increased by a low granulocyte count; low levels of hemoglobin, vitamin B₁₂, or folic acid; and concurrent use of drugs that are myelosuppressive, nephrotoxic, or toxic to circulating blood cells.

Implementation: Administration

Routes

All NRTIs. Oral.

Zidovudine. Oral and IV.

Administration

All NRTIs. Instruct patients to adhere closely to the prescribed dosing schedule.

Didanosine. Instruct patients to take didanosine 30 minutes before meals or 2 hours after.

Instruct patients using enteric-coated capsules to swallow them intact.

Instruct patients taking powdered didanosine to pour the contents of one packet into 4 ounces of water (not fruit juice or any other acid-containing beverage), stir the mixture until the drug dissolves (about 2 to 3 minutes), and then drink the solution immediately.

IV Zidovudine. Administer IV zidovudine slowly (over 1 hour). Do not mix the solution with biologic or colloidal fluids (eg, blood products, protein solutions). Administer within 8 hours (if stored at room temperature) or within 24 hours (if stored under refrigeration).

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Plasma HIV RNA. Success is indicated by a reduction in plasma HIV RNA. With ART, plasma HIV RNA should decline to 10% of baseline within 2 to 8 weeks. After 16 to 20 weeks of treatment, plasma HIV RNA should reach its minimum. Ideally, the minimum will be undetectable with sensitive assays.

CD4 T-Cell Counts. As viral load decreases, CD4 T-cell counts may rise, indicating some restoration of immune function.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Minimizing Adverse Effects

Anemia and Neutropenia. *Zidovudine* can cause severe anemia and neutropenia. Determine hematologic status before treatment and at least every 4 weeks thereafter. In the event of severe anemia (hemoglobin below 7.5 gm/dL or down 25% from the pretreatment baseline) or severe neutropenia (granulocyte count below 750 cells/mL or down 50% from the pretreatment baseline), interrupt treatment until there is evidence of bone marrow recovery. If neutropenia and anemia are less severe, a reduction in dosage may be sufficient. Some patients may require multiple transfusions. Granulocyte colony-stimulating factors can be used to reverse neutropenia. Epoetin alfa (recombinant erythropoietin) can be given to reduce transfusion requirements in patients with anemia, provided endogenous erythropoietin levels are not already elevated.

Lactic Acidosis with Hepatic Steatosis. Potentially fatal lactic acidosis and hepatic steatosis can occur with *all NRTIs*. Inform patients about symptoms—nausea, vomiting, abdominal pain, malaise, fatigue, anorexia, and hyperventilation—and instruct them to report these immediately. Diagnosis is done by measuring lactate in arterial blood. If lactic acidosis is present, the NRTI should be discontinued.

Pancreatitis. *Didanosine* can cause potentially fatal pancreatitis. Monitor patients for signs of developing pancreatitis (elevated serum amylase in association with elevated serum triglycerides, decreased serum calcium, and nausea, vomiting, or abdominal pain). If evolving pancreatitis is diagnosed, didanosine should be withdrawn.

Peripheral Neuropathy. *Didanosine* and *stavudine* can cause painful peripheral neuropathy. Inform patients about early signs of neuropathy (numbness, tingling, or pain in hands and feet), and instruct them to report these immediately. Treat pain of severe neuropathy with opioid analgesics. Neuropathy may reverse if these drugs are withdrawn early.

Hypersensitivity Reactions. *Abacavir* can cause potentially fatal hypersensitivity reactions. Before using abacavir, screen for HLA-B*5701 (a genetic variant associated with abacavir hypersensitivity), and don't use the drug if the variant is detected.

Inform patients of symptoms—fever, rash, myalgia, arthralgia, nausea, vomiting, diarrhea, abdominal pain, pharyngitis, dyspnea, and cough—and instruct them to report these immediately. If a hypersensitivity reaction is diagnosed—or even strongly suspected—abacavir should be discontinued and never used again.

Exacerbation of Hepatitis. In patients co-infected with HBV, withdrawal of *emtricitabine*, *lamivudine*, or *tenofovir* may result in severe exacerbation of hepatitis. Inform patients of this possibility.

Myocardial Infarction. There has been concern that *abacavir* may cause MI. However, in 2011, the FDA analyzed 26 clinical trials, and found no association between abacavir and MI.

HIV Transmission. Reduction of plasma HIV RNA may create a false sense of safety. Accordingly, inform patients that, even when HIV RNA is undetectable, they are still infectious, and hence should avoid behaviors that can transmit HIV.

Minimizing Adverse Interactions

Zidovudine. Drugs that are myelosuppressive, nephrotoxic, or directly toxic to circulating blood cells can increase the risk of hematologic toxicity. Drugs of concern include ganciclovir, dapsone, pentamidine, pyrimethamine, trimethoprim/sulfamethoxazole, amphotericin B, flucytosine, vincristine, vinblastine, and doxorubicin.

Ribavirin and Allopurinol. Ribavirin and allopurinol can increase levels of the active form of *didanosine*, thereby posing a risk of toxicity. Avoid these combinations.

All NRTIs. Giving a combination of NRTIs to a pregnant woman may increase the risk of lactic acidosis and hepatic steatosis. Accordingly, it would seem prudent to avoid these combinations during pregnancy.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Delavirdine
Efavirenz
Etravirine
Nevirapine
Ralpivirine

Preadministration Assessment

Therapeutic Goals

Treatment has six goals: maximal and durable suppression of viral load, restoration and/or preservation of immune function, improvement of quality of life, reduction of HIV-related morbidity and mortality, reduction of HIV sexual transmission, and prevention of vertical HIV transmission.

Baseline Data

Assess the patient's clinical status and obtain a plasma HIV RNA level, CD4 T-cell count, and liver function tests. Perform a pregnancy test prior to giving efavirenz.

Implementation: Administration

Route

Oral.

Administration

All NNRTIs. Instruct patients to adhere closely to the prescribed dosing schedule.

Delavirdine. Inform patients that delavirdine may be taken with or without food. Inform patients who cannot swallow delavirdine tablets whole that they can mix the 100-mg tablets (but not the 200-mg tablets) with 3 or more ounces of water. Advise patients with achlorhydria to take

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

delavirdine with an acidic beverage, such as orange or cranberry juice.

Efavirenz. Instruct patients to take efavirenz once daily on an empty stomach, preferably at bedtime (to reduce CNS effects).

Etravirine. Instruct patients to take etravirine twice daily after a meal.

Nevirapine. Inform patients that nevirapine may be taken with or without food, either once or twice daily, depending on the formulation.

Rilpivirine. Instruct patients to take rilpivirine once daily with food.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See information for NRTIs.

Minimizing Adverse Effects

Rash and Other Hypersensitivity Reactions. Rash is common and may range from mild to severe. Rarely, rash evolves into a life-threatening reaction: Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme. Mild rash can be treated with an antihistamine or topical glucocorticoid. If a severe reaction develops, the NNRTI should be withdrawn immediately. **Inform patients about signs and symptoms of an evolving reaction—severe rash, or rash accompanied by fever, malaise, fatigue, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, muscle aches, or joint aches—and instruct them to report these immediately.** To minimize risk, use a low dosage for the first 14 days of treatment, and then increase the dosage if rash has not occurred.

Hepatotoxicity. NNRTIs can cause hepatotoxicity, which may be severe. Risk is greatest with nevirapine. Perform liver function tests at baseline and periodically thereafter. Interrupt treatment if tests indicate significant liver injury.

CNS Symptoms. *Efavirenz* frequently causes CNS symptoms (eg, dizziness, insomnia, impaired consciousness, drowsiness, vivid dreams, nightmares). **Inform patients that symptoms typically resolve in 2 to 4 weeks, despite ongoing efavirenz use, and that taking efavirenz at bedtime can minimize CNS effects.** If severe symptoms occur (eg, delusions, hallucinations, severe acute depression), efavirenz should be withdrawn.

Depression. *Rilpivirine* can cause depression. **Instruct patients to contact their provider immediately if they start feeling sad, hopeless, or suicidal.**

Birth Defects. *Efavirenz* is teratogenic. **Inform women about the potential for fetal harm, and instruct them to use a barrier method of birth control (eg, condom) in conjunction with a hormonal method (eg, oral contraceptive).** Perform a pregnancy test prior to treatment.

HIV Transmission. Reduction of plasma HIV RNA may create a false sense of safety. Accordingly, **inform patients that, even when HIV RNA is undetectable, they are still infectious, and hence must avoid behaviors that can transmit HIV.**

Minimizing Adverse Interactions

Nevirapine. Nevirapine induces cytochrome P450 and can thereby decrease levels of other drugs. Effects on protease inhibitors, hormonal contraceptives, and methadone are of particular concern.

Combining nevirapine with *St. John's wort* or *rifampin*, which also induce P450, can decrease nevirapine levels, and hence these combinations should be avoided.

Delavirdine. Delavirdine inhibits P450, and can thereby increase levels of other drugs. To avoid toxicity from excessive drug levels, patients must not take cisapride, alprazolam, midazolam, triazolam, lovastatin, or simvastatin—or astemizole or terfenadine, which are no longer available in the United States. In addition, the following drugs should be used with caution: indinavir, saquinavir, clarithromycin, dapson, warfarin, quinidine, ergot alkaloids, PDE5 inhibitors (eg, sildenafil [Viagra]), and the dihydropyridine-type calcium channel blockers.

Antacids, histamine₂-receptor blockers, proton pump inhibitors, and buffered formulations of didanosine can decrease absorption of delavirdine.

Efavirenz. Efavirenz competes with other drugs for metabolism by P450, and can thereby increase their levels. To avoid toxicity from excessive drug levels, the patient must not take astemizole, terfenadine, cisapride, midazolam, triazolam, dihydroergotamine, or ergotamine.

Efavirenz induces P450, and can thereby accelerate metabolism of other drugs, including two PIs: *saquinavir* and *indinavir*. Avoid combined use with saquinavir. Increase indinavir dosage.

By inducing P450, efavirenz can decrease the efficacy of *hormonal contraceptives*. Contraceptive failure can result. **Instruct patients of child-bearing potential to use a barrier contraceptive in addition to any hormonal contraceptive.**

St. John's wort induces P450, and can thereby reduce levels of efavirenz. The combination should not be used.

Etravirine. Etravirine competes with other drugs for metabolism by P450 and can thereby increase their levels.

The plasma concentration of etravirine is lowered by use of *St. John's wort*, anticonvulsants, darunavir/ritonavir, systemic dexamethasone, rifampin, rifapentine, ritonavir, saquinavir/ritonavir, and tipranavir/ritonavir.

Rilpivirine. All of the following drugs significantly reduce rilpivirine levels and hence are *contraindicated*: (1) antiepileptic drugs (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), (2) rifamycins (rifabutin, rifampin, rifapentine), (3) proton pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole), (4) glucocorticoids (when given in repeated doses), and (5) *St. John's wort*.

Antacids (eg, aluminum hydroxide, magnesium hydroxide, calcium carbonate) can reduce rilpivirine levels. **Advise patients to take antacids at least 2 hours before rilpivirine or 4 hours after.**

Histamine₂-receptor blockers (eg, cimetidine, famotidine, ranitidine) can reduce rilpivirine levels. **Advise patients to**

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

take H₂ blockers at least 12 hours before rilpivirine or 4 hours after.

Azole antifungal drugs (eg, ketoconazole, itraconazole, fluconazole) and macrolide antibiotics (eg, erythromycin, clarithromycin, troleandomycin) can increase rilpivirine levels. Use with caution.

PROTEASE INHIBITORS

Atazanavir
Darunavir
Fosamprenavir
Indinavir
Lopinavir/Ritonavir
Nelfinavir
Ritonavir
Saquinavir
Tipranavir

Preadministration Assessment

Therapeutic Goals

Treatment has six goals: maximal and durable suppression of viral load, restoration and/or preservation of immune function, improvement of quality of life, reduction of HIV-related morbidity and mortality, reduction of HIV sexual transmission, and prevention of vertical HIV transmission.

Baseline Data

Assess the patient's clinical status and obtain a plasma HIV RNA level and CD4 T-cell count. Measure serum transaminases and blood glucose.

Identifying High-Risk Patients

Lopinavir/ritonavir oral solution is contraindicated for full-term infants (until 14 days after birth) and preterm infants (until 14 days after their predicted due date).

Use *atazanavir*, *saquinavir*, and *lopinavir/ritonavir* with caution in patients with structural heart disease, cardiac conduction disturbances, and ischemic heart disease, and in those taking other drugs that prolong the PR interval.

Avoid *lopinavir/ritonavir* and *saquinavir* in patients with congenital long QT syndrome, and in those taking drugs that prolong the QT interval.

Implementation: Administration

Route

All protease inhibitors are taken orally.

Administration and Storage

All Protease Inhibitors. Instruct patients to adhere closely to the prescribed dosing schedule.

Atazanavir. Instruct patients to take atazanavir with food, and to store it at room temperature.

Darunavir. Inform patients that darunavir must be boosted with ritonavir. Instruct patients to take darunavir with food, and to store it at room temperature.

Fosamprenavir. Instruct patients to take fosamprenavir suspension without food, and to take fosamprenavir tablets without food or with food. Instruct patients to store the drug at room temperature.

Indinavir. Instruct patients to administer indinavir either (1) with water but on an empty stomach (ie, 1 hour before a meal or 2 hours after); or (2) with skim milk, coffee, tea, or a low-fat meal (eg, corn flakes with skim milk and sugar), but not with a large meal. Inform patients using indinavir boosted with ritonavir that they can take the drug with or without food. Instruct patients to store indinavir at room temperature in the package supplied by the manufacturer.

Lopinavir/Ritonavir. Advise patients using lopinavir/ritonavir tablets to take the drug with or without food, and to store it at room temperature.

Instruct patients using lopinavir/ritonavir solution to take the drug with food, and to store it at room temperature short term (up to 2 months) or under refrigeration long term.

Nelfinavir. Instruct patients to take nelfinavir with food, and to store it at room temperature. Instruct patients to mix the powder formulation with a small amount of water, milk, formula, soy formula, soy milk, or dietary supplement, but not with acidic foods or juices (eg, applesauce, apple juice, orange juice).

Ritonavir. Instruct patients to take ritonavir tablets with food, and to store them at room temperature.

Instruct patients to take ritonavir capsules with food (if possible) and to store unopened bottles under refrigeration. Opened bottles may be kept at room temperature for 30 days.

Instruct patients to take the oral solution with food (if possible) and to store it at room temperature, never cold.

Saquinavir. Inform patients that saquinavir must be boosted with ritonavir.

Instruct patients to take saquinavir with a meal (or within 2 hours after a meal), and to store it at room temperature.

Tipranavir. Inform patients that tipranavir must be boosted with ritonavir.

Advise patients to take tipranavir with meals (when combined with ritonavir tablets), and to take tipranavir with or without food (when combined with ritonavir capsules or solution).

Advise patients to store tipranavir solution at room temperature, never cold, and to store unopened bottles of tipranavir capsules under refrigeration (opened bottles may be kept at room temperature for 60 days).

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See information for NRTIs.

Minimizing Adverse Effects

Hyperglycemia/Diabetes. All PIs can cause hyperglycemia and diabetes. Instruct patients to report any symptoms (eg, polydipsia, polyphagia, polyuria). In patients with existing diabetes, monitor blood glucose closely. To detect

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

new-onset diabetes, measure blood glucose at baseline, every 3 to 4 months during the first year of treatment, and less frequently thereafter. Diabetes can be treated with insulin and oral antidiabetic agents (eg, metformin).

Fat Maldistribution. Forewarn patients that all PIs may cause accumulation of fat on the waist, stomach, breasts, and back of the neck, and loss of fat from the face, arms, buttocks, and legs. Drug withdrawal may cause symptoms to resolve, but is not recommended. Injections of Sculptra can be used to compensate for loss of facial fat. Injection of tesamorelin [Egrifta] can reduce excess visceral abdominal fat.

Hyperlipidemia. All PIs can elevate cholesterol and triglycerides, thereby posing a risk of cardiovascular events and pancreatitis. Monitoring plasma cholesterol and triglycerides every 3 to 4 months may be wise. If drugs are given to lower lipid levels, two agents—lovastatin and simvastatin—should be avoided.

Increased Bleeding in Patients with Hemophilia. Protease inhibitors may increase the risk of bleeding in patients with hemophilia. Higher doses of coagulation factors may be needed.

Increased Transaminase Levels. Protease inhibitors can increase serum levels of transaminases. Exercise caution in patients with chronic liver disease (eg, hepatitis B or C, cirrhosis). Measure serum transaminases before treatment and periodically thereafter.

Nephrolithiasis. *Indinavir* and *fosamprenavir* can cause nephrolithiasis. Instruct patients to report symptoms: pain in the abdomen, groin, testicles, or side of the back. Management consists of hydration and interruption or discontinuation of the PI. To decrease the risk of nephrolithiasis, instruct patients to consume at least 48 ounces (1.5 L) of water daily.

Bone Loss. Protease inhibitors may promote bone loss. To reduce risk, encourage patients to ensure adequate intake of calcium and vitamin D. Osteoporosis can be treated with bisphosphonates, raloxifene, calcitonin, teriparatide, or denosumab.

Diarrhea. *Nelfinavir* causes diarrhea in 20% to 32% of patients. Diarrhea can usually be managed with loperamide or some other over-the-counter antidiarrheal drug.

Cardiac Effects. *Atazanavir*, *saquinavir*, and *lopinavir/ritonavir* prolong the PR interval, and can thereby promote AV block. Use with caution in patients with structural heart disease, cardiac conduction disturbances, and ischemic heart disease, and in those taking other drugs that prolong the PR interval.

Lopinavir/ritonavir and *saquinavir* prolong the QT interval, and thereby pose a risk of torsades de pointes. Avoid these drugs in patients with congenital long QT syndrome, and in those taking other drugs that prolong the QT interval.

Toxicity in Newborns. *Lopinavir/ritonavir* oral solution can be lethal to newborns, owing to its propylene glycol content. Accordingly, the oral solution should be avoided in full-term infants (for the first 14 days after birth) and in preterm infants (until 14 days after their predicted due date).

Indirect Hyperbilirubinemia. *Atazanavir* and *indinavir* can raise plasma levels of unconjugated bilirubin (indirect bilirubin). Be alert for jaundice (yellowing of the skin) and icterus (yellowing of the eyes), which reverse upon drug withdrawal.

HIV Transmission. Reduction of plasma HIV RNA may create a false sense of safety. Accordingly, inform patients that, even when HIV RNA is undetectable, they may still be infectious, and hence should avoid behaviors that can transmit HIV.

Minimizing Adverse Interactions

Interactions Resulting from Inhibition of P450. All PIs inhibit cytochrome P450, and can thereby increase levels of other drugs. To avoid serious toxicity from excessive drug levels, patients must not take *cisapride*, *alprazolam*, *triazolam*, *midazolam*, *ergot alkaloids*, *lovastatin*, or *simvastatin*—or *astemizole* or *terfenadine*, which are no longer available in the United States.

Ritonavir Boosting. Because ritonavir is a powerful inhibitor of P450, the drug is often combined with other PIs to raise their blood levels, and thereby boost antiviral effects.

Didanosine. Buffered formulations of didanosine decrease absorption of *indinavir* and *ritonavir*. Accordingly, buffered didanosine should be administered 1 or 2 hours apart from these drugs.

Rifampin. Rifampin induces P450, and can thereby reduce levels of the PIs. Concurrent use with all PIs should be avoided.

Oral Contraceptives. *Fosamprenavir*, *lopinavir/ritonavir*, *nelfinavir*, *ritonavir*, and *tipranavir/ritonavir* can reduce levels of ethinyl estradiol, a component of many oral contraceptives. Advise patients to use an alternative form of birth control.

St. John's Wort. St. John's wort induces P450, and can thereby reduce levels of PIs. Warn patients not to use St. John's wort.

ENFUVIRTIDE, AN HIV FUSION INHIBITOR

Preadministration Assessment

Therapeutic Goals

Enfuvirtide is indicated for HIV infection that is resistant to traditional antiretroviral drugs.

Treatment has six goals: maximal and durable suppression of viral load, restoration and/or preservation of immune function, improvement of quality of life, reduction of HIV-related morbidity and mortality, reduction of HIV sexual transmission, and prevention of vertical HIV transmission.

Baseline Data

Assess the patient's clinical status and obtain a plasma HIV RNA level and CD4 T-cell count.

Identifying High-Risk Patients

Use enfuvirtide with caution in patients who have pneumonia risk factors: low initial CD4 cell counts, high initial viral load, IV drug use, smoking, and a history of lung disease.

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

Implementation: Administration

Route

Subcutaneous.

Preparation and Storage

Teach patients to reconstitute powdered enfuvirtide with 1.1 mL of sterile water for injection, and advise them to either (1) inject the solution immediately or (2) store it cold (2°C to 8°C; 36°F to 46°F) for up to 24 hours. Inform patients that powdered enfuvirtide may be stored at room temperature.

Administration

Educate patients on aseptic subQ injection technique, and instruct them to

- Make injections into the upper arm, thigh, or abdomen (but not the navel)
- Rotate the injection site
- Avoid sites where there is an ongoing injection-site reaction or tissue that is scarred or bruised

Instruct patients that, before using stored enfuvirtide solution, they should bring it to room temperature and make sure it is clear, colorless, and free of bubbles and particulate matter.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See information for NRTIs.

Minimizing Adverse Effects

Injection-Site Reactions. Inform patients about manifestations of ISRs—pain, tenderness, erythema, induration, nodules, cysts, pruritus, and ecchymosis—and forewarn them that these occur in nearly everyone. Inform patients that they can reduce the risk of a severe ISR by rotating the injection site, avoiding sites with an active ISR, and avoiding unnecessarily deep injections. Instruct patients to seek immediate medical attention if a severe ISR occurs or if local infection develops.

Pneumonia. Enfuvirtide may increase the risk of bacterial pneumonia. Inform patients about signs of pneumonia—cough, fever, and breathing difficulties—and instruct them to report these immediately. Use enfuvirtide with caution in patients who have pneumonia risk factors.

Hypersensitivity Reactions. Enfuvirtide may cause hypersensitivity reactions, manifesting as rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases, or possibly as respiratory distress, glomerulonephritis, Guillain-Barré syndrome, or primary immune complex reaction. Inform patients about signs of hypersensitivity, and advise them to report them immediately. If a systemic hypersensitivity reaction occurs, enfuvirtide should be discontinued and never used again.

HIV Transmission. Reduction of plasma HIV RNA may create a false sense of safety. Accordingly, inform patients

that, even when HIV RNA is undetectable, they are still infectious, and hence must avoid behaviors that can transmit HIV.

MARAVIROC, A CCR5 ANTAGONIST

Preadministration Assessment

Therapeutic Goals

Maraviroc, in combination with other antiretroviral drugs, is indicated for treating patients age 16 years and older who are infected with CCR5-tropic HIV-1 strains.

Treatment has six goals: maximal and durable suppression of viral load, restoration and/or preservation of immune function, improvement of quality of life, reduction of HIV-related morbidity and mortality, prevention of HIV sexual transmission, and prevention of vertical HIV transmission.

Baseline Data

Assess the patient's clinical status and obtain the following laboratory data: HIV RNA level, CD4 T-cell count, serum transaminases, and proof that the infecting HIV strain is CCR5 tropic.

Identifying High-Risk Patients

Patients with elevated liver function and cardiovascular disease must be monitored carefully.

Implementation: Administration

Route

Oral.

Administration

Inform patients that dosing may be done with or without food.

Advise patients that, if they forget to take a dose, to take the missed dose as soon as possible, and take the next scheduled dose at its regular time. If the time to the next dose is less than 6 hours, the patient should skip the missed dose and take the next dose as scheduled.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See information for NRTIs.

Minimizing Adverse Effects

Hepatotoxicity. Liver injury has been seen in some patients, and may be preceded by evidence of an allergic reaction. Inform patients about signs of an evolving reaction (itchy rash, yellow skin, dark urine, vomiting and/or abdominal pain), and instruct them to stop maraviroc and seek medical attention.

Cardiovascular Events. During clinical trials, a few patients experienced cardiovascular events, including myocardial ischemia and myocardial infarction. Exercise caution in patients with cardiovascular risk factors.

HIV Transmission. Reduction of plasma HIV RNA may create a false sense of safety. Accordingly, inform patients

*Patient education information is highlighted as blue text.

Summary of Major Nursing Implications*—cont'd

that, even when HIV RNA is undetectable, they are still infectious, and hence must avoid behaviors that can transmit HIV.

RALTEGRAVIR, AN INTEGRASE STRAND TRANSFER INHIBITOR

Preadministration Assessment

Therapeutic Goals

Raltegravir is indicated for combined use with other antiretroviral drugs to treat adults infected with HIV-1.

Treatment has six goals: maximal and durable suppression of viral load, restoration and/or preservation of immune function, improvement of quality of life, reduction of HIV-related morbidity and mortality, reduction of HIV sexual transmission, and prevention of vertical HIV transmission.

Baseline Data

Assess the patient's clinical status and obtain a plasma HIV RNA level and CD4 T-cell count.

Implementation: Administration

Route

Oral.

Administration

Advise patients that dosing may be done with or without food.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See information for NRTIs.

Minimizing Adverse Effects

Severe Hypersensitivity Reactions. Raltegravir can cause potentially fatal hypersensitivity reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. **Inform patients about signs of a hypersensitivity reaction (eg, severe rash, or rash associated with blisters, fever, malaise, fatigue, oral lesions, facial edema, hepatitis, angioedema, or muscle or joint aches), and instruct them to discontinue raltegravir immediately.**

HIV Transmission. Reduction of plasma HIV RNA may create a false sense of safety. Accordingly, **inform patients that, even when HIV RNA is undetectable, they are still infectious, and hence must avoid behaviors that can transmit HIV.**

*Patient education information is highlighted as blue text.

Drug Therapy of Sexually Transmitted Diseases

Chlamydia trachomatis Infections
 Gonococcal Infections
 Nongonococcal Urethritis
 Pelvic Inflammatory Disease
 Acute Epididymitis
 Syphilis
 Acquired Immunodeficiency Syndrome
 Bacterial Vaginosis
 Trichomoniasis
 Chancroid
 Herpes Simplex Virus Infections
 Proctitis
 Venereal Warts

Sexually transmitted diseases (STDs), also known as *sexually transmitted infections*, are infectious diseases transmitted primarily through sexual contact. STDs are very common in the United States and constitute a major public health problem. In 2009, the Centers for Disease Control and Prevention (CDC) received more than 1.5 million reports of STDs, including 1,244,180 cases of genital *Chlamydia trachomatis* infection, 301,174 cases of gonorrhea, and 13,997 cases of syphilis. However, because most STDs go unreported, the actual incidence is much higher, estimated at 19 million new infections a year, 50% of which occur in people under the age of 25. According to the CDC, Americans now have a 25% lifetime risk of contracting an STD.

Our objective in this chapter is to describe the principal STDs and provide an overview of their treatment. Table 95-1 presents a summary of the common STDs, causative organisms, and drugs of choice for treatment. The basic pharmacology of these drugs is discussed in other chapters.

In 2010, the CDC revised its "Sexually Transmitted Diseases Treatment Guidelines," updating the 2006 version. Most of the treatment recommendations presented in this chapter reflect the 2010 guidelines, which are available online at www.cdc.gov/std/treatment/2010/. This site also contains any recent adjustments to the guidelines, and hence should be consulted for the most current recommendations.

CHLAMYDIA TRACHOMATIS INFECTIONS

Characteristics

Chlamydia trachomatis is the most frequently reported bacterial STD (Fig. 95-1), infecting about 2.8 million people annually (about twice the number of cases reported). The various

strains of *Chlamydia* can cause genital tract infections, proctitis, conjunctivitis, and lymphogranuloma venereum (LGV), as well as ophthalmia and pneumonia in infants. Infection is frequently asymptomatic in women, and may also be asymptomatic in men. In women, untreated infection can cause pelvic inflammatory disease (PID), ectopic pregnancy, and infertility. The CDC estimates that chlamydial infections cause sterility in up to 50,000 women each year, primarily from fallopian tube scarring. Because infection is often asymptomatic in women, and because sequelae can be serious, the CDC now recommends annual screening for all sexually active women age 25 or younger. Screening is also recommended for women over age 25 who have a new sex partner or multiple partners.

Treatment

Adults and Adolescents. For uncomplicated urethral, cervical, or rectal infections in adults or adolescents, two treatments are recommended: (1) a single 1-gm oral dose of *azithromycin* [Zithromax] or (2) 100 mg of *doxycycline* [Vibramycin, others] PO twice daily for 7 days.

Infection in Pregnancy. Preferred treatments for *C. trachomatis* infection during pregnancy are (1) a single 1-gm oral dose of *azithromycin* or (2) 500 mg of *amoxicillin* PO 3 times daily for 7 days. Although doxycycline and other tetracyclines are active against *C. trachomatis*, these drugs are contraindicated because they can damage fetal teeth and bones. Similarly, sulfisoxazole and other sulfonamides are active, but are contraindicated near term because they can promote kernicterus in the infant.

Infants. About half the infants born to women with cervical *C. trachomatis* acquire the infection during delivery, putting them at risk for *pneumonia* and *conjunctivitis* (ophthalmia neonatorum). Pneumonia is generally not severe and lasts about 6 weeks. Conjunctivitis does not result in blindness and spontaneously resolves in 6 months. The preferred treatment for both infections is oral *erythromycin base* or *erythromycin ethylsuccinate*, 12.5 mg/kg 4 times a day for 14 days. Although topical erythromycin, tetracycline, or silver nitrate may be given to prevent conjunctivitis, these drugs are not completely effective—and they have no effect on pneumonia.

Preadolescent Children. Although infection in preadolescent children can result from perinatal transmission, sexual abuse is the more likely cause, especially in children more than 2 years old. Because of the legal implications, diagnosis must be definitive. Treatment depends on the age and weight of the child. For children who weigh less than 45 kg, the preferred treatment is oral *erythromycin base* or *erythromycin ethylsuccinate*, 12.5 mg/kg 4 times a day for 14 days. For children who weigh 45 kg or more, but are less than 8 years

TABLE 95-1 • Drug Therapy of Sexually Transmitted Diseases*

Disease or Syndrome	Recommended Treatment	Causative Organism(s)
<i>Chlamydia trachomatis</i> Infections		<i>Chlamydia trachomatis</i>
Adults and adolescents	Azithromycin, 1 gm PO once <i>or</i> Doxycycline, 100 mg PO 2 times/day × 7 days	
Children		
<45 kg	Erythromycin base/ethylsuccinate, 12.5 mg/kg PO 4 times/day × 14 days	
≥45 kg but <8 yr old	Azithromycin, 1 gm PO once	
≥8 yr old	Azithromycin, 1 gm PO once <i>or</i> Doxycycline, 100 mg PO 2 times/day × 7 days	
Pregnant women	Azithromycin, 1 gm PO once <i>or</i> Amoxicillin, 500 mg PO 3 times/day × 7 days	
Newborns: ophthalmia or pneumonia	Erythromycin base/ethylsuccinate, 12.5 mg/kg PO 4 times/day × 14 days	
Lymphogranuloma venereum	Doxycycline, 100 mg PO 2 times/day × 21 days	
Gonococcal Infections (Gonorrhea)		<i>Neisseria gonorrhoeae</i>
Urethritis, cervicitis, proctitis	Ceftriaxone, 250 mg IM once, <i>plus</i> azithromycin, 1 gm PO once	
Pharyngitis	Ceftriaxone, 250 mg IM once, <i>plus</i> azithromycin, 1 gm PO once	
Disseminated gonococcal infection (DGI) in adults	Ceftriaxone, 1 gm IM or IV every 24 hr	
DGI with meningitis	Ceftriaxone, 1–2 gm IV every 12 hr × 10–14 days	
DGI with endocarditis	Ceftriaxone, 1–2 gm IV every 12 hr × 28 days or more	
Conjunctivitis	Ceftriaxone, 1 gm IM once	
Newborns		
Ophthalmia	Erythromycin 0.5% ophthalmic ointment <i>or</i> ; if the ointment is not available, ceftriaxone, 25–50 mg/kg IM or IV once (max. 125 mg)	
Disseminated infection or scalp abscess	Ceftriaxone, 25–50 mg/kg IM or IV once/day × 7 days <i>or</i> Cefotaxime, 25 mg/kg IM or IV every 12 hr × 7 days	
Children		
Arthritis, bacteremia	Ceftriaxone, 50 mg/kg IM or IV (max. 1 gm) once daily × 7 days	
Vulvovaginitis, cervicitis, proctitis, pharyngitis, urethritis	If 45 kg or less, ceftriaxone 125 mg IM once; if more than 45 kg, same as adult	
Nongonococcal Urethritis		<i>Chlamydia trachomatis</i> , <i>Ureaplasma urealyticum</i> , <i>Trichomonas vaginalis</i> , <i>Mycoplasma genitalium</i>
Acute infection	Azithromycin, 1 gm PO once <i>or</i> Doxycycline, 100 mg PO 2 times/day × 7 days	
Recurrent/persistent	Metronidazole (2 gm PO once) or tinidazole (2 gm PO once), <i>either one plus</i> azithromycin (1 gm PO once) if the drug was not used for initial therapy	
Treatment resistant, <i>Mycoplasma genitalium</i> suspected	Moxifloxacin, 400 mg PO once daily × 7 days	
Pelvic Inflammatory Disease		<i>Neisseria gonorrhoeae</i> , <i>Chlamydia trachomatis</i> , others
Inpatients	Cefoxitin (2 gm IV every 6 hr) or cefotetan (2 gm IV every 12 hr), <i>either one plus</i> doxycycline (100 mg IV or PO every 12 hr) for 14 days [†]	
Outpatients	Cefoxitin (2 gm IM once, boosted with probenecid 1 gm PO once) or ceftriaxone (250 mg IM once), <i>either one plus</i> doxycycline (100 mg PO 2 times/day × 14 days), <i>with or without</i> metronidazole (500 mg PO 2 times/day × 14 days)	
Sexually Acquired Epididymitis	Ceftriaxone (250 mg IM once) <i>plus</i> doxycycline (100 mg PO 2 times/day × 10 days)	<i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i>

*Recommendations from Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2010. MMWR Morb Mortal Wkly Rep 59:1–94, 2010.

[†]Intravenous therapy with cefotetan, cefoxitin, and doxycycline may be discontinued 24 hours after the patient improves clinically; oral therapy with doxycycline should continue to complete 14 days of therapy.

Continued

TABLE 95-1 ■ Drug Therapy of Sexually Transmitted Diseases—cont'd

Disease or Syndrome	Recommended Treatment	Causative Organism(s)
		<i>Treponema pallidum</i>
Syphilis		
Primary syphilis, secondary syphilis, and early latent syphilis	Adults: Benzathine penicillin G, 2.4 million units IM once Children: Benzathine penicillin G, 50,000 units/kg IM once (up to a max. of 2.4 million units)	
Late latent syphilis or latent syphilis of unknown duration	Adults: Benzathine penicillin G, 2.4 million units IM once/wk for 3 wk Children: Benzathine penicillin G, 50,000 units/kg IM once/wk for 3 wk (up to a max. of 7.2 million units)	
Tertiary syphilis	Benzathine penicillin G, 2.4 million units IM once/wk for 3 wk (must rule out CNS involvement)	
Neurosyphilis	Aqueous crystalline penicillin G, 18–24 million units IV daily for 10–14 days, administered by continuous infusion or in separate doses of 3–4 million units each every 4 hr	
Congenital syphilis	Aqueous crystalline penicillin G, 50,000 units/kg IV every 12 hr for the first 7 days of life, followed by 50,000 units/kg every 8 hr for the next 3 days <i>or</i> Procaine penicillin G, 50,000 units/kg IM once daily for 10 days <i>or</i> Benzathine penicillin G, 50,000 units/kg IM once	
Acquired Immunodeficiency Syndrome (AIDS)	See Chapter 94	Human immunodeficiency virus
Bacterial Vaginosis		<i>Gardnerella vaginalis</i> , <i>Mycoplasma hominis</i> , various anaerobes
Nonpregnant women	Metronidazole, 500 mg PO 2 times/day × 7 days <i>or</i> Metronidazole gel (0.75%), 1 full applicator (5 gm) intravaginally once/day × 5 days <i>or</i> Clindamycin cream (2%), 1 full applicator (5 gm) intravaginally at bedtime × 7 days	
Pregnant women	Metronidazole, 500 mg PO 2 times/day × 7 days <i>or</i> Metronidazole, 250 mg PO 3 times/day × 7 days <i>or</i> Clindamycin, 300 mg PO 2 times/day × 7 days	
Trichomoniasis	Metronidazole, 2 gm PO once <i>or</i> Tinidazole, 2 gm PO once	<i>Trichomonas vaginalis</i>
Chancroid	Azithromycin, 1 gm PO once <i>or</i> Ceftriaxone, 250 mg IM once <i>or</i> Ciprofloxacin, 500 mg PO 2 times/day × 3 days <i>or</i> Erythromycin base, 500 mg PO 3 times/day × 7 days	<i>Haemophilus ducreyi</i>
Genital Herpes Simplex Virus Infections		Herpes simplex virus
First episode, genital herpes	Acyclovir, 400 mg PO 3 times/day × 7–10 days (or longer) <i>or</i> Acyclovir, 200 mg PO 5 times/day × 7–10 days (or longer) <i>or</i> Famciclovir, 250 mg PO 3 times/day × 7–10 days (or longer) <i>or</i> Valacyclovir, 1 gm PO 2 times/day × 7–10 days (or longer)	
First episode, proctitis, stomatitis, or pharyngitis	Acyclovir, 400 mg PO 5 times/day for 7–10 days (or longer)	
Severe infection	Acyclovir, 5–10 mg/kg IV every 8 hr for 2–7 days or until clinical improvement, then PO acyclovir to complete at least 10 days	
Recurrent episodes	Acyclovir, 800 mg PO 2 times/day × 5 days <i>or</i> Acyclovir, 800 mg PO 3 times/day × 2 days <i>or</i> Acyclovir, 400 mg PO 3 times/day × 5 days <i>or</i> Famciclovir, 125 mg PO 2 times/day × 5 days <i>or</i> Famciclovir, 1 gm 2 times/day × 1 day <i>or</i> Famciclovir, 500 mg once, followed by 200 mg 2 times/day for 2 days <i>or</i> Valacyclovir, 500 mg PO 2 times/day × 3 days <i>or</i> Valacyclovir, 1 gm PO once/day × 5 days	
Daily suppressive therapy	Acyclovir, 400 mg PO 2 times/day <i>or</i> Famciclovir, 250 mg PO 2 times/day <i>or</i> Valacyclovir, 500 mg PO once/day <i>or</i> Valacyclovir, 1 gm PO once/day	

CNS, central nervous system.

TABLE 95-1 • Drug Therapy of Sexually Transmitted Diseases—cont'd

Disease or Syndrome	Recommended Treatment	Causative Organism(s)
Genital Herpes Simplex Virus Infections—cont'd		
Neonatal herpes	Acyclovir, 20 mg/kg IV every 8 hr × 14 days (for skin or mucous membrane infection) or × 21 days (for disseminated or CNS infection)	
Proctitis	Ceftriaxone (250 mg IM once) plus doxycycline (100 mg PO 2 times/day × 7 days)	<i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , <i>Treponema pallidum</i> , herpes simplex virus
Venereal Warts	See Chapter 105	Human papillomavirus

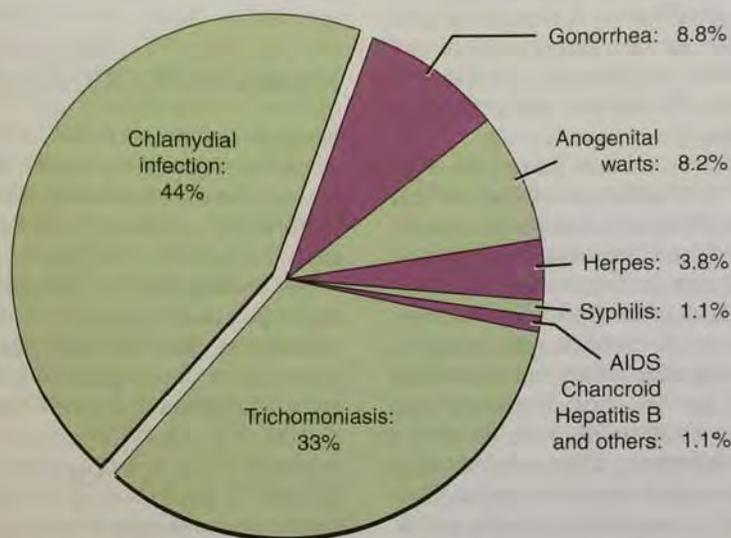


Figure 95-1 • Incidence of sexually transmitted diseases.

old, the preferred treatment is a single 1-gm oral dose of *azithromycin*. For children at least 8 years old, the preferred treatments are (1) a single 1-gm oral dose of *azithromycin* or (2) 100 mg of *doxycycline* PO twice daily for 7 days.

Lymphogranuloma Venereum. LGV is caused by a unique strain of *C. trachomatis*. Transmission is strictly by sexual contact. LGV is most common in tropical countries, but does occur in the United States, especially in the South. Infection begins as a small erosion or papule in the genital region. From this site, the organism migrates to regional lymph nodes, causing swelling, tenderness, and blockage of lymphatic flow. Tremendous enlargement of the genitalia may result. The enlarged nodes, called buboes, may break open and drain. The treatment of choice for genital, inguinal, and anorectal LGV is 100 mg of *doxycycline* PO twice daily for 21 days.

GONOCOCCAL INFECTIONS

Characteristics

Gonorrhea is caused by *Neisseria gonorrhoeae*, a gram-negative diplococcus often referred to as the gonococcus. The incidence of gonorrhea is high: In the United States, about

700,000 new infections occur each year, making gonorrhea second only to chlamydia as our most common STD. Gonorrhea is transmitted almost exclusively by sexual contact.

The intensity of symptoms differs between men and women. In men, the main symptoms are a burning sensation during urination and a pus-like discharge from the penis. In contrast, gonorrhea in women is often asymptomatic, or may present as mild cervicitis. However, serious infection of female reproductive structures (vagina, urethra, cervix, ovaries, fallopian tubes) can occur, ultimately resulting in sterility. Among people who engage in oral sex, the mouth and throat can become infected, causing sore throat and tonsillitis. Among people who engage in receptive anal sex, the rectum can become infected, causing a purulent discharge and constant urge to move the bowels. Bacteremia can develop in males and females, causing cutaneous lesions, arthritis, and, rarely, meningitis and endocarditis.

Treatment

Owing to antibiotic resistance, treatment of gonorrhea has changed over the years—and undoubtedly will continue to evolve. In the 1930s, virtually all strains of the gonococcus were sensitive to sulfonamides. However, within a decade, sulfonamide resistance had become common. Fortunately, by

that time penicillin had become available, and the drug was active against all gonococcal strains. However, in 1976, organisms resistant to penicillin began to emerge. More recently, resistance to fluoroquinolones has become common. As a result, in 2007 the CDC recommended against using fluoroquinolones for gonorrhea, leaving cephalosporins as the preferred treatments.

A high percentage of patients with gonococcal infection are co-infected with *C. trachomatis*. Accordingly, when they are treated for gonorrhea, they should be treated for *C. trachomatis* as well (unless the infection has been ruled out). As noted above, the preferred drugs for *C. trachomatis* are azithromycin and doxycycline.

Urethral, Cervical, and Rectal Infection. Because of increasing resistance to cephalosporins, preferred treatment now consists of two drugs: ceftriaxone [Rocephin], 250 mg IM once, plus azithromycin, 1 gm PO once. The azithromycin helps treat infection with ceftriaxone-resistant gonococci, and can also treat co-infection with *C. trachomatis*. For patients who cannot tolerate IM therapy, PO cefixime (400 mg once) can be substituted for IM ceftriaxone.

Pharyngeal Infection. Gonococcal infection of the pharynx is more difficult to treat than infection of the urethra, cervix, or rectum, and hence parenteral therapy is recommended for all patients. The preferred treatment is ceftriaxone (250 mg IM once) combined with azithromycin (1 gm PO once). Azithromycin will treat co-infection with *C. trachomatis*, in addition to treating ceftriaxone-resistant gonococci.

Conjunctivitis. Gonococcal conjunctivitis can be reliably eradicated with ceftriaxone, 1 gm IM once. Treatment also includes washing the infected eye with saline solution once.

Disseminated Gonococcal Infection. Disseminated gonococcal infection (DGI) occurs secondary to gonococcal bacteremia. Symptoms include petechial or pustular skin lesions, arthritis, arthralgia, and tenosynovitis (inflammation of the tendon sheath). Endocarditis and meningitis occur rarely. Strains of *N. gonorrhoeae* that cause DGI are uncommon in the United States. In the absence of endocarditis or meningitis, treatment consists of IM or IV ceftriaxone, 1 gm every 24 hours. For patients with endocarditis or meningitis, the preferred treatment is IV ceftriaxone, 1 to 2 gm every 12 hours.

Neonatal Infection. Neonatal gonococcal infection is acquired through contact with infected cervical exudates during delivery. Infection can be limited to the eyes or it may be disseminated.

Gonococcal neonatal ophthalmia is a serious infection. The initial symptom is conjunctivitis. Over time, other structures of the eye become involved. Blindness can result. The recommended therapy is IV or IM ceftriaxone, 25 to 50 mg/kg once.

To protect against neonatal ophthalmia, a topical antibiotic should be instilled into both eyes immediately postpartum—as required by law in most states. According to the 2010 CDC guidelines, the preferred agent is 0.5% erythromycin ophthalmic ointment. It should be noted, however, that topical antibiotics are not 100% effective. Furthermore, if parenteral therapy is to be used, topical therapy is unnecessary.

In neonates, disseminated gonococcal infection is rare. Possible manifestations include sepsis, arthritis, meningitis, and scalp abscesses. There are two recommended treatments: (1) ceftriaxone, 25 to 50 mg/kg IV or IM once a day for 7 days (or 10 to 14 days if meningitis is present); and (2) cefotaxime,

25 mg/kg IV or IM every 12 hours for 7 days (or 10 to 14 days if meningitis is present).

Preadolescent Children. Among preadolescent children, the cause of gonococcal infection is sexual abuse. Vaginal, anorectal, and pharyngeal infections are most common. Because of legal implications, diagnosis must be definitive. Growing a specimen in culture is the preferred technique.

Treatment depends on the type of infection and the weight of the child. For children who have localized infection (vulvovaginitis, cervicitis, urethritis, pharyngitis, proctitis) and who weigh 45 kg or less, the preferred treatment is a single 125-mg IM dose of ceftriaxone. For children with localized infection who weigh more than 45 kg, treatment is the same as for adults. For children of any weight who have systemic infection (bacteremia, arthritis), the preferred treatment is ceftriaxone, 50 mg/kg IM or IV once daily for 7 days.

NONGONOCOCCAL URETHRITIS

Nongonococcal urethritis (NGU) is defined as urethritis caused by any organism other than *N. gonorrhoeae*, the gonococcus. The most common infectious agent is *C. trachomatis* (15% to 55%). Other likely agents are *Ureaplasma urealyticum*, *Trichomonas vaginalis*, and *Mycoplasma genitalium*. NGU is diagnosed by the presence of polymorphonuclear leukocytes and a negative culture for *N. gonorrhoeae*. The infection is especially prevalent among sexually active adolescent girls. The recommended treatment is either (1) azithromycin [Zithromax], 1 gm PO once, or (2) doxycycline [Vibramycin], 100 mg PO twice daily for 7 days. For persistent or recurrent NGU, two drugs are recommended—metronidazole [Flagyl] (2 gm PO once) or tinidazole [Tindamax] (2 gm PO once)—in combination with azithromycin (1 gm PO once) if azithromycin had not been used during initial therapy. If the infection still fails to respond, the cause may be *Mycoplasma genitalium*. Unfortunately, we have no easy tests for this bacterium, and hence definitive diagnosis may not be possible. Nonetheless, when *M. genitalium* is suspected, a trial with moxifloxacin [Avelox] may be warranted. A dosage of 400 mg PO once daily for 7 days is highly effective.

PELVIC INFLAMMATORY DISEASE

Acute PID is a syndrome that includes endometritis, pelvic peritonitis, tubo-ovarian abscess, and inflammation of the fallopian tubes. Infertility can result. Prominent symptoms are abdominal pain, vaginal discharge, and fever. Most frequently, PID is caused by *N. gonorrhoeae*, *C. trachomatis*, or both. However, *Mycoplasma hominis* as well as assorted anaerobic and facultative bacteria may also be present. Each year in the United States, more than 750,000 women experience an episode of acute PID.

Because multiple organisms are likely to be involved, drug therapy must provide broad coverage. Since no single drug can do this, combination therapy is required. For the hospitalized patient, treatment can be initiated with either ceftiofur (2 gm IV every 6 hours) or cefotetan (2 gm IV every 12 hours), combined with doxycycline (100 mg IV or PO every 12 hours). After symptoms resolve, IV therapy can be discontinued—but must be followed by oral doxycycline

(100 mg every 12 hours) to complete a 14-day course of treatment. An alternative recommended regimen consists of IV clindamycin plus IV or IM gentamicin.

Outpatients can be treated with either ceftriaxone (250 mg IM once) or cefoxitin (2 gm IM once, boosted with probenecid, 1 gm PO once). Treatment should also include doxycycline (100 mg PO twice daily for 14 days), with or without metronidazole (500 mg PO twice daily for 14 days). Because PID can be difficult to treat, and because the consequences of failure can be severe (eg, sterility), many experts recommend that all patients receive IV antibiotics in a hospital.

ACUTE EPIDIDYMITIS

Epididymitis may be acquired by sexual contact or nonsexually. Sexually acquired epididymitis is usually caused by *N. gonorrhoeae*, *C. trachomatis*, or both. The syndrome occurs primarily in young adults (under 35 years old) and may be associated with urethritis. Primary symptoms are fever accompanied by pain in the back of the testicles that develops over the course of several hours. For patients with gonococcal or chlamydial infection, the recommended treatment is ceftriaxone [Rocephin], 250 mg IM once, plus doxycycline [Vibramycin, others], 100 mg PO twice daily for 7 days. Testicular pain can be managed with analgesics, bed rest, and ice packs.

Non-sexually transmitted epididymitis generally occurs in older men and in men who have had urinary tract instrumentation. Causative organisms are gram-negative enteric bacilli and *Pseudomonas*. Ofloxacin can be used for treatment.

SYPHILIS

Syphilis is caused by the spirochete *Treponema pallidum*. In the United States, the incidence of syphilis increased during the 1980s, decreased throughout the 1990s, but then has risen steadily since 2000. In 2009, reported cases of primary and secondary syphilis totaled 13,997. Fortunately, *T. pallidum* has remained highly responsive to penicillin, the treatment of choice.

Characteristics. Syphilis develops in three stages, termed primary, secondary, and tertiary. *Treponema pallidum* enters the body by penetrating the mucous membranes of the mouth, vagina, or urethra of the penis. After an incubation period of 1 to 4 weeks, a primary lesion, called a chancre, develops at the site of entry. The chancre is a hard, red, protruding, painless sore. Nearby lymph nodes may become swollen. Within a few weeks the chancre heals spontaneously, although *T. pallidum* is still present. In clinical practice, chancres are rarely seen, especially in females.

Two to 6 weeks after the chancre heals, secondary syphilis develops. Symptoms result from spread of *T. pallidum* via the bloodstream. Skin lesions and flu-like symptoms (fever, headache, reduced appetite, general malaise) are typical. Enlarged lymph nodes and joint pain may also be present. The symptoms of secondary syphilis resolve in 4 to 8 weeks—but may recur episodically over the next 3 to 4 years.

Tertiary syphilis develops 5 to 40 years after the initial infection. Almost any organ can be involved. Infection of the brain—neurosyphilis—is common, and can cause senility, paralysis, and severe psychiatric symptoms. The heart valves

and aorta can be damaged. Lesions can also occur in the skin, bones, joints, and eyes. The risk of neurosyphilis is increased in individuals with HIV infection.

Infants exposed to *T. pallidum in utero* can be born with syphilis. Early signs of congenital syphilis include sores, rhinitis, and severe tenderness over bones.

Treatment. Penicillin G is the drug of choice for all stages of syphilis. The form and dosage of penicillin G depend on the disease stage. Early syphilis (primary, secondary, or latent syphilis of less than 1 year's duration) is treated with a single IM dose of benzathine penicillin G (2.4 million units for adults and 50,000 units/kg for children). Late syphilis (more than 1 year's duration) is also treated with IM benzathine penicillin G. However, instead of receiving a single dose, adults and children receive three doses 1 week apart. Neurosyphilis requires more aggressive therapy. The recommended treatment is 18 to 24 million units of penicillin G daily for 10 to 14 days, administered either by continuous infusion or in separate doses (3 to 4 million units every 4 hours). For congenital syphilis, three regimens have been recommended: (1) IV penicillin G, 50,000 units/kg every 12 hours for the first 7 postnatal days followed by the same dose every 8 hours for 3 more days; (2) IM procaine penicillin G, 50,000 units/kg once daily for 10 days; or (3) benzathine penicillin G, 50,000 units IM once. Syphilis in pregnancy should be treated with penicillin G, using a dosage appropriate to the stage of the disease.

How should patients with penicillin allergy be treated? For nonpregnant patients with early or late syphilis, either doxycycline or tetracycline may be used. Dosages for early syphilis are (1) doxycycline, 100 mg PO twice daily for 14 days, or (2) tetracycline, 500 mg PO 4 times a day for 14 days. Dosages for late syphilis are the same as for early syphilis, except that treatment lasts 4 weeks instead of 2. For patients with neurosyphilis, ceftriaxone (2 gm/day IM or IV for 10 to 14 days) can be effective, but possible cross-reactivity with penicillin is a concern. If the patient is pregnant, the U.S. Public Health Service recommends that she go through a penicillin-allergy desensitization protocol to permit penicillin use, rather than substituting another drug for penicillin.

A study reported in 2005 indicates that a single 2-gm oral dose of azithromycin [Zithromax] may be as effective as IM benzathine penicillin G for prevention and treatment of syphilis. However, there is concern that routine use of the drug might lead to increased resistance.

ACQUIRED IMMUNODEFICIENCY SYNDROME

AIDS is caused by the human immunodeficiency virus (HIV). The pathophysiology and treatment of HIV infection are discussed in Chapter 94.

BACTERIAL VAGINOSIS

Bacterial vaginosis is the most common vaginal infection in women of child-bearing age. The condition results from an alteration in vaginal microflora. Organisms responsible for the syndrome include *Gardnerella vaginalis* (also known as *Haemophilus vaginalis*), *Mycoplasma hominis*, and various anaerobes. The syndrome occurs most commonly in sexually

active women, although it may not actually be transmitted sexually. Bacterial vaginosis is characterized by a malodorous vaginal discharge, elevation of vaginal pH (above 4.5), and generation of a fishy odor when vaginal secretions are mixed with 10% potassium hydroxide.

Drug route depends on pregnancy status. For women who are *not* pregnant, treatment may be oral or topical. For women who are pregnant, only oral drugs are used.

Nonpregnant Women. The recommended oral therapy is *metronidazole* [Flagyl], 500 mg twice a day for 7 days. Two intravaginal options are recommended: (1) *metronidazole* (0.75% gel), 5 gm once daily for 5 days; and (2) *short-acting 2% clindamycin cream* [Cleocin, Dalacin[®]], 5 gm every evening for 7 days. In addition, a *long-acting 2% clindamycin cream* [Clindesse] may be used. Clindesse cream is formulated to adhere to the vaginal mucosa for several days, and hence can clear bacterial vaginosis with just one application.

Pregnant Women. Treatment is oral only. Two drugs are recommended: *clindamycin* and *metronidazole*. For clindamycin, the dosage is 300 mg twice daily for 7 days. For metronidazole, dosage may be either (1) 500 mg twice daily for 1 week or (2) 250 mg 3 times a day for 1 week.

TRICHOMONIASIS

Trichomoniasis, caused by *Trichomonas vaginalis*, is the most common STD in the United States. Every year, about 7.4 million men and women get infected. In men, infection is usually asymptomatic. In women, infection may be asymptomatic or may cause a diffuse, malodorous, yellow-green vaginal discharge, along with burning and itching sensations. Most infections can be eliminated with a single, 2-gm oral dose of either *metronidazole* [Flagyl, others] or *tinidazole* [Tindamax]. Dosing can be repeated in the event of treatment failure. Male partners of infected women should always be treated, even if asymptomatic. Although some clinicians remain concerned about giving metronidazole during pregnancy, there is no evidence that the drug causes birth defects in humans.

CHANCROID

Chancroid, also known as soft chancre, is caused by *Haemophilus ducreyi*. Transmission is primarily by sexual contact. The infection is characterized by a painful, ragged ulcer at the site of inoculation, usually the external genitalia. Regional lymph nodes may be swollen. Multiple secondary lesions may develop. Although primarily a tropical disease, chancroid has become an important STD in the United States. There are four recommended treatments: (1) *azithromycin* [Zithromax], 1 gm PO once; (2) *ceftriaxone* [Rocephin], 250 mg IM once; (3) *ciprofloxacin* [Cipro], 500 mg PO twice a day for 3 days; and (4) *erythromycin base*, 500 mg PO 3 times a day for 7 days.

HERPES SIMPLEX VIRUS INFECTIONS

Characteristics. Most genital herpes infections are caused by herpes simplex virus type 2 (HSV-2). A few genital infections are caused by herpes simplex virus type 1, the herpesvirus that causes cold sores. Genital herpes is transmitted

primarily by sexual contact. In the United States, the infection has reached epidemic proportions. Over 50 million people are affected, and 1.6 million new cases develop each year. There is no cure.

Symptoms of primary infection develop 6 to 8 days after contact. In females, blisters or vesicles can appear on the perianal skin, labia, vagina, cervix, and foreskin of the clitoris. In males, vesicles develop on the penis and occasionally on the testicles. Painful urination and a watery discharge can occur in both sexes. Also, the patient may experience systemic symptoms: fever, headache, myalgia, and tender, swollen lymph nodes in the affected region. Within days, the original blisters can evolve into large, painful, ulcer-like sores. Over the next 2 to 3 weeks, all symptoms resolve spontaneously. However, this does not indicate cure: The virus remains present in a latent state and can cause recurrence. Because available drugs can't eliminate the virus, symptoms may recur for life. However, for some patients, subsequent episodes become progressively shorter and less severe, and in rare cases may cease entirely. Transmission of HSV-2 can occur when symptoms are absent as well as when symptoms are present. Using a condom reduces the risk of transmission.

Neonatal Infection. Genital herpes in pregnant women can be transmitted to the infant. Transmission can occur *in utero*, which is very rare, or during delivery. Infection acquired *in utero* can result in spontaneous abortion or fetal malformation. Infection acquired during delivery can cause severe neurologic damage and even death. To protect the infant during delivery, birth should be accomplished by cesarean section if the mother has an active infection. Infants who acquire the infection should be treated with acyclovir (see Table 95-1).

Treatment. Genital herpes can be treated with three drugs: *acyclovir* [Zovirax], *famciclovir* [Famvir], and *valacyclovir* [Valtrex]. These agents cannot eliminate the virus, but they can reduce symptoms and shorten the duration of pain and viral shedding. Patients with recurrent infections may take these drugs every day or just when symptoms appear. Continuous daily administration reduces the frequency and intensity of episodes, whereas episodic treatment simply reduces symptoms once an episode has begun. Dosing information is summarized in Table 95-1.

Suppression of Transmission. *Valacyclovir* (500 mg once daily) can decrease transmission of genital herpes by 50%. No other drug has been shown to reduce transmission of this STD, or any other STD, for that matter. Unfortunately, treatment is somewhat expensive, costing about \$3.50 a day (about \$1280 a year). Also, valacyclovir only *reduces* transmission, it doesn't stop it entirely. Accordingly, patients must continue to use condoms, and must abstain from sex at times when the infection is active.

PROCTITIS

Sexually acquired proctitis (inflammation of the rectum) results primarily from receptive anal intercourse. Symptoms include anorectal pain, tenesmus (painful straining at stool), and rectal discharge. Usual causative organisms are *N. gonorrhoeae*, *C. trachomatis*, *T. pallidum*, and HSV. The preferred treatment is *ceftriaxone* (125 mg IM once) plus *doxycycline* (100 mg PO twice daily for 7 days).

VENEREAL WARTS

Genital and perianal warts are caused by human papillomaviruses (HPVs). Characteristics of these warts and their treatment are presented in Chapter 105. As discussed in

Chapter 68 (Childhood Immunization), an HPV vaccine, sold as *Gardasil*, can protect against both venereal warts and cervical cancer. Another HPV vaccine, sold as *Cervarix*, protects against cervical cancer, but not against venereal warts.

KEY POINTS

- *Chlamydia trachomatis* is the most common bacterial cause of STDs.
- Two drugs—doxycycline and azithromycin—are preferred agents for treating chlamydial infection in nonpregnant adolescents and adults.
- Gonorrhea is caused by *Neisseria gonorrhoeae*, a gram-negative diplococcus often referred to as the gonococcus.
- Gonorrhea is the second most common bacterial STD in the United States.
- Two cephalosporins—cefixime and ceftriaxone—are preferred drugs for gonorrhea.
- Syphilis is caused by the spirochete *Treponema pallidum*.
- Penicillin G is the drug of choice for treating all stages of syphilis.
- Bacterial vaginosis can be caused by multiple microorganisms, including *Gardnerella vaginalis*, *Mycoplasma hominis*, and various anaerobes.
- In nonpregnant women, bacterial vaginosis can be treated orally with metronidazole, or intravaginally with metronidazole or clindamycin.
- In pregnant women, bacterial vaginosis is treated only with oral medication, either metronidazole or clindamycin.
- Most genital herpes infections are caused by herpes simplex virus type 2. Over 50 million Americans have this STD.
- Genital herpes can be treated with three drugs: acyclovir, famciclovir, and valacyclovir. These agents do not eliminate the virus, but they can reduce symptoms and shorten the duration of viral shedding and pain.

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General Considerations**Properties of Individual Antiseptics and Disinfectants**

Alcohols

Aldehydes

Iodine Compounds: Iodine Solution and Iodine Tincture

Iodophors: Povidone-Iodine

Chlorine Compounds

Phenols

Miscellaneous Agents

Hand Hygiene for Healthcare Workers

Specific CDC Hand-Hygiene Recommendations

Antiseptics and disinfectants are locally acting antimicrobial drugs. These agents are used to reduce acquisition and transmission of infection. Drugs suitable for antiseptics and disinfection cannot be used internally because of toxicity.

GENERAL CONSIDERATIONS**Terminology**

The terms *antiseptic* and *disinfectant* are not synonymous. In common usage, the term *antiseptic* is reserved for agents *applied to living tissue*. *Disinfectants* are preparations *applied to objects*. As a rule, agents used as disinfectants are too harsh for application to living tissue. Disinfectants are employed most frequently to decontaminate surgical instruments and to cleanse hospitals and other medical facilities. Most uses of antiseptics are prophylactic. For example, antiseptics are used to cleanse the hands of medical personnel; they are applied to the patient's skin prior to invasive procedures (eg, surgery, insertion of needles); and they are used to bathe neonates. Rarely, antiseptics are employed to treat an existing local infection. However, in most cases, established infections are best treated with a systemic antimicrobial drug.

Several related terms may need clarification. *Sterilization* indicates complete destruction of all microorganisms. In contrast, *sanitization* implies only that contamination has been reduced to a level compatible with public health standards. A *germicide* is a drug that *kills* microorganisms. Germicides may be divided into subcategories: *bactericides*, *virucides*, *fungicides*, and *amebicides*. In contrast to a germicide, a *germistatic drug* is one that suppresses the growth and replication of microorganisms, but does not kill them.

Properties of an Ideal Antiseptic

The ideal antiseptic, like any other ideal drug, should be safe, effective, and selective. The preparation should be germicidal (rather than germistatic) and should have a broad spectrum of antimicrobial activity: The drug should kill bacteria and their spores, along with viruses, protozoa, yeasts, and fungi. Effects should have a rapid onset and long duration. Development of microbial resistance should be low. The drug should have no harmful effects on humans: It should not produce local injury, impair healing, or produce systemic toxicity following topical application. Lastly, the drug should not cause stains and should be devoid of offensive odor. No antiseptic has all of these properties.

Time Course of Action

Toxicity to microorganisms is determined in part by duration of exposure to an antiseptic or disinfectant. However, some agents act more quickly than others. For example, ethanol (70% solution) reduces cutaneous bacterial count by 50% in just 36 seconds. In contrast, benzalkonium chloride (at a dilution of 1:1000) requires 7 minutes to produce the same effect. Because such differences exist, effective use of antiseptics and disinfectants requires that healthcare personnel understand the exposure requirements of each agent.

Using Antiseptics to Treat Established Local Infection

In the past, topical agents were used routinely to treat established local infection. Today, *systemic* anti-infective drugs are the treatment of choice. Why? First, systemic agents are more effective than topical drugs. Second, systemic agents don't damage inflamed or abraded tissue. Experience has shown that antiseptics do little to reduce infection in wounds, cuts, and abrasions. This lack of efficacy is attributed to poor penetration to the site of infection, and to diminished activity in the presence of wound exudates. Although of limited value for *established* local infection, antiseptics are quite useful as *prophylaxis*: When applied properly, antiseptics can help cleanse wounds and decrease microbial contamination.

Using Antiseptics and Disinfectants Most Effectively

The principal value of antiseptics and disinfectants derives from their ability to prevent contamination of the patient by microorganisms in the *environment*: It appears that antiseptics applied directly to the *patient* contribute relatively little to prophylaxis against infection (except in patients who are neutropenic). A number of clinical studies support this conclusion. In one study, over 5000 preoperative patients were bathed with hexachlorophene. Although this treatment greatly reduced the concentration of surface bacteria, it had no effect

on the incidence of postoperative infection. Similarly, in a study of patients who had undergone cardiothoracic surgery, it was found that most postoperative infections were caused by organisms not present at the site of incision. From these studies and others, we can conclude that infections are caused primarily by environmental microorganisms rather than by organisms living on the skin of the patient. Consequently, use of antiseptics by nurses, physicians, and others who contact the patient confers much greater protection than does application of antiseptics to the patient. Patients also benefit greatly by the rigorous use of disinfectants to decontaminate surgical supplies and medical buildings.

PROPERTIES OF INDIVIDUAL ANTISEPTICS AND DISINFECTANTS

Antiseptics and disinfectants derive from a variety of chemical families, ranging from alcohols to iodine compounds to phenols. The various antiseptics and disinfectants differ from one another with respect to mechanism of action, time course, and antimicrobial spectrum. In almost all cases, the drugs employed as disinfectants are not used for antisepsis and vice versa. The more commonly employed antiseptics and disinfectants are listed in Table 96-1. For each drug, the table indicates chemical family and clinical use (antisepsis, disinfection, or both).

Alcohols

Ethanol

Ethanol (ethyl alcohol) is an effective virucide and kills most common pathogenic bacteria as well. However, the drug is inactive against bacterial spores, including those of *Clostridium difficile*, and has erratic activity against fungi. Bactericidal effects result from precipitating bacterial proteins and dissolving membranes. Ethanol can enhance the effects of

several other antimicrobial preparations (eg, chlorhexidine, benzalkonium chloride).

Ethanol is employed almost exclusively for antisepsis. The most frequent uses are hand washing by hospital staff and cleansing the skin prior to needle insertion and minor surgery. Because it has limited activity against bacterial spores and fungi, ethanol is not a good disinfectant.

Optimal bacterial kill requires that ethanol be present in the proper concentration. The drug is most effective at a concentration of 70%. Higher concentrations are less active.

Ethanol should not be applied to open wounds. Why? Because the drug can increase tissue damage and, by causing coagulation of proteins, can form a mass under which bacteria can thrive.

Ethanol for antisepsis is available in three formulations: solutions, gels, and foams. No one formulation has been proved more effective than the others.

Isopropanol

Isopropanol (isopropyl alcohol) is employed primarily as an antiseptic. When applied in concentrations greater than 70%, isopropanol is somewhat more germicidal than ethanol. Like ethanol, isopropanol can increase the effects of other antiseptics (eg, chlorhexidine). Isopropanol promotes local vasodilation and can thereby increase bleeding from needle punctures and incisions. Isopropanol is available in concentrations ranging from 70% to 100%.

Aldehydes

Glutaraldehyde

Glutaraldehyde [Cidex-7, Cidex Plus 28] is lethal to all microorganisms; the drug kills bacteria, bacterial spores, viruses, and fungi. Antimicrobial effects result from cross-linking and precipitating proteins. Glutaraldehyde is used to disinfect and sterilize surgical instruments and other medical supplies, including respiratory and anesthetic equipment, catheters, and thermometers. The drug is too harsh for antiseptic use. To completely eliminate bacterial spores, instruments and equipment must be immersed in glutaraldehyde for

TABLE 96-1 ■ Antiseptics and Disinfectants: Chemical Category and Application

Chemical Category	Drug	Application	
		Antisepsis	Disinfection
Alcohols	Ethanol	✓	
	Isopropanol	✓	
Aldehydes	Glutaraldehyde		✓
	Formaldehyde		✓
Iodine Compounds	Iodine tincture	✓	
	Iodine solution	✓	
Iodophors	Povidone-iodine	✓	✓
Chlorine Compounds	Oxychlorosene	✓	
	Sodium hypochlorite	✓	✓
Phenolic Compound	Hexachlorophene	✓	
Miscellaneous Agents	Chlorhexidine	✓	
	Hydrogen peroxide		✓
	Benzalkonium chloride	✓	✓

at least 10 hours. All blood should be removed first. Glutaraldehyde is most active at alkaline pH. However, under alkaline conditions, glutaraldehyde eventually becomes inactive owing to gradual polymerization. Consequently, alkaline solutions of glutaraldehyde are active for only 2 to 4 weeks. Glutaraldehyde should be used with adequate ventilation because fumes can irritate the respiratory tract.

Formaldehyde

Formaldehyde kills bacteria, bacterial spores, viruses, and fungi. Like glutaraldehyde, formaldehyde is too harsh for application to the skin. Accordingly, use is limited to disinfection and sterilization of equipment and instruments. For two reasons, formaldehyde is less desirable than glutaraldehyde. First, formaldehyde acts slowly: Destruction of bacterial spores may take 2 to 4 days. Second, formaldehyde is more volatile than glutaraldehyde, and hence tends to cause more respiratory irritation. As with glutaraldehyde, blood should be removed before instruments and equipment are sterilized.

Iodine Compounds: Iodine Solution and Iodine Tincture

Iodine was first employed as an antiseptic more than 160 years ago. Despite the introduction of numerous other drugs, iodine remains one of our most widely used germicidal agents. The drug is extremely effective, having the ability to kill all known bacteria, fungi, protozoa, viruses, and yeasts. Additional assets are low cost and low toxicity.

The composition of iodine solution and iodine tincture is very similar. Iodine *solution* consists of 2% elemental iodine and 2.4% sodium iodide in water. Iodine *tincture* contains the same amounts of elemental iodine and sodium iodide and also contains 47% ethanol. The ethanol enhances the antimicrobial activity of iodine tincture.

The germicidal activity of iodine tincture and iodine solution is due only to *free* (dissolved) elemental iodine. In both the tincture and the solution, the concentration of free elemental iodine is very low—about 0.15%—owing to the poor solubility of iodine in water. Because only free iodine is active, most of the elemental iodine and all of the sodium iodide present in both iodine tincture and iodine solution do not contribute *directly* to microbicidal activity. However, these components do contribute *indirectly* by serving as reservoirs from which free elemental iodine can be released.

Iodine tincture and iodine solution are employed primarily for antiseptics of the skin, a use for which they are the most effective agents available. When the skin is *intact*, iodine *tincture* is preferred. This preparation is commonly employed to cleanse the skin prior to IV injection and withdrawal of blood for microbial culture. For treatment of *wounds* and *abrasions*, iodine *solution* should be employed. (Because alcohol is an irritant, iodine tincture is less appropriate for application to broken skin.)

Iodophors: Povidone-Iodine

An iodophor is simply a complex composed of elemental iodine plus a solubilizing agent. Antimicrobial effects derive from release of free iodine. The intact iodophor is inactive.

Povidone-iodine is an iodophor composed of elemental iodine plus povidone, an organic polymer that increases the solubility of the iodine. Povidone-iodine has no antimicrobial activity of its own. Rather, it serves as a reservoir from which elemental iodine can be released. Free elemental iodine is the active germicide. The concentration of free iodine achieved with application of povidone-iodine is lower than that produced with application of iodine tincture or iodine solution. Hence, povidone-iodine is less effective than these other iodine preparations.

Povidone-iodine is employed primarily for prophylaxis of postoperative infection. Additional uses include hand washing, surgical scrubbing, and preparing the skin prior to invasive procedures (eg, surgery, aspiration, injection). In addition, povidone-iodine is employed to sterilize equipment, although superior disinfectants are available.

The drug is supplied in a variety of formulations (ointments, solutions, aerosols, gels). It is also impregnated in swabs, sponges, and wipes. Trade names include ACU-dyne, Betadine, and Operand.

Chlorine Compounds

Chlorine is lethal to a wide variety of microbes, and is active both as elemental chlorine and as hypochlorous acid, which is formed by reaction of chlorine with water. Chlorine is used extensively to sanitize water supplies and swimming pools. However, because of physical properties that make working with chlorine difficult, chlorine itself is rarely used clinically. Instead, chlorine-containing compounds that release hypochlorous acid are employed.

Oxychlorosene Sodium

Oxychlorosene sodium [Clorpactin WCS 90] is a complex mixture of hypochlorous acid with alkylphenyl sulfonates. Antimicrobial effects derive from releasing hypochlorous acid. Oxychlorosene is lethal to bacteria, yeasts, fungi, viruses, molds, and spores. The preparation is employed as a topical antiseptic and can be especially useful for treating localized infection caused by drug-resistant microbes. Oxychlorosene is also employed as an antiseptic for surgical prophylaxis and to irrigate and cleanse fistulas, sinus tracts, wounds, and empyemas (pus-filled cavities).

Sodium Hypochlorite

Sodium hypochlorite kills bacteria, bacterial spores, fungi, protozoa, and viruses. Undiluted (5%) solutions are employed commonly as household bleach. These concentrated solutions are too irritating for application to human tissue. For antiseptic use, dilute (0.5%) solutions are employed. These preparations can be used to irrigate wounds and to cleanse and deodorize necrotic tissue. To minimize local irritation, solutions of sodium hypochlorite should be rinsed off promptly. A 1% solution can be used to sterilize equipment. Solutions of sodium hypochlorite are unstable and must be prepared fresh before each use.

Phenols

The family of phenolic compounds consists of phenol itself and several phenol derivatives. Following its introduction in 1867, phenol rapidly became both the antiseptic and disinfectant of choice. Today, use of phenol for antiseptic purposes is rare. However, the drug is still employed in some hospitals for disinfection. One member of the phenol family—hexachlorophene—is discussed below.

Hexachlorophene

Actions. Hexachlorophene is *bacteriostatic*, not bactericidal. The drug is quite active against gram-positive bacteria—the bacteria found most frequently on the skin. However, hexachlorophene has little or no effect on gram-negative bacteria. In fact, when used on a regular basis, hexachlorophene encourages overgrowth with gram-negative organisms. (By killing off gram-positive bacteria, hexachlorophene makes conditions more conducive to gram-negative growth.)

Uses. In the past, hexachlorophene was used for hand cleansing by healthcare personnel. However, the drug is no longer an accepted ingredient for hand disinfectants, and should not be used in the clinical setting.

Adverse Effects. Hexachlorophene can be absorbed through intact skin and mucous membranes. Absorption through denuded areas can be especially significant. If absorbed in sufficient amounts, hexachlorophene causes central nervous system stimulation. Responses range from confusion to twitching to seizures. Deaths have occurred. To minimize systemic toxicity, hexachlorophene should not be applied extensively to burns, wounds, cuts, or mucous membranes. In addition, total body bathing, especially of

TABLE 96-2 ■ Selected Chlorhexidine Products

Product Description	Trade Names	Healthcare Uses
Rinse: 0.5% CHG with 70% isopropanol	Hibistat Germicidal Hand Rinse	Hand cleansing
Wipes: 0.5% CHG with 70% isopropanol	Hibistat Towelettes	Hand cleansing
Brush with Sponge: 4% CHG with 4% isopropanol	Hibiclens	Surgical hand cleansing
Solution: 2% or 4% CHG with 4% isopropanol	Exidine Scrub, BactoShield	Surgical scrub for hands and forearms
Liquid: 2% or 4% CHG with 4% isopropanol	Betasept, Dyna-Hex Skin Cleanser, Exidine Skin Cleanser, Hibiclens Antiseptic/Antimicrobial Skin Cleanser	Preoperative skin cleanser for surgical site or entire body
Gauze dressing: CHG-impregnated gauze		Protection of wounds or burns
Catheter dressing: CHG-impregnated transparent dressing	Tegaderm	Protection of central venous catheters
Catheter dressing: CHG-impregnated disk	BioPatch	Protection of central venous catheters
Oral rinse: 0.12% CHG	Peridex, Periogard	Treatment of gingivitis

CHG = chlorhexidine gluconate.

infants, should be avoided. For bathing infants, chlorhexidine is safer and more effective.

Preparations. Hexachlorophene is available only by prescription. The drug is supplied in solution and emulsion under the trade name pHisoHex.

Miscellaneous Agents

Chlorhexidine

Chlorhexidine is a fast-acting antiseptic lethal to most gram-positive and gram-negative bacteria, but not to bacterial spores. How does chlorhexidine work? At low concentrations, it disrupts the bacterial cell membrane, causing leakage of intracellular components. At higher concentrations, it precipitates intracellular proteins and nucleic acids. Antibacterial effects are reduced somewhat in the presence of soap, blood, and pus. Chlorhexidine that remains on the skin after rinsing is sufficient to exert continuing germicidal effects. Bacterial resistance is rare.

As indicated in Table 96-2, chlorhexidine is available in several formulations for use in various situations. The drug is used for preoperative preparation of the skin and as a surgical scrub, hand-wash preparation, and wound cleanser. It is also the preferred agent for preventing infection associated with central venous catheters. In patients with gingivitis and periodontitis, chlorhexidine is used as an oral rinse.

Chlorhexidine is very safe. Even with routine preoperative use, local adverse effects are uncommon. Rarely, severe contact dermatitis has developed at the site of a central venous catheter. Inadvertent IV injection has been reported twice: in one patient, hemolysis occurred; in the other, no ill effects were observed.

Hydrogen Peroxide

Hydrogen peroxide is an excellent disinfectant and sterilizing agent, but is useless as an antiseptic. The entity in hydrogen peroxide solution responsible for antimicrobial effects is the hydroxyl free radical. These free radicals are destroyed when hydrogen peroxide is acted upon by catalase, an enzyme

found in all tissues. Hence, contact with tissue terminates germicidal actions. The only benefit resulting from application of hydrogen peroxide to wounds derives from liberation of oxygen (by the reaction with catalase), which causes frothing that is sufficient to loosen debris and thereby facilitate cleansing. The principal use of hydrogen peroxide is disinfection and sterilization of instruments. A 3% to 6% solution is employed.

Thimerosal

Thimerosal is an organic compound that contains 49% mercury, the active antimicrobial factor. Thimerosal has only weak bacteriostatic and fungistatic properties, and hence does not kill bacteria or fungi. Antimicrobial actions are reduced in the presence of blood and tissue proteins. Thimerosal is less effective than ethanol. Use on large areas of denuded skin may yield systemic toxicity from absorption of mercury. Poisoning from thimerosal ingestion can be treated with dimercaprol (see Chapter 109). Thimerosal has been employed to irrigate wounds and prepare the skin prior to surgery. It has also been employed as an antiseptic for the eyes, nose, throat, and genitourinary tract. However, given that thimerosal has low efficacy and a significant potential for harm, and given that more effective and safer drugs are available, thimerosal has been withdrawn from the market.

In the past, thimerosal was widely used as a preservative in vaccines. However, owing to concerns about a possible (albeit unproved) link between thimerosal and autism, nearly all vaccines used by Americans are now devoid of this agent. The only exception is the inactivated influenza vaccine.

Benzalkonium Chloride

Actions. Benzalkonium chloride (BAC) is an organic quaternary ammonium compound that has antimicrobial and detergent properties. BAC is active against many gram-positive and gram-negative bacteria as well as some fungi, protozoa, and viruses. The drug is relatively inactive against *Mycobacterium tuberculosis*, *C. difficile*, and other spore-forming bacteria. Germicidal effects result from disruption of membranes, and are enhanced by ethanol. BAC is inactivated by soaps and organic material. BAC is slow acting compared with iodine.

Antiseptic Uses. BAC is employed for preoperative preparation of the skin and mucous membranes; as a surgical scrub; as an antiseptic for abrasions and minor wounds; as a vaginal douche; and for irrigation of the eyes, body cavities, and genitourinary tract. Because BAC is inactivated by soap, all soap must be removed by rinsing with water and 70% alcohol prior to BAC application. Concentrated solutions of BAC can cause severe local injury, and hence healthcare personnel must take care to use solutions of appropriate dilution. For several reasons (limited antimicrobial spectrum, lack of rapid action, potential for toxicity, availability of superior agents), there seems to be little to recommend BAC for antiseptic use.

Disinfectant Use. Immersion in BAC solution is employed for sterile storage of instruments and supplies. Adsorption of BAC onto porous material can significantly reduce the concentration of BAC in solutions. To ensure continuing efficacy, solutions should be changed (or at least replenished with BAC) on a regular basis.

Preparations and Dosage. BAC is supplied in concentrated (17%) and dilute (1:750) solution. Trade names include Benza and Mycocide NS. Recommended dilutions are 1:750 (for application to intact skin and to minor wounds and abrasions); 1:2000 to 1:5000 (for application to mucous membranes and diseased or seriously damaged skin); and 1:750 to 1:5000 (for storage of instruments and supplies).

HAND HYGIENE FOR HEALTHCARE WORKERS

Effective hand hygiene is the single most important factor in preventing the spread of infection in healthcare settings. Each year, an estimated 2 million patients in the United States acquire an infection while in a hospital; about 90,000 of them die as a result. Patients can also acquire infections in other settings, including clinics, dialysis centers, and long-term care facilities. In all of these places, the leading cause of infection spread is the transfer of pathogens from one patient to another on the hands of healthcare workers (HCWs). Accordingly, the best way to reduce new infections in these settings is to improve hand hygiene.

Traditionally, HCWs cleaned their hands with soap and water. Unfortunately, this technique has several drawbacks: it takes considerable time, requires a sink and hand-washing supplies, and promotes skin irritation and dryness. As a result, adherence tends to be poor.

In 2002, the Centers for Disease Control and Prevention (CDC) issued guidelines designed to improve hand-hygiene practices among HCWs and to reduce transmission of pathogenic microorganisms to patients and personnel in healthcare settings. A central recommendation in the guidelines is the use of *alcohol-based handrubs*, rather than soap and water, for *routine* hand antisepsis. There are four reasons for this recommendation:

- **Accessibility**—Handrubs don't require a sink or towels, and hence are more accessible than washing with soap and water.
- **Time savings**—Using a handrub is much faster than washing with soap and water. All you do is apply the handrub to the palm of one hand, and then rub your hands together until they are dry. The CDC estimates that, during an 8-hour shift, an intensive care unit nurse would save about 1 hour by using a handrub instead of soap and water.
- **Lessened skin damage**—Today's alcohol-based handrubs contain emollients and moisturizers, and hence don't irritate or dry the skin like soap and water do.
- **Greater efficacy**—Alcohol-based handrubs reduce the number of bacteria on the skin more effectively than does washing with soap and water.

Studies have shown that, because of these advantages, switching from soap and water to an alcohol-based handrub can significantly improve adherence among HCWs.

It is important to note that alcohol-based handrubs have limitations. First, alcohol does not kill bacterial spores, including those of *C. difficile* and *Bacillus anthracis*. Washing with soap and water doesn't kill spores either, but

does physically remove them. Second, alcohol-based handrubs can't remove dirt or organic material. Accordingly, when the hands are visibly soiled, soap and water must be used first. Third, alcohol lacks residual killing power. For routine clinical practice, this lack is no concern. However, under certain conditions—including infectious disease outbreaks and performance of invasive procedures—an antiseptic that does have residual effects (eg, chlorhexidine) should be used.

Table 96-3 lists the antimicrobial spectrum, speed of onset, and unique properties of some antiseptic agents used in hand-hygiene products.

Specific CDC Hand-Hygiene Recommendations

Major recommendations from the CDC hand-hygiene guidelines are presented below. Each recommendation is categorized on the basis of existing scientific data, theoretical rationale, applicability, and economic impact. The five categories employed are defined as follows:

Category IA—Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies

Category IB—Strongly recommended for implementation and supported by certain experimental, clinical, or epidemiologic studies and a strong theoretical rationale

Category IC—Required for implementation, as mandated by federal or state regulation or standard

Category II—Suggested for implementation and supported by suggestive clinical or epidemiologic studies or a theoretical rationale

No recommendation/Unresolved issue—Practices for which insufficient evidence or no consensus regarding efficacy exists

Indications for Hand Washing and Hand Antisepsis

- When hands are visibly dirty or contaminated with proteinaceous material or are visibly soiled with blood or other body fluids, wash hands with either a non-antimicrobial soap and water or an antimicrobial soap and water (IA).
- If hands are not visibly soiled, use an alcohol-based handrub for routinely decontaminating hands in all clinical situations described in italics below (IA). Alternatively, wash hands with an antimicrobial soap and water in all clinical situations described in italics below (IB).
 - *Decontaminate hands before having direct contact with patients (IB).*
 - *Decontaminate hands before donning sterile gloves when inserting a central intravascular catheter (IB).*
 - *Decontaminate hands before inserting indwelling urinary catheters, peripheral vascular catheters, or other invasive devices that do not require a surgical procedure (IB).*
 - *Decontaminate hands after contact with a patient's intact skin (eg, when taking a pulse or blood pressure, and lifting a patient) (IB).*
 - *Decontaminate hands after contact with body fluids or excretions, mucous membranes, nonintact skin, and wound dressings if hands are not visibly soiled (IA).*

TABLE 96-3 ■ Antimicrobial Spectrum and Characteristics of Hand-Hygiene Antiseptic Agents

Group	Gram-Positive Bacteria	Gram-Negative Bacteria	Mycobacteria	Fungi	Viruses	Speed of Action	Comments
Alcohols	+++	+++	+++	+++	+++	Fast	Optimum concentration 60%–95%; no persistent activity; not lethal to bacterial spores, including those of <i>C. difficile</i>
Chlorhexidine (2% and 4% aqueous)	+++	++	+	+	+++	Intermediate	Persistent activity; rare allergic reactions
Iodine compounds	+++	+++	+++	++	+++	Intermediate	Causes skin burns; usually too irritating for hand hygiene
Iodophors	+++	+++	+	++	++	Intermediate	Less irritating than iodine; acceptance varies
Phenol derivatives	+++	+	+	+	+	Intermediate	Activity neutralized by nonionic surfactants

+++ = excellent, ++ = good, but does not include the entire bacterial spectrum, + = fair.

From Centers for Disease Control and Prevention: Guideline for hand hygiene in health-care settings: Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. MMWR Recomm Rep 51(RR-16), 2002.

- Decontaminate hands if moving from a contaminated body site to a clean body site during patient care (II).
- Decontaminate hands after contact with inanimate objects (including medical equipment) in the immediate vicinity of the patient (II).
- Decontaminate hands after removing gloves (IB).

- Before eating and after using a restroom, wash hands with a non-antimicrobial soap and water or with an antimicrobial soap and water (IB).
- Antimicrobial-impregnated wipes (ie, towelettes) may be considered as an alternative to washing hands with non-antimicrobial soap and water. Because they are not as effective as alcohol-based handrubs or washing hands with an antimicrobial soap and water for reducing bacterial counts on the hands of HCWs, they are not a substitute for using an alcohol-based handrub or antimicrobial soap (IB).
- Wash hands with non-antimicrobial soap and water or with antimicrobial soap and water if exposure to spore-forming bacteria, such as *C. difficile** or *Bacillus anthracis*, is suspected or proven. The physical action of washing and rinsing the hands will remove spores, although it won't kill them. Alcohols, chlorhexidine, iodophors, and other antiseptics have poor activity against spores, and hence are not as ineffective as soap and water (II).
- No recommendation can be made regarding the routine use of non-alcohol-based handrubs for hand hygiene in health-care settings (Unresolved issue).

*The 2002 CDC guidelines do not specify exposure to *C. difficile* as a reason for washing with soap and water. This precaution was added by this author.

Hand-Hygiene Technique

- When decontaminating hands with an alcohol-based hand-rub, apply product to palm of one hand and rub hands together, covering all surfaces of hands and fingers, until hands are dry (IB). Follow the manufacturer's recommendations regarding the volume of product to use.
- When washing hands with soap and water, wet hands first with water, apply an amount of product recommended by the manufacturer to hands, and rub hands together vigorously for at least 15 seconds, covering all surfaces of the hands and fingers. Rinse hands with water and dry thoroughly with a disposable towel. Use towel to turn off the faucet (IB). Avoid using hot water, because repeated exposure to hot water may increase the risk of dermatitis (IB).
- Liquid, bar, leaflet, or powdered forms of plain soap are acceptable when washing hands with a non-antimicrobial soap and water. When bar soap is used, soap racks that facilitate drainage and small bars of soap should be used (II).
- Multiple-use cloth towels of the hanging or roll type are not recommended for use in healthcare settings (II).

Surgical Hand Antisepsis

- Remove rings, watches, and bracelets before beginning the surgical hand scrub (II).
- Remove debris from underneath fingernails using a nail cleaner under running water (II).
- Surgical hand antisepsis using either an antimicrobial soap or an alcohol-based handrub with persistent activity is recommended before donning sterile gloves when performing surgical procedures (IB).
- When performing surgical hand antisepsis using an antimicrobial soap, scrub hands and forearms for the length of

time recommended by the manufacturer, usually 2 to 6 minutes. Long scrub times (eg, 10 minutes) are not necessary (IB).

- When using an alcohol-based surgical hand-scrub product with persistent activity, follow the manufacturer's instructions. Before applying the alcohol solution, prewash hands and forearms with a non-antimicrobial soap and dry hands and forearms completely. After application of the alcohol-based product as recommended, allow hands and forearms to dry thoroughly before donning sterile gloves (IB).

Other Aspects of Hand Hygiene

- Do not wear artificial fingernails or extenders when having direct contact with patients at high risk (eg, those in intensive care units or operating rooms) (IA).
- Keep natural nail tips less than 1/4-inch long (II).
- Wear gloves when contact with blood or other potentially infectious materials, mucous membranes, and nonintact skin could occur (IC).
- Remove gloves after caring for a patient. Do not wear the same pair of gloves for the care of more than one patient,

and do not wash gloves between uses with different patients (IB).

- Change gloves during patient care if moving from a contaminated body site to a clean body site (II).
- No recommendation can be made regarding wearing rings in healthcare settings (Unresolved issue). (Note: A 2003 study demonstrated that wearing a ring reduced the efficacy of hand cleansing.)

Administrative Measures Regarding Hand Hygiene

- As part of a multidisciplinary program to improve hand-hygiene adherence, provide HCWs with a readily accessible alcohol-based handrub product (IA).
- To improve hand-hygiene adherence among personnel who work in areas in which high workloads and high intensity of patient care are anticipated, make an alcohol-based handrub available at the entrance to the patient's room or at the bedside, in other convenient locations, and in individual pocket-sized containers to be carried by HCWs (IA).

KEY POINTS

- Because the various antiseptics and disinfectants require different durations of exposure to be effective, you must know the time course of action of the specific agent you are working with.
- Although antiseptics can help prevent *development* of a local infection, systemic anti-infective drugs are preferred for treating an *established* local infection.
- Washing with antiseptics by nurses, physicians, and others who contact patients will do more to protect patients from infection than will application of antiseptics to patients themselves.
- For routine hand antisepsis, alcohol-based handrubs are preferred to soap and water.
- Soap and water are preferred to alcohol-based handrubs following exposure to spore-forming bacteria, such as *C. difficile* or *B. anthracis*.

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Classification of Parasitic Worms

Helminthic Infestations

Nematode Infestations (Intestinal)

Nematode Infestations (Extraintestinal)

Cestode Infestations

Trematode Infestations

Drugs of Choice for Helminthiasis

Mebendazole

Albendazole

Pyrantel Pamoate

Praziquantel

Diethylcarbamazine

Ivermectin

Helminths are parasitic worms, and *anthelmintics* are the drugs used against them. Helminthiasis (worm infestation) is the most common affliction of humans, affecting more than 2 billion people worldwide. The intestine is a frequent site of infestation. Other sites include the liver, lymphatic system, and blood vessels. Infestation is frequently asymptomatic. However, infestation with some parasites can cause severe complications. Helminthiasis is most prevalent where sanitation is poor. Cleanliness greatly reduces infestation risk.

Treatment of helminthiasis is not always indicated. Most parasitic worms do not reproduce in the human body. Hence, in the absence of reinfestation, many infections simply subside as adult worms die. Accordingly, treatment may be optional. In countries where providers and medication are readily available, drug therapy is definitely indicated. However, in less fortunate locales, several factors—cost of medication, limited medical facilities, and high probability of reinfestation—may render individual treatment impractical. In these places, preventative measures, such as improved hygiene and elimination of carriers, may be the most valuable interventions.

In approaching the anthelmintic drugs, we begin by reviewing classification of the parasitic worms. Next we briefly discuss the characteristics of the more common helminthic infestations. After this, we discuss preferred drugs for treatment.

CLASSIFICATION OF PARASITIC WORMS

The most common parasitic worms belong to three classes: Nematoda (roundworms), Cestoda (tapeworms), and Trematoda (flukes). Nematodes belong to the phylum Nematelminthes. Cestodes and trematodes belong to the phylum Platyhelminthes (flat worms).

Nematodes (Roundworms)

Parasitic nematodes can be subdivided into two groups: (1) those that infest the intestinal lumen and (2) those that inhabit tissues. There are five major species of intestinal nematodes. Their common names are giant roundworm, pinworm, hookworm, whipworm, and threadworm. Official names (eg, *Ascaris lumbricoides*) are listed in Table 97-1. Two types of nematodes invade tissues: (1) pork roundworms (responsible for trichinosis) and (2) filariae. The three species of filariae encountered most commonly are listed in Table 97-1.

Cestodes (Tapeworms)

Three species of cestodes infest humans. Common names for these parasites are beef tapeworm, pork tapeworm, and fish tapeworm. Their official names appear in Table 97-1.

Trematodes (Flukes)

Five species of trematodes infest humans. These organisms fall into four groups having the following common names: blood fluke, liver fluke, intestinal fluke, and lung fluke. Official names of the five species belonging to these groups are given in Table 97-1.

HELMINTHIC INFESTATIONS

This section describes the major characteristics of infestation by specific helminths. These infestations can differ with respect to anatomic site and danger to the host. Infestations also differ with respect to the drugs employed for treatment (see Table 97-1 for a summary).

The name applied to an infestation is based on the official name of the invading organism. For example, infestation with the giant roundworm, whose official name is *Ascaris lumbricoides*, is referred to as *ascariasis*.

In the discussion below, the helminthic infestations are grouped in four categories: (1) nematode infestations of the intestine, (2) nematode infestations of extraintestinal sites, (3) cestode infestations, and (4) trematode infestations.

Nematode Infestations (Intestinal)

Ascariasis (Giant Roundworm Infestation). Ascariasis is the most prevalent helminthic infestation. Worldwide, one of every three people is affected. Adult worms inhabit the small intestine. Ascariasis is usually asymptomatic. However, serious complications can result if worms migrate into the pancreatic duct, bile duct, gallbladder, or liver. In addition, if infestation is extremely heavy, intestinal blockage may occur. Because of these potential hazards, ascariasis should always be treated. Drugs of choice are *albendazole*, *mebendazole*, and *ivermectin*.

Enterobiasis (Pinworm Infestation). Enterobiasis is the most common helminthic infestation in the United States. Adult pinworms inhabit the ileum and large intestine. Their life span is approximately 2 months. Although usually asymptomatic, some patients experience intense perianal itching. Serious complications are rare. Drugs of choice are *albendazole*, *mebendazole*, and *pyrantel pamoate*. Because enterobiasis is readily transmitted, all family members of an infected individual should be treated simultaneously.

Ancylostomiasis and Necatoriasis (Hookworm Infestation). Hookworm infestation is most common in rural areas where hygiene is poor and people go barefoot. Adult hookworms attach to the wall of the small intestine and suck blood. As a result, infestation is associated with chronic blood loss and progressive anemia. Symptomatic anemia is most likely in menstruating women and undernourished individuals. Nausea, vomiting, and abdominal pain may accompany the infestation. *Albendazole*, *mebendazole*, and *pyrantel pamoate* are treatments of choice.

Trichuriasis (Whipworm Infestation). Trichuriasis is extremely common, affecting about 1 billion people worldwide. Larvae and adult

TABLE 97-1 ■ Drugs of Choice for Parasitic Worms

Worm Class	Parasitic Organism		Drugs of Choice
	Common Name	Official Name	
Nematodes (roundworms): intestinal	Giant roundworm	<i>Ascaris lumbricoides</i>	Albendazole or mebendazole or ivermectin
	Pinworm	<i>Enterobius vermicularis</i>	Albendazole or mebendazole or pyrantel pamoate
	Hookworm	<i>Ancylostoma duodenale</i> , <i>Necator americanus</i>	
	Whipworm	<i>Trichuris trichiura</i>	Albendazole
	Threadworm	<i>Strongyloides stercoralis</i>	Ivermectin
Nematodes (roundworms) extraintestinal	Pork roundworm	<i>Trichinella spiralis</i>	Albendazole*
	Filariae	<i>Brugia malayi</i> , <i>Loa loa</i> , <i>Wuchereria bancrofti</i> , <i>Onchocerca volvulus</i>	Diethylcarbamazine [†] Ivermectin
Cestodes (tapeworms)	Beef tapeworm	<i>Taenia saginata</i>	Praziquantel*
	Pork tapeworm	<i>Taenia solium</i>	
	Fish tapeworm	<i>Diphyllobothrium latum</i>	
Trematodes (flukes)	Blood fluke	<i>Schistosoma</i> species	Praziquantel
	Intestinal fluke	<i>Fasciolopsis buski</i>	
	Lung fluke	<i>Paragonimus westermani</i>	
	Liver flukes	<i>Fasciola hepatica</i> (sheep liver fluke) <i>Clonorchis sinensis</i> (Chinese liver fluke)	Triclabendazole [‡] Praziquantel or albendazole*

*Not approved by the Food and Drug Administration for this indication.

[†]Available from the Centers for Disease Control and Prevention (CDC).

[‡]Not available in the United States.

worms inhabit the large intestine. Mature worms may live for 10 years or more. The disease is usually devoid of symptoms. However, when the worm burden is very large, rectal prolapse may occur. Patients with severe infestation require therapy. *Albendazole* is the treatment of choice.

Strongyloidiasis (Threadworm Infestation). Strongyloidiasis is common in the southern United States. Larval and adult threadworms inhabit the small intestine. The disease can be very dangerous, although symptoms are usually absent. Mild infestation may cause abdominal pain and occasional diarrhea. Severe infestation can cause vomiting, massive diarrhea, dehydration, electrolyte imbalance, and secondary bacteremia. Death has occurred. Affected individuals should always be treated. *Ivermectin* is the treatment of choice.

Nematode Infestations (Extraintestinal)

Trichinosis (Pork Roundworm Infestation). Trichinosis, also called *trichinellosis*, is acquired by eating undercooked pork that contains encysted larvae of *Trichinella spiralis*. Adult worms reside in the intestine, whereas larvae migrate to skeletal muscle and become encysted. Some encysted larvae live for years, others die and calcify within months. Symptoms of trichinosis include GI upset, fever, muscle pain, and sore throat. Potentially lethal complications (heart failure, meningitis, neuritis) arise in some patients. *Albendazole* is the drug of choice for killing adult worms and migrating larvae. However, this agent may not be active against larvae that have become encysted. *Prednisone* (a glucocorticoid) is given to reduce inflammation during larval migration.

Wuchereriosis and Brugiasis (Lymphatic Filarial Infestation). *Wuchereria bancrofti* and *Brugia malayi* are filarial nematodes that invade the lymphatic system. Infestation with either organism can cause severe complications. When infestation is heavy, lymphatic obstruction occurs, resulting in *elephantiasis* (usually of the scrotum or legs). In addition, "filarial fever" may develop. Symptoms include chills, fever, headache, nausea, vomiting, constipation, and lymphadenitis. The drug of choice for killing both filarial species is *diethylcarbamazine*.

Onchocerciasis (River Blindness). *Onchocerca volvulus* is a filarial nematode found in streams and rivers of Mexico, Guatemala, northern South America, and equatorial Africa. The parasite is transmitted to humans by the bite of certain flies. Heavy infestation with *O. volvulus* causes dermatologic and ophthalmic symptoms. Dermatologic manifestations include subcutaneous nodules (filled with adult worms) and persistent pruritic dermatitis. Ocular lesions, caused by the infiltration and death of microfilariae, result in optic neuritis, optic atrophy, and then blindness. The drug of choice for treating onchocerciasis is *ivermectin*.

Cestode Infestations

Taeniasis (Beef and Pork Tapeworm Infestation). Taeniasis is acquired by eating undercooked beef or pork that contains tapeworm larvae. Adult tapeworms live attached to the wall of the small intestine. Infestation is usually asymptomatic. Taeniasis is treated with *praziquantel*.

Diphyllobothriasis (Fish Tapeworm Infestation). *Diphyllobothrium latum* is acquired by ingestion of undercooked fish that is infested with tapeworm larvae. Adult worms inhabit the ileum. Infestation is usually devoid of symptoms. Worms can be killed with *praziquantel*.

Trematode Infestations

Schistosomiasis (Blood Fluke Infestations). The term *schistosomiasis* refers to infestation with blood flukes of any species (eg, *Schistosoma mansoni*, *S. japonicum*). Specific snails serve as intermediate hosts for these flukes. Schistosomiasis cannot be acquired in the continental United States because the appropriate snails are not indigenous.

Schistosomiasis has an acute and a chronic phase. The acute phase subsides in 3 to 4 months. Symptoms during this phase include lymphadenopathy, fever, anorexia, malaise, muscle pain, and rash. During the chronic phase, schistosomes take up residence in the vascular system, primarily in veins of the intestines and liver. This late infestation can produce intestinal polyposis.

TABLE 97-2 ■ First-Choice Anthelmintic Drugs: Target Organisms and Dosages

Generic Name [Trade Name]	Target Organism	Adult and Pediatric Dosages
Mebendazole [Vermox]	Giant roundworm	100 mg 2 times/day for 3 days <i>or</i> 500 mg once
	Hookworm	
Albendazole [Albenza]	Pinworm	100 mg; repeat in 2 wk
	Giant roundworm	400 mg once
	Hookworm	
	Whipworm	400 mg/day for 3 days
	Pork roundworm	400 mg 2 times/day for 8–14 days
	Pinworm	400 mg; repeat in 2 wk
Triclabendazole*	Chinese liver fluke	10 mg/kg/day for 7 days
	Sheep liver fluke	10 mg/kg once or twice
Pyrantel pamoate [Pin-X, others]	Hookworm	11 mg/kg (max. 1 gm) for 3 days
	Pinworm	11 mg/kg (max. 1 gm); repeat in 2 wk
Praziquantel [Biltricide]	Beef tapeworm [†]	5–10 mg/kg once
	Pork tapeworm [†]	
	Fish tapeworm [†]	20 mg/kg 3 times/day for 1 day
	Blood flukes	
	<i>S. japonicum, S. mekongi</i>	20 mg/kg 2 times/day for 1 day
	<i>S. mansoni, S. haematobium</i>	
	Intestinal fluke	25 mg/kg 3 times/day for 1 day
	Chinese liver fluke	25 mg/kg 3 times/day for 2 days
	Lung fluke	
	Diethylcarbamazine [‡] [Hetrazan]	<i>Wuchereria bancrofti</i>
<i>Brugia malayi</i>		
Ivermectin [Stromectol]	<i>Loa loa</i>	3 mg/kg 3 times/day for 12 days
	Threadworm	200 mcg/kg/day for 2 days
	Giant roundworm	150–200 mcg/kg once
	<i>Onchocerca volvulus</i>	150 mcg/kg every 6–12 months until asymptomatic

*Not available in the United States.

[†]Treatment of adult (intestinal) stage.

[‡]Available from the Centers for Disease Control and Prevention.

hepatosplenomegaly, and portal hypertension. For either the acute or the chronic stage, praziquantel is the treatment of choice.

Fascioliasis (Liver Fluke Infestation). Fascioliasis is caused by two liver flukes: *Fasciola hepatica* (sheep liver fluke) and *Clonorchis sinensis* (Chinese liver fluke). Both parasites inhabit the biliary tract. Symptoms (anorexia, mild fever, fatigue, aching in the region of the liver) are delayed for 1 to 3 months.

Liver flukes differ in drug sensitivity. The preferred drug for use against *F. hepatica* is triclabendazole (a veterinary anthelmintic). The preferred drugs for use against *C. sinensis* are praziquantel and albendazole.

Fasciolopsiasis (Intestinal Fluke Infestation). Fasciolopsiasis is most common in Southeast Asia. Adult worms inhabit the small intestine. The disease is usually asymptomatic. However, some people experience ulcer-like pain; some develop constipation or diarrhea; and, in the presence of massive infestation, bowel obstruction may occur, requiring surgery for clearance. Praziquantel is the treatment of choice.

DRUGS OF CHOICE FOR HELMINTHIASIS

The major anthelmintic drugs are considered below. These agents differ in antiparasitic spectra: some are active against several worms; others are more selective. Because of these differences, it is important to identify the invading organism so that the most appropriate drug can be chosen. Table 97-2 lists the major anthelmintic drugs and indicates the parasites against which each

is most effective. Although the discussion that follows is limited to drugs of choice, be aware that additional anthelmintics are available.

Mebendazole

Target Organisms. Mebendazole [Vermox] is a drug of choice for most intestinal roundworms. This agent clears infestation with pinworms, hookworms, and giant roundworms. Because of its relatively broad spectrum of action, mebendazole is especially useful for treatment of mixed infestations.

Mechanism of Action. Mebendazole prevents uptake of glucose by susceptible intestinal worms. Glucose deprivation results in immobilization followed by slow death. Since the worms die slowly, up to 3 days may elapse between treatment onset and complete clearance of parasites. Mebendazole does not influence glucose uptake or utilization by humans.

Pharmacokinetics. Only a small fraction (5% to 10%) of orally administered mebendazole is absorbed, and this fraction undergoes rapid metabolism. Consequently, plasma levels of mebendazole remain low.

Adverse Effects. Systemic effects are rare at usual doses, perhaps because the drug is so poorly absorbed. In patients with massive parasitic infestations, transient abdominal pain and diarrhea may occur.

Relatively low doses are embryotoxic and teratogenic in rats. However, these effects have not been observed in dogs, sheep, or horses. Limited experience with mebendazole in pregnant women has shown no increase in spontaneous abortion or fetal malformation. Nonetheless, pregnant women should avoid this drug, especially during the first trimester.

Preparations, Dosage, and Administration. Mebendazole [Ver-mox] is available in 100-mg tablets for oral administration. The tablets may be chewed, crushed, or swallowed whole. Dosages are summarized in Table 97-2.

Albendazole

Target Organisms. Albendazole [Albenza] is active against many cestode and nematode parasites, including larval forms of *Taenia solium* and *Echinococcus granulosus*. In the United States, the drug is approved only for (1) parenchymal neurocysticercosis caused by larval forms of the pork tapeworm, *Taenia solium*; and (2) cystic hydatid disease of the liver, lung, and peritoneum caused by larval forms of the dog tapeworm, *E. granulosus*. However, despite lack of Food and Drug Administration (FDA) approval, albendazole is considered a drug of choice for infestation with hookworms, pinworms, whipworms, Chinese liver flukes, giant roundworms, and pork roundworms, the cause of trichinosis.

Mechanism of Action. Albendazole inhibits polymerization of tubulin, and thereby prevents formation of cytoplasmic microtubules. As a result, microtubule-dependent uptake of glucose is prevented.

Pharmacokinetics. Albendazole is poorly absorbed from the GI tract, owing largely to low solubility in water. Absorption is enhanced by administration with a fatty meal. Following absorption, albendazole is rapidly converted to albendazole sulfoxide, its active form. Albendazole sulfoxide is distributed widely to body fluids and tissues, and undergoes excretion in the bile. The half-life is 8 to 12 hours.

Adverse Effects. Albendazole is generally well tolerated. Mild to moderate liver impairment has occurred in 16% of patients, as indicated by elevation of liver transaminases in plasma. Liver function should be assessed before each cycle of treatment and 14 days later.

Albendazole suppresses bone marrow function, and can thereby cause granulocytopenia, agranulocytosis, and even pancytopenia. Liver impairment may increase risk. Blood cell counts should be obtained before each cycle of treatment and 14 days later.

Albendazole is teratogenic in animals and hence should not be used during pregnancy. If pregnancy occurs, the drug should be discontinued immediately.

Preparations, Dosage, and Administration. Albendazole [Albenza] is supplied in 200-mg tablets for oral use. Dosing should be done with food to enhance absorption. Dosages for hookworms, pinworms, whipworms, giant roundworms, pork roundworms, and Chinese liver flukes are shown in Table 97-2.

For neurocysticercosis or cystic hydatid disease, each dose is 400 mg (for patients greater than 60 kg) or 7.5 mg/kg (for patients less than 60 kg). The dosing schedule for neurocysticercosis is two doses twice daily with meals for 8 to 30 days. Dosing for cystic hydatid disease is done in three consecutive cycles, each consisting of two doses twice daily with meals for 28 days followed by 14 days with no drug.

Pyrantel Pamoate

Target Organisms. Pyrantel pamoate [Pin-X, Reese's Pinworm, Combantrin* (and formerly available as Antiminth)] is active against intestinal nematodes. The drug is an alternative to mebendazole or albendazole for infestations with hookworms or pinworms.

Mechanism of Action. Pyrantel is a depolarizing neuromuscular blocking agent that causes spastic paralysis of intestinal parasites. The paralyzed worms are cleared in the feces.

Pharmacokinetics. Pyrantel is poorly absorbed, and plasma levels remain low. Most of an administered dose is excreted unchanged in the feces.

Adverse Effects. Serious reactions are rare. The most common effects are GI reactions (nausea, vomiting, diarrhea, stomach pain, cramps). Possible central nervous system effects include dizziness, drowsiness, headache, and insomnia.

Preparations, Dosage, and Administration. Pyrantel pamoate is supplied in soft-gel capsules (180 mg) and liquid formulations (50 mg/mL) for oral use. The entire prescribed dose should be taken at one time. Dosages for pinworm and hookworm infestations are given in Table 97-2.

Praziquantel

Target Organisms. Praziquantel [Biltricide] is very active against flukes and cestodes (tapeworms), and is the drug of choice for tapeworms, schistosomiasis, and other fluke infestations.

Mechanism of Action. Praziquantel is readily absorbed by helminths. At low therapeutic concentrations, the drug produces spastic paralysis, causing detachment of worms from body tissues. At high therapeutic concentra-

tions, praziquantel disrupts the integument of the worms, rendering the parasites vulnerable to lethal attack by host defenses.

Pharmacokinetics. Praziquantel is rapidly absorbed from the GI tract. The drug undergoes extensive hepatic metabolism, followed by excretion in the urine. The half-life is short (about 1.5 hours).

Adverse Effects. Praziquantel is relatively free of toxicity. Transient headache and abdominal discomfort are the most frequent reactions. Drowsiness may occur, and hence patients should avoid driving and other hazardous activities.

Preparations, Dosage, and Administration. Praziquantel [Biltricide] is available in 600-mg tablets for oral dosing. Tablets should be swallowed intact. Dosages for tapeworm and fluke infestations are presented in Table 97-2.

Diethylcarbamazine

Target Organisms. Diethylcarbamazine [Hetrazan] is the drug of choice for filarial infestations. The drug destroys microfilariae of *W. bancrofti*, *B. malayi*, and *Loa loa*. In addition, it kills adult females of these species.

Mechanism of Action. Diethylcarbamazine has two antifilarial actions. First, it reduces muscular activity, causing parasites to be dislodged from their site of attachment. Second, by altering the surface properties of the parasites, it renders the organisms more vulnerable to attack by host defenses.

Pharmacokinetics. Diethylcarbamazine is readily absorbed and undergoes rapid and extensive metabolism. Metabolites are excreted in the urine.

Adverse Effects. Adverse effects caused directly by diethylcarbamazine are minor (headache, weakness, dizziness, nausea, vomiting). Indirect effects, occurring secondary to death of the parasites, can be more serious. These include rashes, intense itching, encephalitis, fever, tachycardia, lymphadenitis, leukocytosis, and proteinuria. Fortunately, these reactions are transient, lasting just a few days—and can be minimized by pretreatment with glucocorticoids.

Preparations, Dosage, and Administration. Diethylcarbamazine citrate [Hetrazan] is supplied in 50-mg tablets for oral use. The drug is available from the Centers for Disease Control and Prevention (CDC). Dosages for filarial infestations are presented in Table 97-2.

Ivermectin

Target Organisms. Ivermectin [Stromectol] is active against many nematodes. Currently, the drug has two approved indications: onchocerciasis (a major cause of blindness worldwide) and intestinal strongyloidiasis. Ivermectin is active against the tissue microfilariae of *O. volvulus* (the cause of onchocerciasis), but not against the adult form. As discussed in Chapter 100, ivermectin can also be used to kill mites and lice, although these parasites are not approved targets. In addition to its use in humans, ivermectin is used widely in veterinary medicine.

Mechanism of Action. Ivermectin disrupts nerve traffic and muscle function in target parasites. How? By opening chloride channels on the cell surface, which allows chloride ions to rush into nerve and muscle cells. The resultant hyperpolarization of these cells causes paralysis followed by death. Host cells are not affected because ivermectin is selective for chloride channels in parasites.

Pharmacokinetics. Ivermectin is administered orally and achieves peak plasma levels in 4 hours. Distribution to the central nervous system is poor. The drug is metabolized in the liver and excreted in the feces. Less than 1% of each dose appears in urine. The half-life is 16 hours.

Adverse Effect: Mazotti Reaction. The Mazotti reaction occurs in patients treated for onchocerciasis. Principal symptoms are pruritus (28%), rash (23%), fever (23%), lymph node tenderness (13%), and bone and joint pain (9%). The apparent cause is an allergic and inflammatory response to the death of microfilariae. Mazotti-type reactions do not occur in patients treated for strongyloidiasis. Abdominal pain and headache are seen in less than 5% of patients. Hypotension develops rarely.

Use in Pregnancy. Ivermectin is teratogenic in mice, rats, and rabbits. Cleft palate is the most common effect. There are no adequate data on teratogenesis in humans. Until more is known, ivermectin should be avoided during pregnancy.

Preparations, Dosage, and Administration. Ivermectin [Stromectol] is available in 3-mg tablets. Instruct patients to take the drug with water. Dosages for strongyloidiasis (threadworm), *Ascaris lumbricoides* (giant roundworm) and onchocerciasis (river blindness) are summarized in Table 97-2.

KEY POINTS

- Because each anthelmintic drug is active against a limited range of worms, we must match the drug with the infecting worm.
- Many worm infestations are both asymptomatic and self-limited, and hence drug therapy can be optional. When cost is not an issue, treatment is clearly indicated. However, in countries where funds are limited, preventative public health measures directed at improved hygiene and

elimination of carriers may be more cost-effective than treating each infested individual.

- The drugs discussed in this chapter are generally devoid of serious adverse effects.

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Antiprotozoal Drugs I: Antimalarial Agents

Life Cycle of the Malaria Parasite

Types of Malaria

Vivax Malaria

Falciparum Malaria

Principles of Antimalarial Therapy

Therapeutic Objectives

Drug Selection

Pharmacology of the Major Antimalarial Drugs

Chloroquine

Primaquine

Quinine

Quinidine Gluconate

Mefloquine

Artemisinin Derivatives

Atovaquone/Proguanil

Pyrimethamine/Sulfadoxine

Antibacterial Drugs

Malaria is a parasitic disease caused by protozoa of the genus *Plasmodium*. With the exception of tuberculosis, malaria kills more people than any other infectious disease. According to the World Health Organization, between 350 and 500 million people are afflicted each year, and over 1 million die. About 90% of deaths occur in sub-Saharan Africa, almost entirely among young children. In the United States, of the 1300 cases reported annually, almost all were acquired outside the country.

Large-scale attempts to eradicate the disease have achieved only partial success. Eradication programs have been directed at the malarial parasite as well as the *Anopheles* mosquito, the insect that transmits malaria to humans. Failure to produce complete control has resulted largely from development of drug resistance by both the parasite and the mosquito. The incidence of malaria is rising in regions where it had once been suppressed. There remains a great need for safe, effective, and affordable agents capable of killing the malaria parasite and its mosquito carrier. Vaccines against malaria, which are in development, would be the ideal way to manage the disease.

In approaching the antimalarial drugs, we begin by reviewing the life cycle of the malaria parasite. After that we discuss the two major subtypes of malaria: falciparum malaria and vivax malaria. Next, we consider basic principles of treatment, focusing on therapeutic objectives and drug selection. Lastly, we discuss the pharmacology of the antimalarial drugs.

LIFE CYCLE OF THE MALARIA PARASITE

In order to understand the actions and specific applications of antimalarial drugs, we must first understand the life cycle of the malaria parasite. As indicated in Figure 98-1, the cycle takes place in two hosts: humans and the female *Anopheles* mosquito. Asexual reproduction occurs in humans. Sexual reproduction occurs in the mosquito.

The human phase begins when *sporozoites* are injected into the bloodstream by a feeding *Anopheles* mosquito. The sporozoites invade hepatocytes (liver cells), where they either (1) multiply and transform into *merozoites* or (2) transform into *hypnozoites* and lie dormant. The process of merozoite production, which takes 12 to 26 days (depending upon the species of parasite), is referred to as the *pre-erythrocytic* or *exoerythrocytic* phase of the life cycle. Following their release from hepatocytes, merozoites infect erythrocytes. Within the erythrocyte, each parasite differentiates and divides, becoming first a *trophozoite* and then a multinucleated *schizont*. The schizont then evolves into new merozoites. This asexual reproductive process takes 2 to 3 days, after which red blood cells burst, releasing new merozoites into the blood. The new merozoites then infect fresh erythrocytes, thereby establishing an escalating cycle of red cell invasion and lysis. Each time the erythrocytes rupture, they release pyrogenic (fever-inducing) agents, which cause the repeating episodes of fever that characterize malaria.

Sexual reproduction begins with the formation of *gametocytes*, which differentiate from some of the merozoites in red blood cells (see Figure 98-1). Following their release from red cells, gametocytes enter a female *Anopheles* mosquito when she ingests blood while feeding. Within the mosquito, the gametocytes differentiate into mature forms, after which fertilization takes place. The resulting zygote then produces sporozoites, thus completing sexual reproduction.

TYPES OF MALARIA

Malaria is caused by four different species of *Plasmodium*. In this chapter, we limit discussion to the two species encountered most: *Plasmodium vivax* and *Plasmodium falciparum*. Malaria caused by either species is characterized by high fever, chills, and profuse sweating. However, despite similarity of symptoms, these forms of malaria are very different—especially with regard to severity of symptoms, relapse, and drug resistance. These and other differences are summarized in Table 98-1.

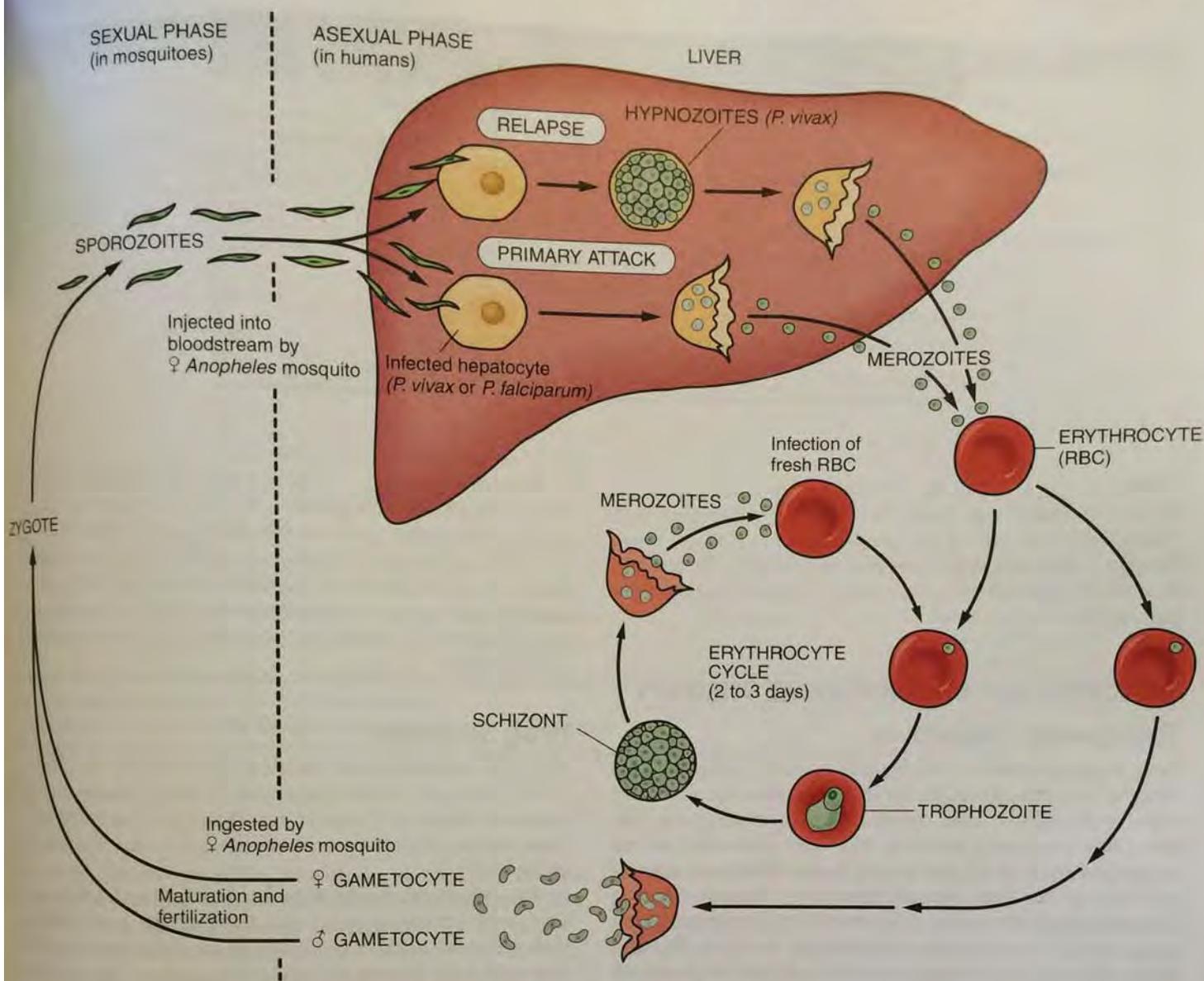


Figure 98-1 ■ Life cycle of the malaria parasite.
(RBC = red blood cell.)

Vivax Malaria

Vivax malaria, caused by *P. vivax*, is the most common form of malaria. Fortunately, the disease is relatively mild and usually self-limiting. Because drug resistance by *P. vivax* is relatively uncommon, symptoms can be readily suppressed with medication.

Infection begins when the host is inoculated with *P. vivax* sporozoites. After 26 days, merozoites emerge from hepatocytes and begin their attack on erythrocytes. Symptoms of malaria (eg, chills, fever, sweating) commence as infected erythrocytes rupture, releasing pyrogens and other substances into the blood. Symptoms peak, decline, and peak again every 48 hours in response to cyclic reinfection and red cell lysis. This cycle continues until terminated by drugs or by acquired immunity. Unfortunately, relapse is likely following termination of the acute attack. Why? Because with *P. vivax* infection, dormant parasites (hypnozoites) remain in the liver. Periodically, these hypnozoites evolve into merozoites, undergo release into the blood, and start the erythrocytic cycle anew. Relapse becomes less frequent with the passage of time, and,

after 2 or more years, ceases entirely. Relapse can be stopped with drugs that kill hypnozoites.

Falciparum Malaria

Malaria caused by *P. falciparum* is less common than malaria caused by *P. vivax*, but is much more severe. In the absence of treatment, the disease kills about 10% of its victims. Making matters worse, many strains of *P. falciparum* are now drug resistant. Unlike the symptoms of vivax malaria, which peak every 48 hours, symptoms of falciparum malaria occur at irregular intervals. The erythrocytic cycle of *P. falciparum* can destroy up to 60% of circulating red blood cells, resulting in profound anemia and weakness. The hemoglobin released from these cells causes the urine to darken, giving rise to the term *black-water fever*. Falciparum malaria can produce serious complications, including pulmonary edema, hypoglycemia, and toxic encephalopathy, characterized by confusion, coma, and convulsions. When treated immediately, falciparum malaria usually responds well. However, if treatment is delayed (by

TABLE 98-1 • Comparison of Vivax Malaria and Falciparum Malaria

Characteristics	Type of Malaria	
	Vivax Malaria	Falciparum Malaria
Causative organism	<i>Plasmodium vivax</i>	<i>Plasmodium falciparum</i>
Frequency of infection	More common	Less common
Latency of symptoms	26 days	12 days
Intensity of symptoms	Mild	Severe
Timing of febrile paroxysms	Every 2 days	Irregular
Probability of relapse	High	None
Drug resistance	Uncommon	Common

as little as 1 or 2 days), the disease may progress rapidly to irreversible shock and death. In contrast to infection with *P. vivax*, infection with *P. falciparum* does *not* relapse. Why? Because *P. falciparum* does not form hypnozoites. As a result, once the erythrocytic forms have been eliminated, the patient is parasite free.

PRINCIPLES OF ANTIMALARIAL THERAPY

Therapeutic Objectives

Drug responsiveness of the malaria parasite changes as the parasite goes through its life cycle. The *erythrocytic* forms are killed with relative ease, whereas the *exoerythrocytic* (hepatic) forms are much harder to kill—and *sporozoites* do not respond to drugs at all. Because of these differences, antimalarial therapy has three separate objectives: (1) treatment of an acute attack (clinical cure), (2) prevention of relapse (radical cure), and (3) prophylaxis (suppressive therapy). Because sporozoites are insensitive to available drugs, drugs cannot prevent primary infection of the liver.

Treatment of an Acute Attack. Clinical cure is accomplished with drugs that are active against erythrocytic forms of the malaria parasite. By eliminating parasites from red blood cells, the erythrocytic cycle is stopped and symptoms cease. For patients with vivax malaria, clinical cure will not prevent relapse, because hypnozoites remain in the liver. However, for patients with falciparum malaria, successful treatment of the acute attack prevents further episodes (until reinfection occurs).

Prevention of Relapse. People infected with *P. vivax* harbor dormant parasites in the liver. In order to prevent relapse, a drug that can kill these hepatic forms must be taken. The use of drugs to eradicate hepatic *P. vivax* is referred to as *radical cure*. Since reinfection by a mosquito bite is a virtual certainty as long as one remains in a malaria-endemic region, radical cure is often postponed until departure from the area.

Prophylaxis. Persons anticipating travel to an area where malaria is endemic should take antimalarial medication for prophylaxis. Although drugs cannot prevent primary infection of the liver, they *can* prevent infection of erythrocytes. Hence, although the parasite may be present, symptoms are avoided. Because prophylactic treatment prevents only symptoms but not invasion of the liver, such treatment is often referred to as *suppressive therapy*.

Nondrug measures can help greatly to prevent infection. Since *Anopheles* mosquitoes only bite between dusk and dawn, clothing that covers as much skin as possible should be worn during this time. A diethyltoluamide (DEET)-containing insect repellent should be applied to skin that remains exposed. Sleeping under mosquito netting that has been impregnated with an insecticide (eg, permethrin) further reduces the risk of a bite.

Drug Selection

Selection of antimalarial drugs is based largely on two factors: (1) the goal of treatment and (2) drug resistance of the causative strain of *Plasmodium*. Drugs of choice for treatment and prophylaxis are discussed below and summarized in Table 98-2.

Treatment of Acute Attacks. For *mild to moderate* malaria, *oral* therapy is employed. Chloroquine is the drug of choice for an acute attack caused by chloroquine-sensitive strains of *P. falciparum* or *P. vivax*. As a rule, a 3-day course of treatment produces clinical cure. For strains of *P. falciparum* or *P. vivax* that are chloroquine resistant, quinine is a drug of first choice, combined with either doxycycline, tetracycline, or clindamycin. Malarone, a fixed-dose combination of atovaquone plus proguanil, is an effective alternative. Mefloquine may also be used, but is considered less desirable owing to concerns about neuropsychiatric effects.

For *severe* malaria caused by *P. falciparum* or *P. vivax*, *parenteral* therapy is required. In the United States, only one drug—quinidine gluconate—is approved by the Food and Drug Administration (FDA) for parenteral use in malaria. When used for severe malaria, IV quinidine should be combined with doxycycline, tetracycline, or clindamycin. An alternative to quinidine, known as artesunate, is recommended by the World Health Organization. Unfortunately, artesunate is not commercially available here, although it can be obtained by special request from the Centers for Disease Control and Prevention (CDC).

Prevention of Relapse. The agent of choice for preventing relapse of vivax malaria is primaquine, a drug that is highly active against the hepatic forms of *P. vivax*. For falciparum malaria, no treatment is needed, since relapse does not occur following clinical cure.

Prophylaxis. Selection of drugs for prophylaxis is based on the drug sensitivity of the plasmodial species found in the

TABLE 98-2 • Drugs of Choice for Malaria*

Therapeutic Objective	<i>Plasmodium falciparum</i>		<i>Plasmodium vivax</i>	
	Chloroquine Sensitive	Chloroquine Resistant	Chloroquine Sensitive	Chloroquine Resistant
Treatment of a moderate attack	Chloroquine	Atovaquone/proguanil OR Artemether/lumefantrine OR Quinine plus either doxycycline, tetracycline, or clindamycin	Chloroquine	Atovaquone/proguanil plus primaquine OR Artemether/lumefantrine plus primaquine OR Quinine plus either doxycycline, tetracycline, or clindamycin plus primaquine OR Mefloquine plus primaquine
Treatment of a severe attack by <i>P. vivax</i> or <i>P. falciparum</i>	Intravenous quinidine gluconate plus either doxycycline, tetracycline, or clindamycin OR Intravenous artesunate [†] followed by either atovaquone/proguanil, doxycycline, or mefloquine			
Relapse prevention	NA [‡]	NA [‡]	Primaquine	Primaquine
Prophylaxis	Chloroquine	Atovaquone/proguanil, doxycycline, or mefloquine	Chloroquine	Atovaquone/proguanil, doxycycline, or mefloquine

*All drugs are given orally except where noted otherwise.

[†]Artesunate is available from the Centers for Disease Control and Prevention.

[‡]Not applicable. Malaria caused by *P. falciparum* does not relapse following successful treatment of the acute attack.

region to which travel is intended. In regions where chloroquine-sensitive strains are endemic, chloroquine is the preferred drug for prophylaxis. In regions of chloroquine resistance, either mefloquine, doxycycline, or atovaquone/proguanil may be used. Recommendations regarding preferred drugs for prophylaxis in specific countries are available online at www.cdc.gov/malaria/travelers/index.html.

PHARMACOLOGY OF THE MAJOR ANTIMALARIAL DRUGS

Table 98-3 lists the major antimalarial drugs, and indicates their activity against hepatic and erythrocytic stages of the parasite. As indicated, for most of these drugs, activity is limited to the erythrocytic stage of the parasite. Only two preparations—primaquine and atovaquone/proguanil—are active against the hepatic stage.

Chloroquine

Actions and Use. Chloroquine [Aralen Phosphate] is the most generally useful antimalarial drug. Because of its high activity against erythrocytic forms of the parasite, chloroquine is the drug of choice for mild to moderate acute attacks caused by sensitive strains of *P. vivax* or *P. falciparum*. Chloroquine is also the drug of choice for prophylaxis (suppressive therapy).

Chloroquine is not active against *exoerythrocytic* forms of the malaria parasite. Hence, the drug is unable to prevent primary infection by *P. vivax* or *P. falciparum*. Nor is it able to

prevent relapse of vivax malaria, which is caused by emergence of dormant hypnozoites.

Several mechanisms have been proposed to explain the lethal effects of chloroquine on erythrocytic malaria parasites. The most likely is that chloroquine prevents the organism from converting heme to nontoxic metabolites. (Heme, a potentially toxic compound, is produced by the parasite as it digests hemoglobin in the host's red blood cells.) Chloroquine concentrates in parasitized erythrocytes, and this may explain the selective actions against erythrocytic forms of *Plasmodium*.

Pharmacokinetics. Chloroquine is rapidly and completely absorbed from the GI tract. A substantial fraction of absorbed drug is deposited in certain tissues, including the lungs, spleen, liver, and kidneys. Slow release from these sites helps maintain therapeutic levels. Hence, when used for prophylaxis, chloroquine can be administered just once a week. Excretion is primarily nonrenal.

Adverse Effects. Because the doses required for prophylaxis are low, and because the higher doses required for treatment are taken only briefly, chloroquine rarely causes serious adverse effects. When employed to treat an acute attack, chloroquine may cause visual disturbances, pruritus, headache, and GI effects (abdominal discomfort, nausea, diarrhea). Gastrointestinal effects can be minimized by taking the drug with meals. Because chloroquine concentrates in the liver, caution is needed in patients with hepatic disease.

Routes of Administration. Chloroquine may be administered orally or IM. Oral therapy is preferred. Intramuscular administration is employed only when emesis precludes oral treatment or when infection is especially severe.

TABLE 98-3 • Activity of Antimalarial Drugs Against Hepatic and Erythrocytic Stages of the Malaria Parasite

Antimalarial Drugs		Target Malarial Stage	
Generic Name	Trade Name	Hepatic	Erythrocytic
Chloroquine	Aralen	No	Yes
Quinine	Qualaquin	No	Yes
Quinidine gluconate		No	Yes
Mefloquine	Lariam	No	Yes
Artemether/lumefantrine	Coartem	No	Yes
Artesunate		No	Yes
Doxycycline	Vibramycin	No	Yes
Clindamycin	Cleocin	No	Yes
Primaquine		Yes	No
Atovaquone/proguanil	Malarone	Yes	Yes

Preparations, Dosage, and Administration. Chloroquine phosphate [Aralen Phosphate] is available in tablets (250 and 500 mg) for oral administration. A parenteral formulation—chloroquine hydrochloride—is no longer available in the United States.

For *prophylaxis* of malaria, the adult dosage is 500 mg once a week. The pediatric dosage is 8.3 mg/kg once a week. Treatment should commence 1 week before expected exposure to malaria and should continue 4 weeks after leaving the endemic region.

To *treat an acute attack*, the adult dosage is 1 gm of chloroquine phosphate initially, followed by doses of 500 mg given 6, 24, and 48 hours later. The pediatric dosage is 17 mg/kg initially, followed by doses of 8 mg/kg given 6, 24, and 48 hours later.

Primaquine

Actions and Use. Primaquine is highly active against hepatic forms of *P. vivax*, but not against erythrocytic forms. The drug is used to eradicate *P. vivax* from the liver, thereby preventing relapse. The mechanism of plasmodial kill has not been determined.

Pharmacokinetics. Primaquine is well absorbed following oral administration. Absorbed drug is rapidly metabolized to products of low antimalarial activity. Metabolites are excreted in the urine.

Adverse Effect: Hemolysis. The most serious and frequent effect is hemolysis, which can develop in patients whose red blood cells are deficient in glucose-6-phosphate dehydrogenase (G6PD). This deficiency is an inherited trait, occurring most commonly in black populations and in darker skinned whites, such as Sardinians, Greeks, Iranians, and Sephardic Jews. When possible, patients suspected of G6PD deficiency should be screened for the trait before treatment. During primaquine therapy, periodic blood counts should be performed. Also, the urine should be monitored (darkening indicates the presence of hemoglobin). If severe hemolysis develops, primaquine should be discontinued.

Preparations, Dosage, and Administration. Primaquine phosphate is supplied in 26.3-mg tablets (containing 15 mg of primaquine base) and as a powder (5, 25, 100, and 500 gm). Dosing should be done with food to minimize GI distress. For radical cure of vivax malaria, the adult dosage is 30 mg of primaquine base daily for 2 weeks. The pediatric dosage is 0.5 mg/kg of primaquine base daily for 2 weeks.

Quinine

At one time, quinine [Qualaquin] was the only drug available to treat malaria. Today, quinine has been largely replaced by more effective and less toxic agents (eg, chloroquine). However, quinine still has an important role: treatment of chloroquine-resistant malaria. Quinine occurs naturally in the bark of the cinchona tree. Commercial preparations are derived from this source.

Actions and Use. Quinine is active against erythrocytic forms of *Plasmodium* but has little effect on sporozoites and hepatic forms. Like chloroquine, quinine concentrates in parasitized red blood cells and may be selective against erythrocytic parasites for this reason. Also like chloroquine, quinine kills plasmodia by causing heme to accumulate within the parasites.

The principal application of quinine is malaria caused by chloroquine-resistant *P. falciparum*. Because quinine is not highly active, adjunctive therapy with another agent is required. Recommended adjuncts are doxycycline, tetracycline, and clindamycin.

Pharmacokinetics. Quinine is well absorbed from the GI tract, even in patients with diarrhea. The drug undergoes hepatic metabolism followed by excretion in the urine. Plasma levels of quinine fall rapidly after stopping treatment.

Adverse Effects. At usual therapeutic doses, quinine frequently causes mild *cinchonism*, a syndrome characterized by tinnitus (ringing in the ears), headache, visual disturbances, nausea, and diarrhea. The prescriber should be notified if these symptoms develop. Because of its adverse effects on vision and hearing, quinine is contraindicated for patients with optic neuritis or tinnitus.

Like primaquine, quinine can cause *hemolysis* in patients with G6PD deficiency, and hence is contraindicated for these people. All patients using the drug should be monitored for hemolytic anemia.

Intravenous administration may cause *hypotension* and *acute circulatory failure*. To minimize risk, IV quinine should be diluted and injected slowly. Patients should be switched to oral medication as soon as possible.

Quinine has *quinidine-like effects on the heart* and must be used cautiously in patients with atrial fibrillation. By

enhancing atrioventricular conduction, quinine can increase passage of atrial impulses to the ventricles, thereby causing a dangerous increase in ventricular rate.

Quinine can cause profound *hypoglycemia*. The mechanism is stimulation of pancreatic beta cells, which causes hyperinsulinemia. Quinine-induced hypoglycemia can be difficult to treat, even with glucose infusions.

Use in Pregnancy. Owing to a risk of fetal harm—namely, deafness from damage to the auditory nerve—quinine was originally classified in FDA Pregnancy Risk Category X. However, the drug is now classified in FDA Pregnancy Risk Category C. Why? Presumably because the risk of fetal harm from malaria is now deemed to outweigh the risk of fetal harm from quinine.

Preparations, Dosage, and Administration. Quinine sulfate (Qualaquin) is available in 324-mg capsules for oral dosing. For chloroquine-resistant falciparum or vivax malaria, the adult dosage is 648 mg every 8 hours for 3 or 7 days. (Duration depends on where the infection was acquired.) The pediatric dosage is 10 mg/kg every 8 hours for 3 or 7 days. In all patients, quinine should be combined with doxycycline, tetracycline, or clindamycin.

Quinidine Gluconate

Quinidine gluconate is the only drug approved by the FDA for parenteral therapy of malaria.* As a result, IV quinidine gluconate is the treatment of choice for severe malaria in the United States. Quinidine is the dextroisomer of quinine and shares that drug's antimalarial mechanism and adverse effects. Because severe malaria can rapidly prove fatal, IV quinidine gluconate should be started immediately. The regimen for adults and children consists of a loading dose (10 mg/kg infused over 1 to 2 hours) followed by a continuous infusion (0.02 mg/kg/min) for at least 24 hours, followed in turn by a switch to oral quinine when the patient can tolerate oral therapy. To enhance antiplasmodial effects, both IV quinidine and PO quinine should be accompanied by doxycycline, tetracycline, or clindamycin.

Intravenous quinidine is more cardiotoxic than quinine. Accordingly, patients require continuous electrocardiographic monitoring and frequent monitoring of blood pressure. The risk of cardiotoxicity is increased by bradycardia and by low levels of potassium or magnesium. The infusion should be temporarily slowed if there is significant widening of the QRS complex or prolongation of the QT interval.

Quinidine may not be immediately available. Why? Because many hospitals no longer keep the drug on hand. Why? Because (1) severe malaria is extremely rare in the United States and (2) there are preferred agents for treating dysrhythmias, the only other use for IV quinidine gluconate (see Chapter 49). In places where the drug is not available, a rapid shipment can be arranged with the manufacturer (Eli Lilly Co).

Mefloquine

Actions and Uses. Mefloquine, formerly available as Lariam, kills erythrocytic forms of *P. vivax* and *P. falciparum*. The mechanism of action has not been determined, but may

be like that of chloroquine. Mefloquine is a drug of choice for prophylaxis of malaria in regions where chloroquine-resistant *P. falciparum* or *P. vivax* is found. The drug is also used to treat acute attacks by these parasites, although neuropsychiatric effects make it a second-choice agent. Resistance to mefloquine, by an unknown mechanism, may develop quickly.

Pharmacokinetics. Mefloquine is well absorbed following oral administration. The drug undergoes metabolism by hepatic CYP3A4 (the 3A4 isozyme of cytochrome P450), followed by excretion in the bile and feces. Mefloquine has a prolonged half-life, ranging from 1 to 4 weeks.

Adverse Effects. Adverse effects are dose related. At the low doses employed for prophylaxis, reactions are generally mild (nausea, dizziness, syncope). However, at the higher doses used to treat an acute attack, more intense reactions may occur, including GI disturbances, nightmares, altered vision, and headache. Some of these effects may be indistinguishable from symptoms of malaria.

Mefloquine can prolong the QT interval, and may thereby pose a risk of severe cardiac dysrhythmias. Accordingly, the drug should be avoided by patients with dysrhythmias or QT prolongation.

Toxicity to the central nervous system is a concern. Mefloquine can cause vertigo, confusion, psychosis, and convulsions. The incidence of these neuropsychiatric effects is about 1 in 13,000 at the low doses used for prophylaxis, but increases to 1 in 250 at the doses used for an ongoing attack. High-dose mefloquine should be avoided by people with epilepsy or psychiatric disorders. Patients who develop psychiatric symptoms (hallucinations, depression, suicidal ideation) should discontinue the drug immediately and contact their prescriber for a substitute (eg, quinine plus doxycycline, atovaquone/proguanil).

Drug Interactions. *Ketoconazole*, a strong inhibitor of CYP3A4, can increase levels of mefloquine, and can thereby increase the risk of dysrhythmias from QT prolongation. Accordingly, ketoconazole should not be administered with mefloquine, or within 15 days of stopping mefloquine.

Rifampin, a strong inducer of CYP3A4, can reduce levels of mefloquine. Therapeutic failure could result. Increased dosage of mefloquine may be required.

Preparations, Dosage, and Administration. Mefloquine is available in 250-mg tablets. All doses should be ingested with at least 8 ounces of water.

For prophylaxis, the adult dosage is 250 mg once a week. The pediatric dosage is 3 to 5 mg/kg once a week. Dosing should begin 1 week prior to travel to an endemic region and should continue 4 weeks after leaving.

The adult dose for acute treatment of *P. falciparum* or *P. vivax* malaria is 750 mg initially followed by 500 mg taken 6 to 12 hours later. The pediatric dosage is 15 mg/kg initially followed by 10 mg/kg taken 6 to 12 hours later.

Artemisinin Derivatives

Artemisinin—obtained by extraction from the sweet wormwood plant, *Artemisia annua*—is highly active against malarial parasites. In fact, artemisinin and its derivatives (eg, artemether, artesunate) are the most effective drugs we have for treating multidrug-resistant falciparum malaria. Although artemisinin derivatives have been used around the world for years, it was not until 2009 that one of these agents—artemether (in combination with lumefantrine)—was approved for use in the United States.

*Another drug—artesunate—is available from the CDC for IV therapy of malaria, but is not yet approved by the FDA.

Artemether/Lumefantrine

Indications and Efficacy. The combination of artemether and lumefantrine, sold as *Coartem*, is indicated for oral therapy of uncomplicated falciparum malaria. The combination is not approved for prophylaxis of falciparum malaria, for treatment of severe falciparum malaria, or for prophylaxis or treatment of vivax malaria. Both artemether and lumefantrine can kill erythrocytic forms of the malarial parasite, but these drugs cannot kill primary or latent hepatic forms. In clinical trials, artemether/lumefantrine has been highly effective against falciparum malaria: 28 days after a short course of treatment, the cure rate is over 95%, even against multidrug-resistant *P. falciparum*. Efficacy against *P. vivax* is less dramatic.

Mechanism of Action. To be effective, artemether must undergo conversion to an active metabolite—*dihydroartemisinin*—which appears to kill plasmodia by releasing free radicals that attack the cell membrane. Kill also requires a high concentration of iron, as found in red blood cells. Lumefantrine probably works like chloroquine, causing death by preventing malaria parasites from converting heme to nontoxic metabolites.

Pharmacokinetics. The kinetics of artemether and lumefantrine differ in three important ways. First, lumefantrine is highly lipophilic, and hence oral absorption is enhanced by dosing with fatty food. Second, absorption of artemether is relatively rapid (plasma levels peak about 2 hours after dosing), whereas absorption of lumefantrine is delayed (plasma levels peak 6 to 8 hours after dosing). Third, the half-life of artemether is short (1.5 hours), whereas the half-life of lumefantrine is prolonged (100 hours).

Why Do We Combine Artemether with Lumefantrine?

Compared with lumefantrine, artemether is much more effective. As a result, when the drugs are administered together, most of the benefit comes from artemether. Why, then, do we combine these drugs? There are two reasons. First, adding lumefantrine *enhances efficacy*. (Since lumefantrine has a much longer half-life than artemether, lumefantrine remains in the body long enough to kill the few parasites not killed by artemether.) Second, adding lumefantrine *helps prevent development of resistance to artemether*. Why? Because the odds of developing resistance to the two drugs simultaneously are much lower than the odds of developing resistance to artemether alone. Accordingly, on January 9, 2006, the World Health Organization requested that all drug companies stop selling artemisinin-only products and replace them with *artemisinin combination therapies* (ACTs). Four ACTs are recommended:

- Artemether/lumefantrine [Coartem]
- Artesunate/mefloquine
- Artesunate/amodiaquine
- Artesunate/pyrimethamine/sulfadoxine

These combinations are indicated only for *treatment* of malaria—not for *prophylaxis*.

Adverse Effects. Artemether/lumefantrine is generally well tolerated. Among *adults*, the most common side effects are headache (56%), anorexia (40%), dizziness (39%), weakness (38%), joint pain (34%), and muscle pain (32%). Among *children*, the most common effects are fever (29%), cough (23%), vomiting (18%), anorexia (13%), and headache (13%).

Lumefantrine may *prolong the QT interval*, thereby posing a risk of serious dysrhythmias. Accordingly, artemether/lumefantrine should not be used by patients with electrolyte disturbances (eg, hypokalemia, hypomagnesemia) or con-

genital prolonged QT syndrome, or by patients using other drugs that prolong the QT interval (eg, quinine, erythromycin, ketoconazole).

Is artemether/lumefantrine safe during pregnancy? Possibly. An observational study involving 500 pregnant women did not show an increase in adverse pregnancy outcomes or teratogenic events. Nonetheless, some experts would avoid artemether/lumefantrine during the first trimester, the time when organogenesis is taking place.

Drug Interactions. Artemether and lumefantrine are metabolized primarily by hepatic CYP3A4. Accordingly, strong inhibitors of CYP3A4 (eg, ketoconazole) could increase levels of both drugs, and might thereby further increase the QT interval.

Lumefantrine inhibits CYP2D6, and hence can raise levels of drugs that are substrates for this enzyme. Accordingly, lumefantrine should not be combined with CYP2D6 substrates, especially ones that can cause QT prolongation (eg, flecainide, imipramine).

Preparations, Dosage, and Administration. Artemether/lumefantrine [Coartem] is supplied in tablets that contain 20 mg artemether and 120 mg lumefantrine. All doses should be taken with fatty food. Doses for children may be crushed and mixed with a small amount of water, and then followed by fatty food, such as milk. One course of treatment consists of 6 doses taken over 3 days.

Adult Dosage. Adults take 24 tablets as follows: 4 tablets initially, 4 tablets 8 hours later, 4 tablets twice daily (morning and evening) on day 2, and 4 tablets twice daily (morning and evening) on day 3.

Pediatric Dosage. Doses for children are given on the same schedule as doses for adults. However, the size of each dose depends on body weight as follows:

- Under 5 kg—not recommended
- 5 to 14.9 kg—1 tablet/dose (6 tablets total)
- 15 to 24.9 kg—2 tablets/dose (12 tablets total)
- 25 to 35 kg—3 tablets/dose (18 tablets total)

Artesunate

Artesunate is an artemisinin derivative with antimalarial actions much like those of artemether. At this time, artesunate, administered IV, is considered the drug of choice for *severe* malaria. Artesunate appears to be more effective than IV quinine, and safer than IV quinidine. The recommended regimen is four doses (2.4 mg/kg each) administered at 0, 12, 24, and 48 hours. To enhance efficacy and minimize development of resistance, dosing with an oral drug (eg, doxycycline, clindamycin, mefloquine) should begin as soon as possible. Artesunate is available only from the CDC, and must be used under the provisions of an Investigational New Drug protocol known as *Intravenous Artesunate for Treatment of Severe Malaria in the United States*. The CDC maintains supplies of artesunate in Atlanta and at eight quarantine stations at major airports around the country.

Atovaquone/Proguanil

Activity and Therapeutic Use. The combination of atovaquone plus proguanil, available as *Malarone*, is highly effective for both the prophylaxis and treatment of malaria caused by chloroquine-resistant plasmodia. Both drugs are active against erythrocytic and exoerythrocytic plasmodial forms, including strains that are resistant to chloroquine, mefloquine, and pyrimethamine/sulfadoxine. In addition to its use in malaria, atovaquone, by itself, has been used for *Pneumocystis pneumonia*.

Mechanism of Action. Atovaquone and proguanil disrupt two separate pathways in pyrimidine synthesis, and thereby suppress DNA replication. Atovaquone has a unique mechanism: disruption of mitochondrial electron

transport. No other antimalarial drug works this way. Proguanil is inactive as administered, but gets converted to cycloguanil, its active form. Like pyrimethamine, cycloguanil inhibits plasmodial dihydrofolate reductase, and thereby prevents activation of folic acid. In the absence of useable folic acid, the parasite is unable to make DNA, RNA, and proteins.

Pharmacokinetics. Absorption of atovaquone is low and variable, but can be greatly enhanced by fatty foods. The drug is 99% bound to plasma proteins, has a prolonged half-life (2 to 3 days), and undergoes excretion unchanged in the feces.

In contrast to atovaquone, proguanil is extensively absorbed, both in the presence and absence of food. The drug concentrates in erythrocytes and undergoes hepatic metabolism followed by renal excretion. Its half-life is 12 to 21 hours.

Adverse Effects and Interactions. The combination of atovaquone plus proguanil is generally well tolerated. When atovaquone is used alone, the principal adverse effect is rash, which occurs in 20% to 40% of patients. Other reactions include nausea, vomiting, diarrhea, headache, fever, and insomnia. When proguanil is used alone, the most common side effects are oral ulceration, GI effects, and headache. In addition, the drug may cause hair loss, urticaria, hematuria, thrombocytopenia, and scaling of the soles and palms. Proguanil is considered safe for use during pregnancy; the safety of atovaquone has not been established. Proguanil appears devoid of significant drug interactions. In contrast, certain drugs, including tetracycline and rifampin, can reduce levels of atovaquone by as much as 50%.

Preparations, Dosage, and Administration. Atovaquone combined with proguanil is available in tablets formulated for adults and for children. Adult-strength tablets [Malarone] contain 250 mg of atovaquone and 100 mg of proguanil. Pediatric-strength tablets [Malarone Pediatric] contain 62.5 mg atovaquone and 25 mg proguanil. To enhance absorption, all tablets should be administered with food or milk.

For prophylaxis of malaria, dosing begins 1 or 2 days before entering an endemic area and continues for 7 days after leaving. The dosage for adults is 1 adult tablet a day. Dosages for children are based on body weight as follows: 11 to 20 kg, 1 pediatric tablet a day; 21 to 30 kg, 2 pediatric tablets once a day; 31 to 40 kg, 3 pediatric tablets once a day; and over 40 kg, 1 adult tablet daily. Atovaquone/proguanil should not be used for prophylaxis during pregnancy.

For treatment of malaria, the dosage for adults is 2 adult tablets twice a day for 3 days. Dosages for children are based on body weight as follows: 11 to 20 kg, 1 adult tablet a day for 3 days; 21 to 30 kg, 2 adult tablets once a day for 3 days; 31 to 40 kg, 3 adult tablets once a day for 3 days; and above 40 kg, 2 adult tablets twice a day for 3 days.

Pyrimethamine/Sulfadoxine

In the past, the combination of pyrimethamine and sulfadoxine, sold as *Fansidar*, was used to treat chloroquine-resistant falciparum malaria. However, because of increasing resistance, the CDC no longer recommends the combination. Fansidar is no longer available in the United States. For more information on this combination, refer to the seventh edition of this text.

Antibacterial Drugs

Tetracyclines. Two members of the tetracycline family—*doxycycline* and *tetracycline*—are used against chloroquine-resistant malaria. Both drugs kill the erythrocytic forms of the malaria parasite, although the rate of kill is slow. Doxycycline is used for prophylaxis and for acute attacks, whereas tetracycline is used for acute attacks only. To treat acute attacks, these drugs are combined with quinine, which acts more quickly than the tetracyclines. All tetracyclines are contraindicated for use by pregnant women and children under 8 years of age. To treat an acute attack, adults take 100 mg of doxycycline twice daily for 7 days, or 250 mg of tetracycline 4 times daily for 7 days. For prophylaxis, adults take 100 mg of doxycycline every day, beginning 2 days before traveling to a malaria-endemic area, and continuing 4 weeks after leaving. The basic pharmacology of the tetracyclines is presented in Chapter 86.

Clindamycin. Clindamycin is active against the erythrocytic forms of the malaria parasite. The drug is used as an adjunct to quinine to treat malaria caused by chloroquine-resistant *P. falciparum* or *P. vivax*. The principal adverse effect is colitis secondary to overgrowth of the bowel with *Clostridium difficile*. The oral dosage for adults and children is 20 mg/kg/day in three divided doses for 7 days.

KEY POINTS

- There are two principal forms of malaria, one caused by *Plasmodium vivax* and the other by *Plasmodium falciparum*.
- Vivax malaria is more common than falciparum malaria, but falciparum malaria is more severe.
- Drug resistance is common with *P. falciparum* but relatively uncommon with *P. vivax*.
- Plasmodia reside in the liver and erythrocytes. Those in the liver are harder to kill.
- Clinical cure of malaria (ie, elimination of symptoms) results from killing plasmodia in erythrocytes.
- Vivax malaria relapses after clinical cure because hypnozoites remain in the liver. Falciparum malaria does not relapse.
- Most antimalarial drugs are active only against the erythrocytic stage of the parasite.
- Chloroquine is the drug of choice for treatment and prophylaxis of malaria caused by chloroquine-sensitive strains of *P. vivax* and *P. falciparum*.
- Atovaquone/proguanil is a treatment of choice for mild to moderate malaria caused by chloroquine-resistant *P. vivax* or *P. falciparum*.
- Intravenous quinidine (combined with doxycycline, tetracycline, or clindamycin) is the treatment of choice for severe malaria caused by *P. vivax* or *P. falciparum*.
- For prophylaxis of chloroquine-resistant malaria, any of three preparations may be used: atovaquone/proguanil, mefloquine, or doxycycline.
- Primaquine, which kills dormant *P. vivax* in the liver, is the drug of choice for preventing relapse of vivax malaria.
- The principal adverse effect of primaquine is hemolytic anemia, which occurs in patients whose red blood cells have a genetically based deficiency of glucose-6-phosphate dehydrogenase.
- The principal adverse effects of quinine are cinchonism (tinnitus, headache, visual disturbances, nausea, vomiting), hemolytic anemia (as with primaquine), and birth defects.
- High therapeutic doses of mefloquine can cause neuropsychiatric reactions, and hence should be avoided in patients with epilepsy or psychiatric disorders.
- Artemisinin derivatives, such as artemether and artesunate, are the most effective drugs for treating falciparum malaria.
- To delay emergence of resistance, artemisinin derivatives should always be combined with another antimalarial drug (eg, artemether/lumefantrine [Coartem]).

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Antiprotozoal Drugs II: Miscellaneous Agents

Protozoal Infections

Drugs of Choice for Protozoal Infections

Iodoquinol
 Metronidazole
 Tinidazole
 Benznidazole
 Nitazoxanide
 Pentamidine
 Suramin
 Melarsoprol
 Eflornithine
 Nifurtimox
 Pyrimethamine
 Sodium Stibogluconate
 Miltefosine
 Amphotericin B

For two reasons—increased world travel by Americans and increased immigration from regions where infectious protozoa are endemic (South America, Asia, Africa)—the incidence of protozoal infection in the United States is rising. The organisms encountered most frequently are *Entamoeba histolytica*, *Trichomonas vaginalis*, and *Giardia lamblia* (also known as *G. duodenalis*). Infections with most other protozoa (eg, *Leishmania* species, trypanosomes) are rare in North America. In approaching the antiprotozoal drugs, we begin with the diseases that protozoa produce, and then discuss the drugs used for treatment.

PROTOZOAL INFECTIONS

Our goal in this section is to describe the major protozoal infections, except for malaria, which is the subject of Chapter 98. Discussion focuses on causative organisms, sites of infection, symptoms, and preferred drug therapy. Causative organisms and drugs of choice are summarized in Table 99-1.

Amebiasis

Amebiasis is an infestation with *Entamoeba histolytica*. The disease affects between 1% and 4% of Americans and about 10% of people worldwide, causing 100,000 deaths each year. The principal site of infestation is the intestine. However, amebas may migrate to other tissues, most commonly the liver, where abscesses may form. Amebiasis is usually asymptomatic. When symptoms are present, the most characteristic are diarrhea, abdominal pain, and weight loss.

Drugs of choice are iodoquinol, paromomycin, metronidazole, and tinidazole. Iodoquinol and paromomycin are only active against amebas residing in the intestine. Metronidazole and tinidazole are active against

amebas that inhabit the intestine, liver, and all other sites. For patients with asymptomatic intestinal infection, therapy with iodoquinol or paromomycin is sufficient. For patients with severe intestinal disease or with liver abscesses, metronidazole or tinidazole is given initially, followed by either iodoquinol or paromomycin.

Iodoquinol, metronidazole, and tinidazole are discussed below. Paromomycin is discussed in Chapter 87.

Cryptosporidiosis

Cryptosporidiosis is caused by *Cryptosporidium parvum*, a protozoan of the subclass Coccidia. *Cryptosporidium parvum* is an obligate intracellular parasite that can infect the intestinal tract of humans, cattle, and other mammals. Transmission is fecal-oral, often by ingesting water contaminated with livestock feces. The infection may also be acquired by animal-to-human contact, person-to-person contact, and ingestion of contaminated fruits or vegetables. Cryptosporidiosis is characterized by diarrhea, abdominal cramps, anorexia, low-grade fever, nausea, and vomiting. For immunocompetent patients, the disease is generally mild and self-limited. However, for those who are severely immunosuppressed (owing to HIV infection, cancer chemotherapy, or other causes), the disease can be prolonged and life threatening, with diarrhea volume up to 20 L/day. Nitazoxanide [Alinia] is the treatment of choice. The drug is very effective in immunocompetent patients, and much less effective in those who are immunosuppressed.

Giardiasis

Giardiasis is an infection with *Giardia lamblia*, also known as *G. duodenalis*. In the United States, giardiasis has a prevalence of 1 in 14,000. Infestation usually occurs by contact with contaminated objects or by drinking contaminated water. The primary habitat of *G. lamblia* is the upper small intestine. Occasionally, organisms migrate to the bile ducts and gallbladder. As many as 50% of affected individuals remain symptom free. However, symptoms that are both unpleasant and uncomfortable can develop. These include profound malaise; heartburn; vomiting; colicky pain after eating; and malodorous belching, flatulence, and diarrhea. The pain associated with giardiasis may mimic that of gallstones, appendicitis, peptic ulcers, or hiatal hernia. Drugs of choice are metronidazole, tinidazole, and nitazoxanide.

Leishmaniasis

The term leishmaniasis refers to infestation by certain protozoal species belonging to the genus *Leishmania*. Worldwide, the incidence of leishmaniasis is estimated at 12 million, with up to 2 million new cases each year. The disease is acquired through the bite of sand flies indigenous to tropical and subtropical regions. In the human host, the parasites take up residence inside cells of the reticuloendothelial system.

Leishmaniasis has three different forms: cutaneous, mucocutaneous, and visceral. The particular form is determined by the species of *Leishmania* involved. The forms of leishmaniasis vary greatly in severity, ranging from mild (cutaneous leishmaniasis) to potentially fatal (visceral leishmaniasis). In cutaneous leishmaniasis, a nodule forms at the site of inoculation; later, this nodule may evolve into an ulcer that is very slow to heal. Mucocutaneous leishmaniasis is characterized by ulceration in the mucosa of the mouth, nose, and pharynx. Symptoms of visceral leishmaniasis include fever, hepatosplenomegaly, liver dysfunction, hypoalbuminemia, pancytopenia, lymphadenopathy, and hemorrhage. Left untreated, visceral disease is frequently fatal. For all forms of leishmaniasis, sodium stibogluconate (given IM or IV) is the traditional treatment of choice. Liposomal amphotericin B (given IV) is an effective alternative. Miltefosine, an oral agent, is highly curative against visceral leishmaniasis, and probably against cutaneous disease. The drug appears reasonably safe and, owing to oral administration, is more convenient than stibogluconate or amphotericin B, both of which are given parenterally. Unfortunately, miltefosine is not available in the United States.

TABLE 99-1 ■ Drugs of Choice for Protozoal Infection

Disease	Causative Protozoan	Drugs of Choice
Amebiasis	<i>Entamoeba histolytica</i>	Iodoquinol, paromomycin, metronidazole, tinidazole
Cryptosporidiosis	<i>Cryptosporidium parvum</i>	Nitazoxanide*
Giardiasis	<i>Giardia lamblia</i>	Metronidazole, tinidazole, nitazoxanide
Leishmaniasis	<i>Leishmania</i> species	Liposomal amphotericin B, sodium stibogluconate, miltefosine [†]
Toxoplasmosis	<i>Toxoplasma gondii</i>	Pyrimethamine plus either sulfadiazine, clindamycin, or atovaquone
Trichomoniasis	<i>Trichomonas vaginalis</i>	Metronidazole, tinidazole
Trypanosomiasis		
American (Chagas' disease)	<i>Trypanosoma cruzi</i>	Nifurtimox, benznidazole [†]
West African (sleeping sickness)	<i>Trypanosoma brucei gambiense</i>	
Early (hemolymphatic) stage		Pentamidine
Late (CNS) stage		Eflornithine, melarsoprol
East African (sleeping sickness)	<i>Trypanosoma brucei rhodesiense</i>	
Early (hemolymphatic) stage		Suramin
Late (CNS) stage		Melarsoprol

*Clearly effective in immunocompetent patients, but of little or no benefit in patients with HIV/AIDS.

[†]Not available in the United States.

Toxoplasmosis

Toxoplasmosis is caused by infection with *Toxoplasma gondii*, a protozoan of the class Sporozoa. The parasite is harbored by many animals and by humans. Infection is acquired most commonly by eating undercooked meat. However, toxoplasmosis may also be congenital. Congenital infection can damage the brain, eyes, liver, and other organs. Extensive disease is usually fatal. In immunocompetent adults, infection is usually asymptomatic, although it may involve the retina. However, in immunocompromised hosts, such as those with HIV/AIDS, the disease may progress to encephalitis and death. The treatment of choice is pyrimethamine plus either sulfadiazine, clindamycin, or atovaquone.

Trichomoniasis

Trichomoniasis is caused by *Trichomonas vaginalis*, a flagellated protozoan. Trichomoniasis is a common disease, affecting about 170 million people worldwide. In the United States, about 8 million new cases occur annually. The usual site of infestation is the genitourinary tract. Parasites may also inhabit the rectum. In females, infection results in vaginitis. In males, infection causes urethritis. The disease is usually transmitted by direct sexual contact but can also be acquired by contact with contaminated objects (eg, dildos). Metronidazole is the traditional drug of choice. However, tinidazole is just as effective and somewhat better tolerated, although much more expensive. Trichomoniasis is discussed further in Chapter 95 (Drug Therapy of Sexually Transmitted Diseases).

Trypanosomiasis

There are two major forms of trypanosomiasis: American trypanosomiasis and African trypanosomiasis. Both forms are caused by protozoal species in the genus *Trypanosoma*.

American Trypanosomiasis (Chagas' Disease). Chagas' disease is caused by infection with *Trypanosoma cruzi*, a flagellated protozoan. The disease is prevalent in South America and the Caribbean, where it affects some 10 million people. In the United States, about 300,000 are affected. The parasites are harbored in the digestive tract of certain blood-sucking bugs, and are transmitted as follows: The bug bites a sleeping person (usually on the face) and also defecates; the parasites, which are contained in the bug's feces, are then forced into the bite wound by rubbing or scratching. An early sign of the disease is swelling and severe inflammation at the site of inoculation. Over time, parasites invade cardiac cells and neurons of the myenteric plexus. Destruction of these cells can cause cardiomyopathy, megacosophagus, and megacolon. Deaths have occurred, usually secondary to cardiac injury. In its early phase, Chagas' disease can be treated with nifurtimox or benznidazole. Unfortunately, these drugs are less effective against chronic infection.

African Trypanosomiasis (Sleeping Sickness). African trypanosomiasis, transmitted by the bite of the tsetse fly, is caused by two subspecies of *Trypanosoma brucei*: *T. brucei gambiense*, which causes West African sleeping sickness, and *T. brucei rhodesiense*, which causes East African sleeping sickness. Disease caused by either subspecies has similar symptoms. Early symptoms, which involve the hemolymphatic system, include fever, lymphadenopathy, hepatosplenomegaly, dyspnea, and tachycardia. Late symptoms, which result from involvement of the central nervous system (CNS), include mental dullness, incoordination, and apathy. As CNS involvement advances, sleep becomes continuous and death may eventually follow. During the early (hemolymphatic) phase of African trypanosomiasis, pentamidine and suramin are the drugs of choice. (Pentamidine is preferred for disease caused by *T. brucei gambiense*, and suramin is preferred for disease caused by *T. brucei rhodesiense*.) During the late (CNS) stage, melarsoprol and eflornithine are drugs of choice. (Either drug can be used against *T. brucei gambiense*, but only melarsoprol is preferred for *T. brucei rhodesiense*.) All four drugs—pentamidine, suramin, eflornithine, and melarsoprol—can produce serious side effects. Treatment is difficult and frequently unsuccessful.

DRUGS OF CHOICE FOR PROTOZOAL INFECTIONS

Iodoquinol

Iodoquinol [Yodoxin] is a drug of choice for asymptomatic intestinal amebiasis. In addition, the drug is employed in conjunction with metronidazole to treat symptomatic intestinal infection and systemic amebiasis. In these last two cases, iodoquinol is administered to eliminate any surviving intestinal parasites after treatment with metronidazole. Very little iodoquinol is absorbed, and hence the drug is not active against systemic amebiasis.

Iodoquinol is generally well tolerated. Mild reactions occur occasionally. These include rash, acne, slight thyroid enlargement, and GI effects (nausea, vomiting, diarrhea, cramps, pruritus ani). Rarely, prolonged therapy at very high doses has caused optic atrophy with permanent loss of vision.

Iodoquinol [Yodoxin] is available in tablets (210 and 650 mg) and as a powder for oral administration, preferably after a meal. The usual adult dosage is 650 mg 3 times a day for 20 days. The dosage for children is 30 to 40 mg/kg/day (given in three divided doses) for 20 days.

Metronidazole

Metronidazole [Flagyl, Protostat, Metric 21], a drug in the nitroimidazole family, is active against several protozoal species, including *E. histolytica*, *G. lamblia*, and *T. vaginalis*. The drug is also active against anaerobic bacteria (see Chapter 91).

Therapeutic Uses. Metronidazole is a drug of choice for symptomatic intestinal amebiasis and systemic amebiasis. Because most of each dose is absorbed in the small intestine, metronidazole concentrations in the colon remain low, allowing amebas there to survive. To kill these survivors, metronidazole is followed by either iodoquinol or paromomycin, amebicidal drugs that achieve high concentrations in the colon.

Metronidazole is a drug of choice for giardiasis, and for trichomoniasis in males as well as females.

Many anaerobic bacteria are sensitive to metronidazole. Antibacterial applications are discussed in Chapter 91.

Mechanism of Action. Metronidazole is a prodrug that remains harmless until converted to a more chemically reactive form, which occurs only in anaerobic cells. Because mammalian cells are aerobic, they cannot activate the drug and hence are largely spared. How does activated metronidazole work? It interacts with DNA, causing strand breakage and loss of helical structure. The resulting impairment of DNA function is thought to be responsible for the drug's antimicrobial and mutagenic actions.

Pharmacokinetics. Metronidazole may be given PO or IV. Blood levels are similar with both routes. Following oral administration, metronidazole is rapidly absorbed and undergoes widespread distribution. The drug crosses membranes with ease, including those of the placenta and the blood-brain barrier. As a result, drug levels in cerebrospinal fluid, saliva, and breast milk equal those in plasma. Extensive metabolism occurs in the liver. Metabolites and unchanged drug are excreted in the urine. The half-life is 8 hours.

Adverse Effects. Metronidazole produces a variety of untoward effects, but these rarely require termination of treatment. The most common side effects are nausea, headache, dry mouth, and an unpleasant metallic taste. Other common effects include stomatitis, vomiting, diarrhea, insomnia, vertigo, and weakness. Harmless darkening of the urine may occur, and patients should be forewarned. Carcinogenic effects have been observed in rodents, but there is no evidence of cancer in humans.

Metronidazole can cause hypersensitivity reactions, including potentially fatal Stevens-Johnson syndrome. There is cross-reactivity with tinidazole, another member of the nitroimidazole family.

Rarely, metronidazole may cause neurologic injury. Some patients have developed convulsive seizures or peripheral neuropathy, characterized by numbness or paresthesia of an extremity. More recently, there have been reports of encephalopathy and aseptic meningitis. If any of these neurologic conditions develop, metronidazole should be withdrawn. In most cases, symptoms quickly resolve.

Use in Pregnancy and Lactation. Metronidazole readily crosses the placenta, and is mutagenic in bacteria. However, experience to date has not shown fetal harm in humans. Nonetheless, it is recommended that metronidazole be avoided during the first trimester, and employed with caution throughout the rest of pregnancy.

Metronidazole can be detected in breast milk up to 72 hours after administration. Ideally, mothers should interrupt breast-feeding until 3 days after the last dose. However, since metronidazole has been given directly to neonates without apparent harm, it would seem that any risk posed by breast feeding is extremely low.

Drug Interactions. Alcohol and Disulfiram. Metronidazole has disulfiram-like actions, and hence can produce unpleasant or dangerous effects if used in conjunction with alcohol. Accordingly, patients must be warned against consuming alcoholic beverages or any product that contains alcohol. The combination of metronidazole with disulfiram itself can cause a psychotic reaction, and hence must be avoided.

Warfarin. Metronidazole inhibits the inactivation of warfarin, an anticoagulant. Dosage of warfarin may need to be reduced during metronidazole therapy and for 8 days after.

Phenytoin, Lithium, Fluorouracil, Cyclosporine, and Tacrolimus. Metronidazole can increase levels of these drugs. Patients should be monitored for signs of toxicity.

Cholestyramine. Cholestyramine can bind with metronidazole in the GI tract, and thereby reduce metronidazole absorption by 20%. Dosing with these drugs should be separated.

Drugs That Affect CYP3A4. Because metronidazole is a substrate for CYP3A4 (the 3A4 isozyme of cytochrome P450), agents that induce the enzyme (eg, phenobarbital, rifampin, phenytoin) can reduce levels of metronidazole, and agents that inhibit the enzyme (eg, ketoconazole) can increase levels of metronidazole.

Preparations, Dosage, and Administration. For treatment of protozoal infections, metronidazole is available in three oral formulations: capsules (375 mg), immediate-release tablets (250 and 500 mg), and extended-release tablets (750 mg). Dosages are as follows:

- *Amebiasis (symptomatic)*—adults, 500 to 750 mg 3 times a day for 7 to 10 days; children, 35 to 50 mg/kg/day in three divided doses for 7 to 10 days. Following treatment with metronidazole, patients are given either iodoquinol for 20 days or paromomycin for 7 days.
- *Trichomoniasis*—adults, 2 gm just once; children, 5 mg/kg 3 times a day for 7 days.
- *Giardiasis*—adults, 250 mg 3 times a day for 5 to 7 days; children, 5 mg/kg 3 times a day for 5 to 7 days.

Tinidazole

Tinidazole [Tindamax] is an antiprotozoal drug similar to metronidazole. Both agents are nitroimidazoles, and both have similar actions, indications, interactions, and adverse effects. Tinidazole has a longer half-life than metronidazole, and hence dosing is more convenient (it's done less often). However, tinidazole is much more expensive. Tinidazole was approved by the Food and Drug Administration (FDA) in 2004, but has been available in other countries for decades.

Therapeutic Uses. Tinidazole is indicated for trichomoniasis in adults, and for giardiasis, intestinal amebiasis, and amebic liver abscesses in adults and children over 3 years of age. Like metronidazole, tinidazole is considered a drug of choice for all of these infections.

Mechanism of Action. Tinidazole has the same mechanism as metronidazole. Both drugs enter anaerobic cells, undergo conversion to a more reactive form, and then interact with DNA to cause strand breakage and loss of helical structure.

Pharmacokinetics. Tinidazole is administered by mouth, and absorption is rapid and complete. Food decreases the rate of absorption but not the extent. Tinidazole crosses membranes with ease, and hence is distributed to virtually all tissues and body fluids. The drug crosses the blood-brain barrier and the placental barrier, and also enters breast milk. Tinidazole is metabolized in the liver by CYP3A4. Excretion is via the bile and urine. Tinidazole has a half-life of 12 to 14 hours, nearly twice that of metronidazole.

Adverse Effects. Adverse effects are much like those of metronidazole, although tinidazole is better tolerated. Gastrointestinal effects—metallic taste, stomatitis, anorexia, dyspepsia, nausea, vomiting—are most common.

Like metronidazole, tinidazole carries a small risk of seizures and peripheral neuropathy. If abnormal neurologic signs develop, tinidazole should be immediately withdrawn. In patients with existing CNS disease, tinidazole should be used with caution.

Like metronidazole, tinidazole can cause hypersensitivity reactions, including potentially fatal Stevens-Johnson syndrome. There is cross-reactivity with metronidazole.

Use in Pregnancy and Lactation. Tinidazole is in FDA Pregnancy Risk Category C: Animal studies show a risk of fetal harm, but no controlled studies have been done in women. Like metronidazole, tinidazole should not be used during the first trimester of pregnancy.

Tinidazole can be detected in breast milk up to 72 hours after administration. Mothers should not breast-feed while taking the drug and for 3 days after.

Drug Interactions. No studies on the interactions of tinidazole with other drugs have been conducted. However, because tinidazole and metronidazole have similar structures and because both are metabolized by CYP3A4, the interactions that occur with metronidazole are likely to occur with tinidazole. Accordingly, tinidazole is likely to potentiate the effects of warfarin, lithium, fluorouracil, cyclosporine, tacrolimus, and injectable phenytoin. Cholestyramine may decrease the absorption of tinidazole, and oxytetracycline may antagonize the effects of tinidazole. Because tinidazole is a substrate for CYP3A4, inducers of the enzyme may reduce the effects of tinidazole, and inhibitors may increase the effects of tinidazole. Like metronidazole, tinidazole has disulfiram-like actions, and hence patients should not consume disulfiram itself, alcoholic beverages, or any product that contains alcohol.

Preparations, Dosage, and Administration. Tinidazole [Tindamax] is available in 250- and 500-mg tablets. For patients unable to swallow tablets whole, the tablets may be crushed and mixed with cherry syrup. To minimize GI distress, tinidazole should be taken with food. Dosages are as follows:

- *Trichomoniasis*—adults, 2 gm once; children age 3 years and older, 50 mg/kg (maximum 2 gm) once
- *Giardiasis*—adults, 2 gm once; children age 3 years and older, 50 mg/kg (maximum 2 gm) once
- *Intestinal amebiasis*—adults, 2 gm once daily for 3 days; children age 3 years and older, 50 mg/kg (maximum 2 gm) once daily for 3 days
- *Amebic liver abscess*—adults, 2 gm once daily for 5 days; children age 3 years and older, 50 mg/kg (maximum 2 gm) once daily for 5 days

Benznidazole

Benznidazole [Rochagan, in Brazil], a relative of metronidazole and tinidazole, is a drug of choice for American trypanosomiasis (Chagas' disease). The adult dosage is 2.5 to 3.5 mg/kg twice daily, and the pediatric dosage is 5 mg/kg twice daily. For adults and children, the duration of treatment is 30 to 90 days. At this time, benznidazole is not available in the United States.

Nitazoxanide

Therapeutic Uses. Nitazoxanide [Alinia] is approved for diarrhea caused by *C. parvum* (in children only) and for diarrhea caused by *G. lamblia* (in children and adults). Although we have other effective drugs for giardiasis (eg, metronidazole, tinidazole), nitazoxanide is our first effective drug for cryptosporidiosis. Unfortunately, when used for *C. parvum* infections, nitazoxanide is only effective in children who are immunocompetent; among children who are immunosuppressed, the drug is no more effective than placebo. Results in immunocompromised adults may be more favorable: When given to adults with cryptosporidiosis and HIV/AIDS, a dosage of 1000 mg twice a day for 14 days cured 67% of patients, compared with 25% of those receiving placebo.

Actions. Nitazoxanide appears to work by disrupting protozoal energy metabolism. Specifically, the drug blocks electron transfer mediated by pyruvate ferredoxin oxidoreductase, and thereby inhibits anaerobic energy metabolism. In addition to its activity against *C. parvum* and *G. lamblia*, nitazoxanide is active against other enteric protozoa (*Isoospora belli* and *Entamoeba histolytica*) as well as some helminths, including *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Trichuris trichiura*, *Taenia saginata*, and *Fasciola hepatica*.

Pharmacokinetics. Nitazoxanide is well absorbed following oral administration. In the blood, the drug undergoes rapid conversion to its active metabolite, tizoxanide, which then undergoes nearly complete (more than 99.9%) binding to plasma proteins. Tizoxanide levels peak between 1 and 4 hours after nitazoxanide administration, and then decline owing to excretion in the urine, bile, and feces.

Adverse Effects. Nitazoxanide is generally well tolerated. In clinical trials, the most common adverse effects were abdominal pain, diarrhea, vomiting, and headache. However, these effects were just as common in subjects taking placebo. In some patients, the drug caused yellow discoloration of the sclerae (whites of the eyes), which resolved following drug withdrawal. Nitazoxanide is in FDA Pregnancy Risk Category B; Animal studies show no evidence of impaired fertility or fetal harm.

Drug Interactions. Because nitazoxanide undergoes extensive protein binding, it might displace other agents that are also highly bound, thereby increasing their effects. Conversely, other highly bound agents could displace nitazoxanide, thereby increasing its effects.

Preparations, Dosage, and Administration. Oral Suspension. Nitazoxanide oral suspension [Alinia] is indicated for diarrhea caused by *G. lamblia* or *C. parvum* in children ages 1 through 11 years, and for diarrhea caused by *G. lamblia* (but not *C. parvum*) in adults. Nitazoxanide is supplied as a pink powder that, when mixed with 48 mL of water, forms a strawberry-flavored, 20-mg/mL suspension. Dosing is done with food. The suspension may be stored at room temperature for 7 days, after which it should be discarded. Dosage depends on age as follows:

- For children ages 12 to 48 months, give 100 mg (5 mL) every 12 hours for 3 days.

- For children ages 4 to 11 years, give 200 mg (10 mL) every 12 hours for 3 days.
- For patients 12 years and older, give 500 mg (25 mL) every 12 hours for 3 days.

Tablets. Nitazoxanide tablets [Alinia] are indicated only for diarrhea caused by *G. lamblia*, but only for patients at least 12 years old. The dosage is 1 tablet (500 mg) every 12 hours for 3 days. Dosing is done with food.

Pentamidine

Target Diseases and Actions. Pentamidine [Pentam 300, Pentacarinat, NebuPent] is highly effective against West African sleeping sickness, a disease caused by *T. brucei gambiense*, and against *Pneumocystis pneumonia* (PCP), a disease caused by the fungus *Pneumocystis jirovecii* (formerly thought to be *Pneumocystis carinii*). The drug has multiple actions, including disrupting the synthesis of DNA, RNA, phospholipids, and proteins. However, we don't know which of these actions is responsible for antiprotozoal effects.

Uses. Pneumocystis Pneumonia. For therapy of PCP, pentamidine is given parenterally and by inhalation. Parenteral therapy is used to treat active PCP. In contrast, inhalational therapy is used to prevent PCP in high-risk HIV-positive patients, defined as patients with (1) a history of one or more episodes of PCP or (2) peripheral CD4 lymphocyte counts below 200 cells/mm³.

West African Sleeping Sickness. Pentamidine is given by IM injection to treat sleeping sickness. However, the drug is not approved by the FDA for this disorder.

Pharmacokinetics. For treatment of active PCP, pentamidine is administered IM or IV. Equivalent blood levels are achieved with both routes. The drug is extensively bound in tissues. Penetration to the brain and cerebrospinal fluid is poor. Between 50% and 65% of each dose is excreted rapidly in the urine. The remaining drug is excreted slowly, over a month or more.

Adverse Effects Associated with Parenteral Pentamidine. Pentamidine can produce serious side effects when given IM or IV. Caution is needed.

Sudden and severe hypotension occurs in about 1% of patients. The fall in blood pressure may cause tachycardia, dizziness, and fainting. To minimize hypotensive episodes, patients should receive the drug while lying down. Blood pressure should be monitored closely.

Hypoglycemia and hyperglycemia have occurred. Hypoglycemia has been associated with necrosis of pancreatic islet cells and excessive insulin levels. The cause of hyperglycemia is unknown. Because of possible fluctuations in glucose levels, blood glucose should be monitored daily.

Intramuscular administration is painful. Necrosis at the injection site followed by formation of a sterile abscess is common.

Some adverse effects can be life threatening when severe. These reactions and their incidences are leukopenia (2.8%), thrombocytopenia (1.7%), acute renal failure (0.5%), hypocalcemia (0.2%), and dysrhythmias (0.2%).

Adverse Effects Associated with Aerosolized Pentamidine. Inhaled pentamidine does not cause the severe effects associated with parenteral dosing. The most common reactions are cough (38%) and bronchospasm (15%). Both reactions are more pronounced in patients with asthma or a history of smoking. Fortunately, these reactions can be controlled with an inhaled bronchodilator, and they rarely necessitate pentamidine withdrawal.

Preparations, Dosage, and Administration. Pneumocystis Pneumonia. Pentamidine isethionate for injection [Pentam 300, Pentacarinat] is supplied in 300-mg, single-dose vials. For treatment of active PCP, the dosage for adults and children is 4 mg/kg IV daily for 2 to 3 weeks. Administration must be done slowly (over 60 minutes).

Pentamidine isethionate aerosol [NebuPent] is used for prophylaxis of PCP in patients with HIV/AIDS. The dosage is 300 mg once every 4 weeks. Administration is performed with a Respigard II nebulizer by Marquest. Solutions should be freshly prepared.

West African Sleeping Sickness. Administration is by IM injection. The dosage for adults and children is 4 mg/kg/day for 7 days.

Suramin

Actions and Uses. Suramin sodium [Germanin, others] is a drug of choice for the early phase of East African trypanosomiasis (sleeping sickness); for the late phase of the disease (CNS involvement), melarsoprol and eflornithine are preferred. Suramin is known to inhibit many trypanosomal enzymes; however, its primary mechanism of action has not been established.

Pharmacokinetics. Suramin is poorly absorbed from the GI tract, and hence must be given parenterally (IV). The drug binds tightly to plasma proteins and remains in the bloodstream for months. Penetration into cells is low. Excretion is renal.

Adverse Effects. Side effects can be severe, and hence treatment should take place in a hospital. Frequent reactions include vomiting, itching, rash, paresthesias, photophobia, and hyperesthesia of the palms and soles. Suramin concentrates in the kidneys and can cause local damage, resulting in the appearance of protein, blood cells, and casts in the urine. If urinary casts are observed, treatment should cease. Rarely, a shock-like syndrome develops after IV dosing. To minimize the risk of this reaction, a small test dose (100 to 200 mg) is given; if there is no severe reaction, full doses may follow.

Preparations, Dosage, and Administration. Suramin sodium [Germanin] is available from the CDC Drug Service. The drug is supplied in 1-gm ampules. Administration is by slow IV infusion. Suramin is unstable, and hence fresh solutions must be made daily. The adult dosage is 1 gm IV on days 1, 3, 7, 14, and 21. The pediatric dosage is 20 mg/kg IV on days 1, 3, 7, 14, and 21. Possible revisions in these dosage recommendations should be obtained from the CDC.

Melarsoprol

Therapeutic Use. Melarsoprol [Arsobal, Mel-B] is a drug of choice for both East African and West African trypanosomiasis (sleeping sickness). The drug is employed during the *late* stage of the disease (ie, after CNS involvement has developed). For earlier stages, suramin and pentamidine are preferred.

Mechanism of Action. Melarsoprol is an organic arsenical compound that reacts with sulfhydryl groups of proteins. Antiparasitic effects result from inactivation of enzymes. This same action appears to underlie the serious toxicity of the drug. Melarsoprol is more toxic to parasites than to humans because it penetrates parasitic membranes more easily than membranes of human cells.

Adverse Effects. Melarsoprol is quite toxic, and hence adverse reactions are common. Frequent effects include hypertension, albuminuria, peripheral neuropathy, myocardial damage, and Herxheimer-type reactions. Reactive encephalopathy develops in 10% of patients, and carries a 15% to 40% risk of death.

Preparations, Dosage, and Administration. Melarsoprol [Arsobal, Mel-B] is administered by slow IV injection. The drug is highly irritating to tissues, and hence avoiding extravasation is important. Because of its toxicity, melarsoprol should be administered in a hospital setting. Melarsoprol is not available commercially, but can be obtained through the CDC Drug Service.

East African Trypanosomiasis. Treatment for adults and children consists of an initial course (2 to 3.6 mg/kg IV daily for 3 days) followed in 7 days by a second course (3.6 mg/kg IV daily for 3 days), followed in 7 days by a third course (3.6 mg/kg IV daily for 3 days).

West African Trypanosomiasis. The dosage for adults and children is 2.2 mg/kg/day for 10 days.

Eflornithine

Actions and Uses. Eflornithine [Ornidyl] is indicated for patients with late-stage African trypanosomiasis (sleeping sickness). The drug is highly effective against *T. gambiense* (West African sleeping sickness), but only variably active against *T. rhodesiense* (East African sleeping sickness). In both cases, benefits derive from irreversible inhibition of ornithine decarboxylase, an enzyme needed for biosynthesis of polyamines, which are required by all cells for division and differentiation. Parasites weakened by eflornithine become highly vulnerable to lethal attack by host defenses. Because cells of the host can readily synthesize more ornithine decarboxylase to replace inhibited enzyme, cells of the host are spared.

As discussed in Chapter 105, eflornithine is also available in a topical formulation, marketed as Vaniqa, for use by women to remove unwanted facial hair.

Pharmacokinetics. Eflornithine is given IV. Once in the blood, the drug is well distributed to body fluids and tissues, including the CNS. Eflornithine has a half-life of 100 minutes and is eliminated largely unchanged in the urine.

Adverse Effects. The most common adverse effects are anemia (48%), diarrhea (39%), and leukopenia (27%). Seizures may occur early in therapy but then subside, despite continued treatment. Because IV administration of eflornithine requires large volumes of fluid, fluid overload may develop over the course of treatment. Eflornithine can also cause hair loss. In fact, the drug is now available for topical use to remove facial hair (see Chapter 105).

Preparations, Dosage, and Administration. Eflornithine is supplied as a concentrated solution (200 mg/mL in 100-mL vials) and must be diluted for IV infusion. To treat West African sleeping sickness in adults and children, the dosage is 100 mg/kg IV 4 times a day for 14 days. Eflornithine is available only from the CDC Drug Service.

Nifurtimox

Therapeutic Use. Nifurtimox [Lampit] is a drug of choice for American trypanosomiasis (Chagas' disease). The drug is most effective in the acute stage of the disease, curing about 80% of patients. Chronic disease is less responsive.

Pharmacokinetics. Nifurtimox is well absorbed from the GI tract and undergoes rapid and extensive metabolism. Metabolites are excreted in the urine.

Adverse Effects. Therapy is prolonged, and significant untoward effects occur often. Gastrointestinal effects (anorexia, nausea, vomiting, abdominal pain) and peripheral neuropathy are especially common. Weight loss resulting from GI disturbance may require treatment cessation. Additional common reactions include rash and CNS effects (memory loss, insomnia, vertigo, headache). In people with a deficiency of glucose-6-phosphate dehydrogenase, nifurtimox can cause hemolysis.

Preparations, Dosage, and Administration. Nifurtimox [Lampit] is supplied in 100-mg tablets. In the United States, the drug is available only from the CDC Drug Service. The adult dosage is 8 to 10 mg/kg/day (in three or four doses) for 90 to 120 days. For young children (ages 1 through 10 years), the dosage is 15 to 20 mg/kg/day (in four doses) for 90 to 120 days. For older children (ages 11 to 16 years), the dosage is 12.5 to 15 mg/kg/day (in four doses) for 90 to 120 days.

Pyrimethamine

Pyrimethamine [Daraprim], combined with sulfadiazine, is the treatment of choice for toxoplasmosis. Pyrimethamine (combined with sulfadoxine) is also used to treat malaria (see Chapter 98). For toxoplasmosis, adult dosing consists of an initial 200-mg oral dose, followed by 50 to 75 mg/day PO for 3 to 6 weeks. The pediatric dosage is 2 mg/kg PO daily for 2 days, followed by 1 mg/kg PO daily for 3 to 6 weeks. For adults and children, each dose of pyrimethamine should be accompanied by 10 to 25 mg of folic acid (to reduce side effects). In addition, the regimen must include sulfadiazine: for adults, 1 to 1.5 gm PO 4 times a day for 3 to 6 weeks; for children, 100 to 200 mg/kg/day for 3 to 6 weeks. The basic pharmacology of pyrimethamine is discussed in Chapter 98.

Sodium Stibogluconate

Sodium stibogluconate [Pentostam] is a drug of choice for leishmaniasis. The mechanism of action is unknown. The drug is poorly absorbed from the GI tract, and hence must be given parenterally (IM or IV). Sodium stibogluconate undergoes little metabolism and is excreted rapidly in the urine. Although severe side effects can occur, the drug is generally well tolerated. The most frequent adverse reactions are muscle pain, joint stiffness, and bradycardia. Changes in the electrocardiogram are common and occasionally precede serious dysrhythmias. Liver and kidney impairment, shock, and sudden death occur rarely. Sodium stibogluconate is supplied in aqueous solution for IM and IV injection. For leishmaniasis, the usual adult and pediatric dosage is 20 mg/kg/day (IM or IV) for 28 days. In the United States, the drug is available only from the CDC Drug Service.

Miltefosine

Miltefosine [Impavido] is the first *oral* agent for leishmaniasis. The drug was originally developed to treat cancer. Antiprotozoal activity wasn't revealed until miltefosine was tested in cancer patients who also had leishmaniasis. The mechanism underlying benefits is unclear. Studies conducted in India indicate that oral miltefosine is both safe and effective for treating visceral leishmaniasis. Preliminary studies indicate the drug is also highly effective against cutaneous disease. Because miltefosine is taken by mouth, rather than by injection, the drug is much more convenient than the alternatives, namely, sodium stibogluconate (administered IM or IV) and amphotericin B (administered IV).

Miltefosine is better tolerated than either sodium stibogluconate or amphotericin B. The most common reactions are vomiting (38%) and diarrhea (20%). Mild hepatotoxicity is seen in some patients, but it resolves during the second week of treatment. Reversible renal damage may also occur. Miltefosine causes fetal abnormalities in laboratory animals, and hence must not be used during pregnancy. Effective contraception is required while taking the drug and for 2 months after.

The recommended dosage for adults and children is 2.5 mg/kg/day (maximum 150 mg/day) for 28 days. At this time, miltefosine is not available in the United States.

Amphotericin B

Amphotericin B is a preferred drug for leishmaniasis. The pharmacology of this drug, and its dosage for leishmaniasis, are presented in Chapter 92.

KEY POINTS

- The principal protozoal infections seen in the United States are trichomoniasis, giardiasis, and amebiasis.
- Metronidazole is a drug of choice for trichomoniasis, giardiasis, and symptomatic or systemic amebiasis.
- Iodoquinol is the drug of choice for asymptomatic amebiasis.
- Patients taking metronidazole should be warned against consuming alcohol because of the risk of a disulfiram-like reaction.

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Ectoparasitic Infestations

Pediculosis (Infestation with Lice)

Scabies (Infestation with Mites)

Pharmacology of the Ectoparasiticides

Permethrin

Pyrethrins Plus Piperonyl Butoxide

Malathion

Benzyl Alcohol

Spinosad

Crotamiton

Lindane

Ivermectin

Ectoparasites are parasites that live on the surface of the host. Most ectoparasites that infest humans live on the skin and hair. Some live on clothing and bedding, moving to the host only to feed. The principal ectoparasites that infest humans are mites and lice. Infestation with lice is known as *pediculosis*. Infestation with mites is known as *scabies*. Both conditions are characterized by intense pruritus (itching). With the exception of ivermectin, all of the drugs used for treatment are topical.

ECTOPARASITIC INFESTATIONS**Pediculosis (Infestation with Lice)**

Pediculosis is a general term referring to infestation with any of several kinds of lice. The types of lice encountered most frequently are *Pediculus humanus capitis* (head louse), *Pediculus humanus corporis* (body louse), and *Phthirus pubis* (pubic or crab louse). Infestation with any of these insects causes pruritus. Infestations with head, body, and pubic lice differ with regard to mode of acquisition and method of treatment.

Head Lice

Head lice are common parasites, infesting 6 to 12 million people annually in the United States, and over 100 million people worldwide. Infestation is most common in children 3 to 11 years old. Head lice reside on the scalp and lay their nits (eggs) on the hair. Adult lice may be difficult to observe. Nits, however, are usually visible. Infestation may be associated with hives, boils, impetigo, and other skin disorders. The head louse is more democratic than the pubic or body louse

and can be found infesting people from all socioeconomic groups. Head lice, which neither jump nor fly, are usually transmitted by head-to-head contact. Transmission by contact with combs, hairbrushes, and hats may also occur, but has not been proven. Because humans are the only host for these obligate parasites, infestation cannot be acquired through contact with pets or any other animals.

According to recommendations from the American Academy of Pediatrics (AAP), released in 2010, the treatments of choice are 1% permethrin and pyrethrins with piperonyl butoxide, provided resistance is not suspected. If resistance is suspected, either malathion, benzyl alcohol, or spinosad should be used. Oral ivermectin can be tried if these other drugs fail, although ivermectin is not approved for killing lice. A few days after drug treatment, dead lice (and remaining live lice) should be removed from the hair with a fine-toothed comb. Eradication of head lice does not require shaving or cutting the hair.

Body Lice

Despite their name, body lice reside not on the body but on clothing. These lice move to the body only to feed. Consequently, body lice are rarely seen on the skin. Rather, they can be found in bed linens and the seams of garments. Transmission of body lice is by contact with infested clothing or bedding. Body lice are relatively uncommon in the United States, where regular laundering precludes infestation. Infestation is most likely among vagrants and other people whose clothes may not be frequently washed. The majority of body lice can be removed from the host simply by removing his or her clothing. Those lice that remain on the body can be killed by applying a pesticide; permethrin and malathion are drugs of choice. Clothing and bedding should be disinfected by washing and drying at high temperature. Oral ivermectin may be tried if topical treatments fail, although ivermectin is not approved for this use.

Pubic Lice

Pubic lice, commonly known as *crabs* (because pubic lice are shaped like crabs), usually reside on the skin and hair of the pubic region. However, pubic lice may also be found on the eyelashes and other places. As a rule, infestation is transmitted through sexual contact. Consequently, crabs are most common among people who have multiple sexual partners. Two preparations—permethrin (1% lotion) and malathion (0.5% lotion)—are drugs of choice for eliminating crabs. Alternatives include pyrethrins with piperonyl butoxide (gel, lotion, shampoo) and oral ivermectin (200 mcg/kg once). Infestation of the eyelashes is treated with petrolatum ophthalmic ointment. Clothing and linen should be disinfected by

washing in very hot water, followed by machine drying at high temperature.

Scabies (Infestation with Mites)

Scabies is caused by infestation with *Sarcoptes scabiei*, an organism known commonly as the itch mite. Irritation results from the female mite burrowing beneath the skin to lay eggs. Burrows may be visible as small ridges or dotted lines. In adults, the most common sites of infestation are the wrists, elbows, nipples, navel, genital region, and webs of the fingers. In children, infestation is most likely on the head, neck, and buttocks. The primary symptom of scabies is pruritus. Itching is most intense just after going to bed. Scratching may result in abrasion and secondary infection. Transmission is usually by direct contact, either sexual or of a less intimate nature. Scabies may also be transmitted through contact with infested linen, towels, or clothing.

Scabies is usually treated with a pesticide-containing lotion or cream. To eradicate mites, the entire body surface must be treated (excluding the face and scalp in adults). To prevent reinfestation, bedding and intimate clothing should be machine washed and dried.

Several drugs can kill mites. *Permethrin* (5% cream formulation) is the drug of choice. This preparation is effective in just one application. *Crotamiton* is a preferred alternative. In addition, there is evidence that a single oral dose (200 mcg/kg) of *ivermectin* [Stromectol] can cure scabies, although the drug is not approved for this use.

PHARMACOLOGY OF ECTOPARASITICIDES

As a rule, ectoparasitic infestations are treated with *topical drugs*. These agents are available in the form of creams, gels, lotions, liquids, and shampoos. Only one ectoparasiticide—ivermectin—is administered orally. Properties of the major ectoparasiticides are summarized in Table 100-1.

Permethrin

Basic Pharmacology

Actions and Uses. Permethrin [Nix, Elimite, Acticin, Kwellada-P⁺] is highly toxic to adult mites and lice, and much less toxic to their ova. Residual activity persists for 2 or more weeks after treatment. The drug kills adult

TABLE 100-1 Preferred Drugs for Mites and Lice

Generic Name	Dosage Form	Trade Name	Uses		Kills Ova	Resistance	Minimum Age/Weight for Use	Adverse Effects
			Pediculosis (Lice)	Scabies (Mites)				
Topical Medications								
Permethrin	1% liquid	Nix, Kwellada-P ⁺	✓		No	Yes	2 months	Occasional: burning, stinging, itching, numbness, pain, rash, erythema, edema
	5% cream	Elimite, Acticin		✓	No	Yes		
Pyrethrins plus piperonyl butoxide	Gel	A-200, Licide, Pronto, RID, R&C ⁺	✓		No	Yes	2 yr	Occasional: allergic reactions; irritation to eyes and mucous membranes following inadvertent contact
	Lotion							
	Mousse							
	Shampoo							
Malathion	0.5% lotion	Ovide	✓		Yes	Not in U.S.	6 yr	Occasional: local irritation. Risk of burns.
Benzyl alcohol	5% lotion	Ulesfia	✓		No	No	6 months	Frequent: eye irritation, contact dermatitis
Crotamiton	10% cream	Eurax		✓	No	Yes		Occasional: rash, conjunctivitis
	10% lotion							
Spirosad	0.9% suspension	Natroba	✓		Yes	No	4 yr	Occasional: Irritation to the scalp and eye
Oral Medication								
Ivermectin	Tablets	Stromectol	✓*	✓*	No	Rare	5 yr/15 kg	Occasional: abdominal pain, headache

*Although ivermectin is effective against mites and lice, the drug is not Food and Drug Administration approved for these infestations.

insects by disrupting nerve traffic, thereby causing paralysis. Since freshly deposited ova do not yet have a nervous system, they are not affected by the drug. In addition to killing mites and lice, permethrin is active against fleas and ticks. The 1% formulation [Nix] is a drug of choice for lice. The 5% formulation [Elimite, Acticin] is the drug of choice for scabies. Permethrin is approved for patients age 2 months and older.

Resistance. Permethrin fails to eradicate head lice in about 5% of patients. Drug resistance is the probable cause. In areas where permethrin resistance is common, treatment with malathion or benzyl alcohol should be tried. Oral ivermectin is an option if these first- and second-line treatments fail.

Pharmacokinetics. Very little (about 2%) of topical permethrin is absorbed. The fraction absorbed is rapidly inactivated and excreted in the urine.

Adverse Effects. Topical permethrin is devoid of serious adverse effects. The drug may cause some exacerbation of the itching, erythema, and edema normally associated with pediculosis. Other reactions include temporary sensations of burning, stinging, and numbness.

Preparations and Administration

Preparations. Permethrin is formulated in two concentrations: (1) a 1% liquid [Nix] used for lice and (2) a 5% cream [Elimite, Acticin] used for scabies.

Administration. Head Lice. Before applying permethrin (1% liquid) to remove head lice, the hair should be washed, rinsed, and towel dried. Permethrin is then applied in an amount sufficient to saturate the hair and scalp. After 10 minutes, permethrin should be removed with a warm-water rinse. Nits should be removed with a fine-toothed comb. Because permethrin is not 100% ovicidal, re-treatment may be needed. The AAP recommends that re-treatment be done in 9 days, rather than 7 days as recommended by the manufacturer. Some patients may require a third treatment, which should be done 9 days after the second.

Scabies. The 5% cream [Elimite, Acticin] is massaged into the skin, from the head to the soles of the feet. After 8 to 14 hours, the cream is removed by washing. Thirty grams is sufficient for the average adult. Only one application is needed.

Pyrethrins Plus Piperonyl Butoxide

The combination of pyrethrins with piperonyl butoxide [A-200, Licide, RID, R&C[®], others] is used to remove pubic lice and head lice. Pyrethrins are the components of this preparation that are toxic to lice. The piperonyl butoxide enhances pyrethrins' action by decreasing the ability of insects to metabolize pyrethrins into inactive products. The combination is active against adult parasites, but not against ova. Pyrethrins undergo little transcutaneous absorption and are one of the safest insecticides available. Principal adverse effects are irritation to the eyes and mucous membranes. Accordingly, contact with these areas should be avoided. Most formulations contain 0.33% pyrethrins and either 2%, 3%, or 4% piperonyl butoxide. Treatment consists of applying the preparation (gel, lotion, shampoo, mousse) to the infested region, followed later by a warm-water rinse. The procedure should be repeated in 9 days, according to the 2010 recommendations of the AAP. Nits are removed by combing. Pyrethrins are approved for patients age 2 years and older.

Malathion

Actions and Uses. Malathion [Ovide] is an organophosphate cholinesterase inhibitor (see Chapter 15). The drug kills lice and their ova. Humans and other mammals are not harmed. Why? Because an enzyme in their blood converts malathion to nontoxic metabolites. The drug is approved for treatment of head lice in patients age 6 years and older. The drug is also used widely as an insecticide.

Adverse Effects and Interactions. The preparation used topically for head lice is devoid of significant adverse effects. Scalp irritation develops occasionally. No systemic toxicity has been reported. Likewise, no drug interactions have been reported. Malathion lotion contains a high concentration of alcohol, and hence presents a risk of fire. Also, the drug smells bad.

Preparations and Administration. Malathion [Ovide] is available in a 0.5% lotion. The preparation is applied to dry hair, gently massaged until the scalp is moist, and allowed to dry naturally. (The lotion is flammable because of its 78% alcohol content. Hence, hair dryers and other sources of heat should be avoided until the alcohol has evaporated.) Package labeling recommends waiting 8 to 12 hours before washing malathion off with shampoo. However, more recent data indicate that malathion is highly effective with only 20 minutes of exposure. Once the drug has been washed away, dead lice and ova can be removed with a fine-toothed comb. Treatment may be repeated in 9 days if needed.

Benzyl Alcohol

Benzyl alcohol [Ulesfia] was approved in 2009 for topical treatment of head lice in patients age 6 months and older. This is the first and only drug that kills lice by suffocation. Specifically, benzyl alcohol prevents adult lice from closing their respiratory spiracles, and then penetrates the spiracles to block the airways. Benzyl alcohol has no effect on ova, and hence must be applied at least twice (to kill lice that hatch after the first application). In clinical trials, two applications, done 1 week apart, eliminated all lice in about 75% of patients. Because benzyl alcohol works by suffocation, resistance is unlikely.

Benzyl alcohol is generally well tolerated. The most common adverse effects are itching (12%), eye irritation (6%), application-site irritation (2%), and application-site numbness (2%). When given to preterm neonates, intravenous benzyl alcohol has caused neonatal gasping syndrome, characterized by metabolic acidosis, gasping respirations, and CNS depression, sometimes progressing to intraventricular hemorrhage and cardiovascular collapse. Whether topical benzyl alcohol can cause this syndrome in very young patients is unknown.

Benzyl alcohol is supplied as a 5% lotion in 8-ounce bottles, costing \$30 each. Dosage depends on hair length. For example, patients with short hair (4 inches or less) need only 1 bottle, whereas patients with longer hair (16 to 22 inches) need 3 to 4 bottles. The lotion should be applied to dry hair, left in place for 10 minutes, and then washed off with water. A second application is required 9 days after the first.

Spinosad

Spinosad [Natroba], approved in 2011, is indicated for topical treatment of head lice in patients age 4 years and older. The drug is highly active against adult lice, and appears to be ovicidal as well. In adult lice, spinosad causes neuronal excitation and involuntary muscle contraction, followed by

paralysis and death. Resistance has not been reported. How spinosad kills ova is unknown.

In clinical trials, spinosad was more effective than permethrin, a drug of choice for head lice. After a single application, spinosad eliminated lice in 94% of patients, whereas only 65% of patients who got permethrin were lice free. Furthermore, with spinosad, most patients needed only one application, whereas with permethrin, the majority needed a second application. Unfortunately, although spinosad is more effective than permethrin, it is also much more expensive.

Spinosad is very safe. The most common reactions are local irritation (1%), and erythema of the scalp (3%) and eyes (2%). Topical spinosad is not absorbed, and hence systemic effects are absent. The drug is classified in Food and Drug Administration (FDA) Pregnancy Risk Category B, indicating there is no evidence of risk in pregnant women.

Spinosad is supplied as a 0.9% suspension for topical use only. The suspension should be applied to dry hair and scalp, left in place for 10 minutes, and then washed off with warm water. The volume applied depends on hair length. Because spinosad is ovicidal, one application is usually sufficient. However, if any lice persist after 7 days, a second application should be made.

Crotamiton

Crotamiton [Eurax] is used to treat *scabies*. The drug is not indicated for pediculosis. This agent has scabidicidal actions and may also relieve itching by an independent mechanism. Mild adverse reactions (dermatitis, conjunctivitis) occur occasionally. Crotamiton is available in cream and lotion formulations.

To treat scabies, crotamiton is massaged into the skin of the entire body, starting with the chin and working down. The head and face are treated only if needed. Special attention should be given to skinfolds and creases. Contact with the eyes, mucous membranes, and any regions of inflammation should be avoided. A second application is made 24 hours after the first. A cleansing bath should be taken 48 hours after the second application. If needed, treatment can be repeated in 7 days.

Lindane

Actions and Uses

Lindane is absorbed through the chitin shell of adult mites and lice and causes death by inducing convulsions. The drug is also lethal to ova. At one time, lindane was a drug of choice for pediculosis and scabies. However, owing to a risk of seizures, the FDA now recommends that lindane be reserved for patients who have not responded to safer drugs (eg, permethrin, malathion). Repeat dosing should be avoided. The drug was banned in California owing to concerns about contamination of drinking water, rivers, and lakes.

Adverse Effects

Irritation. Lindane is irritating to the eyes and mucous membranes. Application to the face should be avoided. If contact occurs, the affected area should be flushed with water.

Convulsions. Lindane can penetrate the intact skin and, if absorbed in sufficient amounts, can cause convulsions. Convulsions can also result from lindane ingestion. Fortunately, convulsions are rare, resulting most often from drug ingestion or from inappropriate administration. If a seizure develops, it can be controlled with an IV barbiturate (eg, phenobarbital) or with IV diazepam.

The risk of convulsions is highest for infants, children, and patients with pre-existing seizure disorders. Risk is also high for the elderly and for all patients who weigh less than 110 pounds (50 kg). Premature infants are especially vulnerable. Why? Because lindane can penetrate their skin with relative ease, and because limited liver function prevents detoxification of absorbed drug.

To reduce seizure risk, the FDA recommends that lindane *not* be used to treat babies, women who are breast-feeding, and anyone who

- Has used lindane in the past few months
- Has not tried a safer medicine for lice or scabies
- Has a seizure disorder or history of seizures
- Has reacted adversely to lindane in the past
- Has open or crusted sores or extensive areas of broken skin in the treatment region
- Has psoriasis or atopic dermatitis

Giving a second treatment too soon after the first increases seizure risk. How soon is too soon? No one knows what a truly safe interval is. Until we know more, patients should wait several months or more before using lindane again.

Preparations and Administration

Preparations. Lindane is available in a 1% lotion and a 1% shampoo.

Administration. Scabies. To treat scabies, a thin layer of lotion is applied to the entire body below the head. No more than 30 gm (1 oz) should be used. The drug is removed by washing 8 to 12 hours later. As a rule, only one application is required. Pruritus may persist because of residual insect products. This itching does not indicate a need for additional treatment. If a second treatment is deemed necessary, several months should elapse before doing it.

Head Lice. To kill head lice and their nits, lindane shampoo (30 to 60 gm) should be worked into dry hair and left in place for no more than 4 minutes. After this, the shampoo should be rinsed off with warm water. Dead nits can be removed with a comb or tweezers. Lindane cream can be employed to treat head lice, but this formulation is less convenient than the shampoo.

Pubic Lice. The affected region should receive the same treatment employed for head lice. Shampoo is preferred to lotion. One treatment is usually sufficient. Sexual partners should be treated concurrently. Lindane should not be used to treat infestation of the eyelashes by the pubic louse. For this condition, petrolatum ophthalmic ointment is employed.

Body Lice. Body lice can be killed by applying a thin layer of lindane ointment or cream to affected areas. The drug should be washed off 8 to 12 hours after application.

Ivermectin

Ivermectin [Stromectol] is the only *oral* medication for ectoparasitic infestations. Although not approved for these applications in the United States, ivermectin is used for them off-label nonetheless. The drug kills parasites by disrupting nerve and muscle function—but does not disrupt nerve or muscle function in the host. Adult parasites are killed within 24 hours of dosing. Ova are not affected. A single dose can be highly effective against both mites and lice. However, since ivermectin does not kill ova, a second dose is usually needed. In one trial, two doses (400 mcg/kg) given 7 days apart were more effective than 0.5% malathion at eradicating treatment-resistant head lice. Similarly, efficacy against mites is excellent: the two-dose cure rate is about 95%. Resistance to ivermectin is uncommon, but has been observed with repeated dosing. At this time, ivermectin is considered a third-choice drug for treating head lice, and hence should be reserved for patients who have not responded to preferred agents.

Significant adverse effects are rare. The most common reactions are headache and abdominal pain, which develop in less than 5% of patients. Owing to concerns of possible neurotoxicity, patients under 15 kg and those under 5 years old should not use this drug. Ivermectin is teratogenic in laboratory animals and should be avoided during pregnancy.

Ivermectin is available in 3-mg tablets that should be taken with water. The dosage for head lice is 200 to 400 mcg/kg, repeated in 7 to 10 days. In the United States, ivermectin is approved only for infestation with two nematodes: *Strongyloides stercoralis* (threadworms) and *Onchocerca volvulus*, the cause of "river blindness." The basic pharmacology of ivermectin and its use against these worm infestations is discussed in Chapter 97 (Anthelmintics).

KEY POINTS

- Pediculosis (infestation with lice) and scabies (infestation with mites) are usually treated with topical drugs. The only exception is ivermectin, which is dosed orally.
- The major topical drugs for pediculosis and scabies have minimal side effects.
- According to the AAP, the drugs of first choice for head lice are 1% permethrin and pyrethrins with piperonyl butoxide. In areas where resistance to these two drugs is common, malathion or benzyl alcohol should be tried instead. Oral ivermectin can be used if these topical treatments fail.
- With the exception of malathion, the major topical drugs for mites and lice have low activity against ova, and

hence a second application is needed (to kill ova that hatched after the first application). For head lice, the AAP recommends a 9-day interval between the first and second treatments.

- Oral ivermectin is highly active against mites and lice, but should be reserved for patients who have not responded to permethrin and other traditional agents.

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Basic Principles of Cancer Chemotherapy

What Is Cancer?

The Growth Fraction and Its Relationship to Chemotherapy

Obstacles to Successful Chemotherapy

Toxicity to Normal Cells

Cure Requires 100% Cell Kill

Absence of Truly Early Detection

Solid Tumors Respond Poorly

Drug Resistance

Heterogeneity of Tumor Cells

Limited Drug Access to Tumor Cells

Strategies for Achieving Maximum Benefits from Chemotherapy

Intermittent Chemotherapy

Combination Chemotherapy

Optimizing Dosing Schedules

Regional Drug Delivery

Major Toxicities of Chemotherapeutic Drugs

Bone Marrow Suppression

Digestive Tract Injury

Nausea and Vomiting

Other Important Toxicities

Making the Decision to Treat

Looking Ahead

As mortality from infectious diseases has declined, thanks to antimicrobial drugs and public health measures, cancer has emerged as the second leading cause of death. The American Cancer Society estimated that 571,950 Americans died from cancer in the year 2011. Only heart disease kills more people. Among women ages 30 to 74, neoplastic diseases lead all other causes of mortality. Among children ages 1 to 14 years, cancer is the leading nonaccidental cause of death. As shown in Table 101-1, among women, the most common cancers are cancers of the breast, lung, colon, and rectum. Among men, the most common cancers are cancers of the prostate, lung, colon, and rectum.

We have three major modalities for treating cancer: *surgery*, *radiation therapy*, and *drug therapy*. Surgery is the most common treatment for *solid* cancers. In contrast, drug therapy is the treatment of choice for *disseminated* cancers (leukemias, disseminated lymphomas, and metastases) along with several localized cancers (eg, choriocarcinoma, testicular carcinoma). Drug therapy also plays an important role as

an adjunct to surgery and irradiation: By suppressing or killing malignant cells that surgery and irradiation leave behind, adjuvant drug therapy can reduce recurrence and improve survival.

Anticancer drugs fall into four major classes: *cytotoxic agents* (ie, drugs that kill cells directly), *hormones and hormone antagonists*, *biologic response modifiers* (eg, immunomodulating agents), and *targeted drugs* (ie, drugs that bind with specific molecules [targets] that promote cancer growth). Of the four classes, the cytotoxic agents are used most often. You should note that the term *cancer chemotherapy* applies *only to the cytotoxic drugs*—it does not apply to the use of hormones, biologic response modifiers, or targeted drugs. In this chapter, our discussion of anticancer drugs pertains almost exclusively to the cytotoxic agents.

The modern era of cancer chemotherapy dates from 1942, the year in which “nitrogen mustards” were first used for cancer. Since the introduction of nitrogen mustards, chemotherapy has made significant advances. For patients with some forms of cancer (Table 101-2), drugs can often be curative. Cancers with a high cure rate include Hodgkin’s disease, testicular cancer, and acute lymphocytic leukemia. For many patients whose cancer is not yet curable, chemotherapy can still be of value, offering realistic hopes of palliation and prolonged life. However, although progress in chemotherapy has been encouraging, the ability to cure most cancers with drugs alone remains elusive. At this time, the major impediment to successful chemotherapy is toxicity of anticancer drugs to normal tissues.

Our principal objectives in this chapter are to examine the major obstacles confronting successful chemotherapy, the strategies being employed to overcome those obstacles, the major toxicities of the chemotherapeutic drugs, and steps that can be taken to minimize drug-induced harm and discomfort. As background for addressing these issues, we begin by discussing (1) the nature of cancer itself and (2) the tissue growth fraction and its relationship to cancer chemotherapy.

WHAT IS CANCER?

In the discussion below, we consider properties shared by neoplastic cells as a group. However, although the discussion addresses cancers in general, be aware that the term *cancer* refers to a large group of disorders and not to a single disease: There are more than 100 different types of cancer, most of which have multiple subtypes. These various forms of cancer differ in clinical presentation, aggressiveness, drug sensitivity, and prognosis. Because of this diversity, treatment must be

TABLE 101-1 • Estimated New Cancer Cases and Deaths, United States, 2011

Type of Cancer	Females		Males	
	New Cases	Deaths	New Cases	Deaths
All types	774,370	271,520	822,300	300,430
Breast	230,480	39,520	2140	450
Prostate			240,890	33,720
Lung and bronchus	106,070	71,340	115,060	85,600
Colon and rectum	39,360	24,130	71,850	25,250
Leukemias and lymphomas	53,590	19,150	66,200	23,250
Endometrium	46,470	8120		
Cervix	11,070	4290		
Ovary	21,990	15,460		
Melanoma of skin	30,220	3040	40,010	5750
Pancreas	21,980	18,300	22,050	19,360
Urinary bladder	17,230	4320	52,020	10,670
Kidney	23,800	4850	37,120	8270
Oral cavity and pharynx	11,690	2440	27,710	5460
Stomach	8400	4080	13,120	6260
Esophagus	3530	2800	13,450	11,910
Liver	6930	6330	19,260	13,260
Brain and other CNS	10,080	5670	12,260	7440
Multiple myeloma	9120	4840	11,400	5770
Thyroid	36,550	980	11,470	760

Data from American Cancer Society. Cancer Facts & Figures 2011. Atlanta: American Cancer Society, 2011.

individualized, based on the specific biology of the cells involved.

Characteristics of Neoplastic Cells

Persistent Proliferation. Unlike normal cells, whose proliferation is carefully controlled, cancer cells undergo unrestrained growth and division. This capacity for persistent proliferation is the most distinguishing property of malignant cells. In the absence of intervention, cancerous tissues will continue to grow until they cause death.

It was once believed that cancer cells divided more rapidly than normal cells and that this excessive rate of division was responsible for the abnormal growth patterns of cancerous tissues. We now know that this concept is not correct. Division of neoplastic cells is not necessarily rapid: Although some cancers are composed of cells that divide rapidly, others are composed of cells that divide slowly. The correct explanation for the relentless growth of tumors is that *malignant cells are unresponsive to the feedback mechanisms that regulate cellular proliferation in healthy tissue*. Hence, cancer cells are able to continue multiplying under conditions that would suppress further growth and division of normal cells.

Invasive Growth. In the absence of malignancy, the various types of cells that compose a tissue remain segregated from one another; cells of one type do not invade territory that belongs to cells of a different type. In contrast, malignant cells are free of the constraints that inhibit invasive growth. As a

result, cells of a solid tumor can penetrate adjacent tissues, thereby allowing the cancer to spread.

Formation of Metastases. Metastases are secondary tumors that appear at sites distant from the primary tumor. Metastases result from the unique ability of malignant cells to break away from their site of origin, migrate to other parts of the body (via the lymphatic and circulatory systems), and then re-implant to form a new tumor.

Immortality. Unlike normal cells, which are programmed to differentiate and eventually die, cancer cells can undergo endless divisions. The underlying cause for this difference is *telomerase*, an enzyme that is active in most cancers, and expressed only rarely in normal cells. Telomerase permits repeated division by preserving *telomeres*—the DNA-protein “caps” found on the end of each chromosome. As normal cells divide and differentiate, their telomeres become progressively shorter. When telomeres have lost a critical portion of their length, the cell is unable to keep on dividing. In cancer cells, telomerase continually adds back lost pieces of the telomere, and thereby preserves or extends telomere length. As a result, cancer cells can divide indefinitely.

Etiology of Cancer

The abnormal behavior of cancer cells results from alterations in their DNA. Specifically, malignant transformation results from a combination of activating *oncogenes* (cancer-causing genes) and inactivating *tumor suppressor genes* (genes that

TABLE 101-2 • Some Cancers for Which Drugs May Be Curative*

Type of Cancer	Drug Therapy†
Hodgkin's lymphoma	Doxorubicin + bleomycin + vinblastine + dacarbazine
Burkitt's lymphoma	Cyclophosphamide + vincristine + methotrexate + doxorubicin + prednisone
Choriocarcinoma	Methotrexate ± leucovorin
Small cell cancer of lung	Etoposide + either cisplatin or carboplatin
Testicular cancer	Cisplatin + etoposide ± bleomycin
Wilms' tumor‡	Dactinomycin + vincristine ± doxorubicin ± cyclophosphamide
Ewing's sarcoma‡	Cyclophosphamide + doxorubicin + vincristine alternating with etoposide + ifosfamide (with mesna)
Acute myeloid leukemia	Daunorubicin + cytarabine + etoposide
Breast cancer‡	Fluorouracil + doxorubicin + cyclophosphamide
Colorectal cancer‡	Fluorouracil + leucovorin + oxaliplatin
Acute lymphocytic leukemia	Vincristine + prednisone + asparaginase + daunorubicin or doxorubicin ± cyclophosphamide

*"Cure" is defined as a 5-year disease-free interval following treatment.

†These are representative regimens. Other regimens may also be highly effective.

‡Chemotherapy is combined with surgery and/or radiotherapy in these cancers.

prevent replication of cells that have become cancerous). These genetic alterations are caused by chemical carcinogens, viruses, and radiation (x-rays, ultraviolet light, radioisotopes). Malignant transformation occurs in three major stages, called initiation, promotion, and progression. These stages suggest that DNA in cancer cells undergoes a series of small modifications, rather than a single large change. This accumulated genetic damage leads to dysregulation of cell division and protection against cell death.

It is important to appreciate that the changes in cellular function caused by malignant transformation are primarily *quantitative* (rather than *qualitative*). That is, malignant transformation simply results in the overexpression or underexpression of the same gene products made by normal cells. As a result, cancer cells employ the same metabolic machinery as normal cells, use the same signaling pathways as normal cells, and express the same surface antigens as normal cells. Nonetheless, even though these changes are only quantitative, they are still sufficient to allow unrestrained growth and avoidance of cell death.

THE GROWTH FRACTION AND ITS RELATIONSHIP TO CHEMOTHERAPY

The growth fraction of a tissue is a major determinant of its responsiveness to chemotherapy. Consequently, before we discuss the anticancer drugs, we must first understand the growth fraction. In order to define the growth fraction, we need to review the cell cycle.

The Cell Cycle

The cell cycle is the sequence of events that a cell goes through from one mitotic division to the next. As shown in Figure 101-1, the cell cycle consists of four major phases,

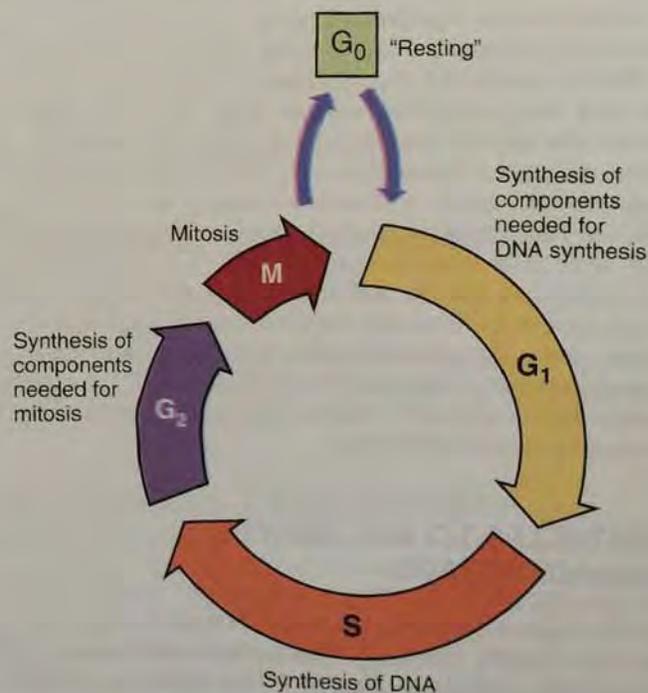


Figure 101-1 • The cell cycle.

named G₁, S, G₂, and M. (The length of the arrows in the figure is proportional to the time spent in each phase.) For our purpose, we can imagine the cycle as beginning with G₁, the phase in which the cell prepares to make DNA. Following G₁, the cell enters S phase, the phase in which DNA synthesis actually takes place. After synthesis of DNA is complete, the cell enters G₂ and prepares for mitosis (cell division). Mitosis

occurs next during M phase. Upon completing mitosis, the resulting daughter cells have two options: they can enter G_1 and repeat the cycle, or they can enter the phase known as G_0 . Cells that enter G_0 become mitotically dormant; they do not replicate and are not active participants in the cycle. Cells may remain in G_0 for days, weeks, or even years. Under appropriate conditions, resting cells may leave G_0 and resume active participation in the cycle.

The Growth Fraction

In any tissue, some cells are going through the cell cycle, whereas others are "resting" in G_0 . The ratio of proliferating cells to G_0 cells is called the *growth fraction*. A tissue with a large percentage of proliferating cells and few cells in G_0 has a *high* growth fraction. Conversely, a tissue composed mostly of G_0 cells has a *low* growth fraction.

Impact of Tissue Growth Fraction on Responsiveness to Chemotherapy

As a rule, *chemotherapeutic drugs are much more toxic to tissues that have a high growth fraction than to tissues that have a low growth fraction*. Why? Because most cytotoxic agents are more active against proliferating cells than against cells in G_0 . Proliferating cells are especially sensitive to chemotherapy because cytotoxic drugs usually act by disrupting either DNA synthesis or mitosis—activities that only proliferating cells carry out. Unfortunately, toxicity of anticancer drugs is not restricted to cancers: These drugs are also toxic to normal tissues that have a high growth fraction (eg, bone marrow, GI epithelium, hair follicles, sperm-forming cells).

Having established the relationship between growth fraction and drug sensitivity, we can apply this knowledge to predict how specific cancers will respond to chemotherapy. As a rule, *the most common cancers*—solid tumors of the breast, lung, prostate, colon, and rectum—have a *low* growth fraction, and hence *respond poorly to cytotoxic drugs*. In contrast, only some rarer cancers—such as acute lymphocytic leukemia, Hodgkin's disease, and certain testicular cancers—have a *high* growth fraction, and hence tend to *respond well to cytotoxic drugs*. In practical terms, this means that the most common cancers, which don't respond well to drugs, must be managed primarily with surgery. Only a few cancers can be managed primarily with drugs.

OBSTACLES TO SUCCESSFUL CHEMOTHERAPY

In this section we consider the major factors that limit success in chemotherapy. Foremost among these is the serious and unavoidable toxicity to normal cells caused by cytotoxic drugs. Other important factors include resistance to chemotherapy and high tumor load (owing to late diagnosis).

Toxicity to Normal Cells

Toxicity to normal cells is a major barrier to successful chemotherapy. Injury to normal cells occurs primarily in tissues where the growth fraction is high; bone marrow, GI epithelium, hair follicles, and germinal epithelium of the testes. Drug-induced injury to each of these tissues is discussed in detail below. For now, let's consider injury to normal cells as a group.

Toxicity to normal cells is dose limiting. That is, dosage cannot exceed an amount that produces the maximally tolerated injury to normal cells. Hence, although very large doses of cytotoxic drugs might be able to produce cure, these doses cannot be given because they are likely to kill the patient.

Why are cytotoxic anticancer drugs so harmful to normal tissues? Because these drugs lack *selective toxicity*. That is, *they cannot kill target cells without also killing other cells with which the target cells are in intimate contact*. We first encountered this concept in Chapter 83 (Basic Principles of Antimicrobial Therapy). As noted there, successful antimicrobial therapy is possible because antimicrobial drugs are highly selective in their toxicity. Penicillin, for example, can readily kill invading bacteria while being virtually harmless to cells of the host. This high degree of selective toxicity stands in sharp contrast to the lack of selectivity displayed by cytotoxic anticancer drugs.

Why have we been unable to develop drugs that selectively kill neoplastic cells? Because neoplastic cells and normal cells are very similar: Differences between them are quantitative rather than qualitative. To make a cytotoxic drug that is truly selective, the target cell must have a biochemical feature that normal cells lack. By way of illustration, let's consider penicillin, which kills bacteria by disrupting the bacterial cell wall. Because our cells don't have a cell wall, penicillin can't hurt us. Unfortunately, we have yet to identify unique biochemical features that would render cancer cells vulnerable to selective attack. Nonetheless, as discussed below under *Looking Ahead*, there is reason for hope: Our expanding knowledge of cancer biology is revealing potential new targets for anticancer drugs. Exploiting these targets may lead to anticancer drugs that are more selective than the drugs we have now.

Cure Requires 100% Cell Kill

To cure a patient of cancer, we must eliminate virtually every malignant cell. Why? Because just one remaining cell can proliferate and cause relapse. For most patients, 100% cell kill cannot be achieved. Factors that make it difficult to achieve complete cell kill include (1) the kinetics of drug-induced cell kill, (2) minimal participation of the immune system in eliminating malignant cells, and (3) disappearance of symptoms before all cancer cells are gone.

Kinetics of Drug-Induced Cell Kill. Killing of cancer cells follows *first-order kinetics*. That is, at any given dose, a drug will kill a *constant percentage* of malignant cells, *regardless of how many cells are actually present*. This means that the dose required to shrink a cancer from 10^3 cells down to 10 cells will be just as big, for example, as the dose required to reduce that cancer from 10^9 cells down to 10^7 cells. Hence, with each successive round of chemotherapy, drug dosage must remain the same, even though the cancer is getting progressively smaller. Accordingly, if treatment is to continue, the patient must be able to tolerate the same degree of toxicity late in therapy that he or she could tolerate when therapy began. For many patients, this is not possible.

Host Defenses Contribute Little to Cell Kill. In contrast to the antimicrobial drugs, anticancer agents receive very little help from host defenses. There are three reasons why. First, because cancer cells express the same surface antigens as normal cells, the immune system generally fails to recognize cancer cells as foreign, and hence appropriate

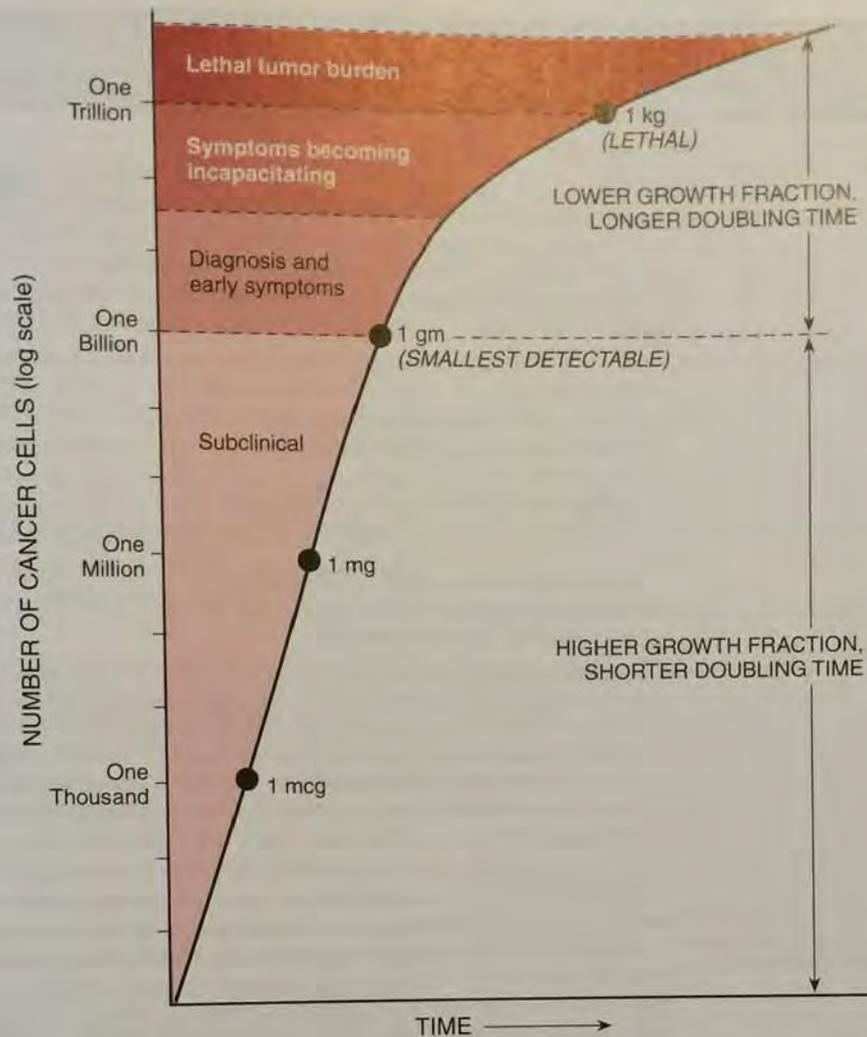


Figure 101-2 ■ Gompertzian tumor growth curve showing the relationship between tumor size and clinical status.

for attack. Second, because many anticancer drugs are immunosuppressants, these agents can seriously compromise immune function. Third, with cancers such as lymphomas and leukemias, which involve components of the immune system, the immune system may be compromised by the cancer itself. Because the immune system offers little help against cancer, anticancer agents must produce cell kill almost entirely on their own.

When Should Treatment Stop? We have no way of knowing when 100% cell kill has been achieved. As a result, there is no definitive method for deciding just when chemotherapy should stop. As indicated in Figure 101-2, symptoms disappear long before the last malignant cell has been eliminated. Once a cancer has been reduced to less than 1 billion cells, it becomes undetectable by usual clinical methods; all signs of disease are absent, and the patient is considered in complete remission. It is obvious, however, that a patient harboring a billion malignant cells is by no means cured. It is also obvious that further chemotherapy is indicated. However, what is not so obvious is just how long therapy should last. Because the patient is already asymptomatic, we have no objective means of determining when to stop treatment. The clinical dilemma is this: If therapy con-

tinues too long, the patient will be needlessly exposed to serious toxicity; conversely, if drugs are discontinued prematurely, relapse will occur.

Absence of Truly Early Detection

Early detection of cancer is rare. Cancer of the cervix, which can be diagnosed with a Papanicolaou (Pap) test, is the primary exception. All other forms of cancer are significantly advanced by the time they have grown large enough for discovery. The smallest detectable cancers are about 1 cm in diameter, have a mass of 1 gm, and consist of about 1 billion cells (see Fig. 101-2). Detection at this stage cannot be considered early.

Late detection has three important consequences. First, by the time the primary tumor is discovered, metastases may have formed. Second, the tumor will be less responsive to drugs than it would have been at an earlier stage (see below). Third, if the cancer has been present for a long time, the patient may be debilitated by the disease, and therefore less able to tolerate treatment.

Even though *truly* early detection is largely impossible, every effort at *relatively* early detection should be made.

TABLE 101-3 ■ American Cancer Society Recommendations for the Early Detection of Breast, Colorectal, Prostate, and Cervical Cancers, 2011

Type of Cancer	Recommendation
Breast	Women age 40 and older should have an <i>annual mammogram</i> and an <i>annual clinical breast examination (CBE)</i> by a healthcare professional. Ideally, the CBE should be conducted before the scheduled mammogram. Women ages 20–39 should have a CBE at least every 3 years. Beginning in their early 20s, women may perform periodic <i>breast self-examinations</i> , in addition to receiving recommended CBEs.
Colon and rectum	Beginning at age 50, men and women should follow one of the 7 examination schedules below: <i>Tests that find cancer and precancerous polyps</i> <ul style="list-style-type: none"> • Flexible sigmoidoscopy (FSIG) every 5 years <i>or</i> • Colonoscopy every 10 years <i>or</i> • Double-contrast barium enema every 5 years <i>or</i> • Computed tomographic colonography (virtual colonoscopy) every 5 years <i>Tests that mainly find cancer</i> <ul style="list-style-type: none"> • Fecal occult blood test (FOBT) every year <i>or</i> • Fecal immunochemical test (FIT) every year <i>or</i> • Stool DNA test (interval uncertain)
Prostate	<i>Prostate-specific antigen (PSA) test, with or without a digital rectal examination.</i> Beginning at age 50, asymptomatic men with a life expectancy of 10 years or longer should be given an opportunity to make an <i>informed</i> decision with their healthcare provider about screening for prostate cancer. Prostate screening should not occur until candidates have been told what is known and what is uncertain about the benefits and limitations of early detection and treatment of prostate cancer.*
Cervix	Cervical cancer screening should begin about 3 years after a woman begins having vaginal intercourse, but no later than age 21. Screening should be done every year (using a conventional Pap test) or every 2 years (using a liquid-based Pap test). At or after age 30, women who have had three normal test results in a row may get screened every 2–3 years (using cervical cytology alone—either conventional or liquid-based Pap tests), or every 3 years (using a human papillomavirus DNA test plus cervical cytology). Women at least 70 years old who have had 3 or more normal Pap tests in the last 10 years (and no abnormal tests in that time) may choose to stop cervical cancer screening, as may women who have had a total hysterectomy.

*There is good evidence that PSA screening can detect early prostate cancer, but little or no evidence that detection improves health outcomes. In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended *against* routine screening for prostate cancer in men age 75 and older, because the available evidence indicated little or no benefit to screening, but a clear potential for harm (incontinence, erectile dysfunction, increased mortality). In 2011, the USPSTF went even further, recommending *against* routine PSA screening for *all* men, citing new evidence that there is a moderate or high certainty that testing has no benefit or that the harms of testing outweigh any benefit. Needless to say, this new recommendation was not greeted with universal praise. Adapted from American Cancer Society. Cancer Facts & Figures 2011. Atlanta: American Cancer Society, 2011.

Why? Because the smaller a cancer is when treatment begins, the better the chances of long-term survival. Hence, even if a cancer has 1 billion cells when it's detected, that's still far better than a gazillion. Accordingly, the American Cancer Society recommends routine testing for several cancers, including cancers of the prostate, breast, uterus, rectum, and colon. Table 101-3 indicates who should be tested, how often, and what test or procedure should be performed. With breast cancer, a yearly mammogram can detect disease before it becomes widely invasive, thereby greatly increasing survival—even though more than a billion cells may be present at the time of discovery. Along with routine testing, patients should be counseled about ways to reduce cancer risk, especially avoiding tobacco and excessive exposure to

ultraviolet radiation, and receiving a human papillomavirus (HPV) vaccination to protect against cervical cancer (see Chapter 68).

Solid Tumors Respond Poorly

As noted, solid tumors have a low growth fraction (high percentage of G_0 cells) and hence generally respond poorly to cytotoxic drugs. There are two reasons for low responsiveness. First, G_0 cells do not perform the activities that most anticancer drugs are designed to disrupt. Second, because G_0 cells are not active participants in the cell cycle, they have time to repair drug-induced damage before it can do them serious harm.

Not all solid tumors are equally unresponsive: As a rule, *large tumors are even less responsive than small ones*. This difference occurs because, as solid tumors increase in size, more of their cells leave the cell cycle and enter G_0 , causing the growth fraction to decline even further. Tumor growth slows, in large part, because blood flow in the tumor core is low, depriving cells of nutrients and oxygen. The decrease in growth fraction in older tumors is a major reason why therapeutic success is more likely when cancers are detected early. Because the rate of growth declines as a tumor gets larger, the tumor growth curve is said to follow *Gompertzian kinetics* (see Fig. 101-2).

The drug sensitivity of a solid tumor can be enhanced by *debulking*. When a solid tumor is reduced by surgery or irradiation, many of the remaining cells leave G_0 and re-enter the cell cycle, thereby increasing their sensitivity to chemotherapy. This phenomenon is known as *recruitment*. Because of recruitment, chemotherapy can be very useful as an adjunct to surgery or irradiation, even though drugs may have been largely ineffective before debulking was done.

Drug Resistance

During the course of chemotherapy, cancer cells can develop resistance to the drugs used against them. Drug resistance can be a significant cause of therapeutic failure. Mechanisms of resistance include reduced drug uptake, increased drug efflux, reduced drug activation, reduced target molecule sensitivity, and increased repair of drug-induced damage to DNA.

One mechanism of resistance—cellular production of a drug transport molecule known as *P-glycoprotein*—can confer *multiple drug resistance* upon cells. As discussed in Chapter 4, P-glycoprotein is a large molecule that spans the cytoplasmic membrane and pumps drugs out of the cell. Induction of P-glycoprotein synthesis during exposure to a single anticancer drug produces cross-resistance to agents in other drug classes. Several drugs, including cyclosporine, have been used investigatively to inhibit the P-glycoprotein pump and reverse multiple drug resistance.

Drug resistance mechanisms, including production of P-glycoprotein, result from a change in DNA. Mutation to a drug-resistant form is a spontaneous event, and is not caused by the anticancer drugs themselves. However, although drugs do not *cause* the mutations that render cells resistant, drugs do *create selection pressure* favoring the drug-resistant mutants. That is, by killing drug-sensitive cells, anticancer agents create a competition-free environment in which drug-resistant mutants can flourish. This is the same phenomenon we encountered in our discussion of antibacterial drugs.

Because the presence of anticancer agents favors the growth of drug-resistant clones, as therapy proceeds, the number of resistant cells will increase. Since patients are usually exposed to drugs over an extended time, therapeutic failure owing to drug resistance is a significant problem. As discussed below, using a combination of drugs can help overcome resistance.

Heterogeneity of Tumor Cells

Tumors do not consist of a single population of identical cells. Rather, owing to ongoing mutation, tumors are composed of subpopulations of dissimilar cells. These subpopulations can

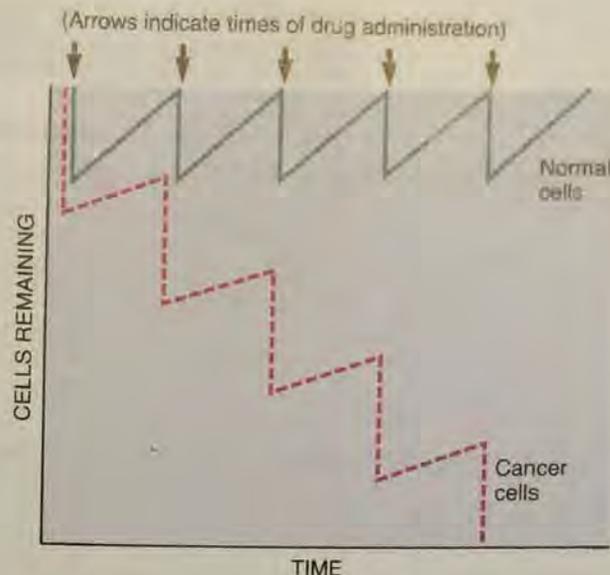


Figure 101-3 ■ Recovery of critical normal cells during intermittent chemotherapy.

Cancer cells and normal cells (eg, cells of the bone marrow) are killed each time cytotoxic drugs are given. In the interval between doses, both types of cells proliferate. Because, in this example, normal cells repopulate faster than the cancer cells, normal cells are able to recover entirely between doses, whereas regrowth of the cancer cells is only partial. As a result, with each succeeding round of treatment, the total number of cancer cells becomes smaller, whereas the number of normal cells remains within a tolerable range. Note that differential loss of malignant cells is possible only if these cells repopulate more slowly than the normal cells. If cancer cells grow back as fast as normal cells do, intermittent chemotherapy will fail.

differ in morphology, growth rate, and metastatic ability. More importantly, they can differ in responsiveness to drugs—primarily because of increased resistance. As tumors age, cellular heterogeneity increases.

Limited Drug Access to Tumor Cells

Because of a tumor's location or blood supply, drugs may have limited access to its cells. Large solid tumors have poor vascularization, especially near the core. Hence, cells within these tumors are difficult for drugs to reach. Similarly, tumors of the central nervous system (CNS) are hard to reach because it is difficult for most anticancer drugs to cross the blood-brain barrier.

STRATEGIES FOR ACHIEVING MAXIMUM BENEFITS FROM CHEMOTHERAPY

Intermittent Chemotherapy

The ultimate goal of chemotherapy is to produce 100% kill of neoplastic cells while causing limited injury to normal tissues—especially the bone marrow and GI epithelium. Intermittent therapy is the primary technique for achieving this goal. When cytotoxic anticancer drugs are administered intermittently, normal cells have time to repopulate between rounds of therapy. However, for this approach to succeed, one

TABLE 101-4 ■ Single-Drug Treatment Versus Combination Chemotherapy

Type of Cancer	Method of Treatment and Drugs Employed	Percentage of Patients with Complete Remission
Acute lymphocytic leukemia of childhood	<i>Single-Drug Therapy</i>	
	Daunorubicin	38
	Prednisone	63
	Vincristine	57
	<i>Combination Chemotherapy</i>	
	Prednisone + vincristine	90
Prednisone + vincristine + daunorubicin	97	
Hodgkin's disease	<i>Single-Drug Therapy</i>	
	Vincristine	<10
	Prednisone	<5
	Procarbazine	<10
	Mechlorethamine	20
	<i>Combination Chemotherapy</i>	
	Vincristine + prednisone + mechlorethamine + procarbazine	81

Data from DeVita VT, Young RC, Canellos GP: Combination versus single agent chemotherapy: A review of the basis for selection of drug treatment of cancer. *Cancer* 35:98, 1975.

TABLE 101-5 ■ Effects of Cyclophosphamide and Vincristine Alone and in Combination

Therapeutic Regimen	Anticancer Effect	Toxicity	
		Neutropenia	Neurotoxicity
Cyclophosphamide	++	++	0
Vincristine	++	0	++
Cyclophosphamide + vincristine	++++	++	++

obvious requirement must be met: *Normal cells must repopulate faster than malignant cells.* If malignant cells grow back faster than normal cells, there can be no reduction in tumor burden between treatment rounds. The successful use of intermittent therapy is depicted in Figure 101-3.

Combination Chemotherapy

Chemotherapy employing a combination of drugs is generally much more effective than chemotherapy with just one drug. Accordingly, most patients are treated with two or more agents.

Benefits of Drug Combinations

Combination chemotherapy offers three advantages: (1) suppression of drug resistance, (2) increased cancer cell kill, and (3) reduced injury to normal cells (at any given level of anticancer effect).

Suppression of Drug Resistance. Drug resistance occurs less frequently with multiple-drug therapy than with single-drug therapy. To understand why, we need to recall that

resistance is acquired through random mutational events. The probability of a cell undergoing two or more mutations, and therefore developing resistance to a combination of drugs, is smaller than the probability of a cell undergoing the single mutation needed for resistance to one drug. Because drug resistance is reduced with combination chemotherapy, the chances of therapeutic success are increased.

Increased Cancer Cell Kill. If we administer several anticancer drugs, each with a different mechanism of action, we will kill more malignant cells than if we use only one drug. Therapeutic effects are enhanced because the combination attacks the cancer in two or more ways, not just one. Greater cell kill is especially likely if a drug-resistant subpopulation of cells is present. The superiority of drug combinations over single-drug therapy is illustrated by the data in Table 101-4.

Reduced Injury to Normal Cells. By using a combination of drugs that do not have overlapping toxicities, we can achieve a greater anticancer effect than we could safely achieve using any of the agents alone. The data in Table 101-5 show why. The table summarizes responses to two drugs—vincristine and cyclophosphamide—when given alone and in combination. Both drugs kill malignant cells, but they act by different mechanisms: cyclophosphamide damages DNA, whereas vincristine blocks mitosis. Furthermore, these drugs have different dose-limiting toxicities: Cyclophosphamide causes *neutropenia*, whereas vincristine causes *neuropathy*. In the table, the intensity of effects is indicated by plus (+) symbols—the more pluses, the more intense the response. With either drug, ++ represents the maximum degree of toxicity that can be tolerated. When administered alone in doses that produce ++ toxicity, each drug produces an anticancer effect of ++ intensity—the greatest therapeutic effect that we can safely achieve with either drug by itself. Now let's consider the effect of combining these drugs, giving

TABLE 101-6 • Effect of Dosing Schedule on Therapeutic Response

Experimental Group	Dosage	Dosing Schedule	Size	Surviving Mice
I	240 mg/kg	1 dose/day*	None	100%
II	15 mg/kg	8 doses/day*	None	100%

*Cytarabine was administered on days 2, 6, 10, and 14 after mice were inoculated with leukemia cells. See text for further details.

each in its maximally tolerated dose. The total anticancer effect of the combination is + + + +, twice the effect that could be achieved safely with either agent alone. Because the toxicities of these agents do not overlap, overall toxicity of the combination remains at a tolerable level—although the patient is now exposed to two kinds of toxicity rather than one.

Guidelines for Drug Selection

From the preceding, we can extract three guidelines for selecting drugs to use in combination: (1) each drug should be effective by itself, (2) each drug should have a different mechanism of action, and (3) the drugs should have minimally overlapping toxicities.

Optimizing Dosing Schedules

The dosing schedule is an important determinant of treatment outcome. The experiment summarized in Table 101-6 provides a dramatic illustration. In this experiment, two groups of mice were inoculated with cancer cells and then treated with cytarabine. Mice in group I received a *single large dose* of cytarabine on days 2, 6, 10, and 14 after being inoculated. The mice in group II were treated on the same days as the mice in group I, but, rather than receiving one large dose of cytarabine, they were given *eight small doses*, one every 3 hours. By the end of the study, all of the group II mice were cured. In stark contrast, all of the group I mice were dead. Since the two groups had the same disease burden and were given the same total dose of the same drug, we must conclude that the life-and-death difference was due to the dosing schedules employed.

To understand these results, we need to know two properties of cytarabine: (1) the drug kills cells by disrupting DNA synthesis, and (2) it undergoes rapid inactivation. Because cytarabine acts by disrupting DNA synthesis, it can only affect cells during S phase. Because the drug is rapidly inactivated, and because many cells will not be in S phase during the short time before inactivation occurs, many cells will escape injury following each dose. The group I mice died because giving just one large dose every 4 days did not maintain active drug in the body for a time sufficient to catch all cancer cells as they cycled through S phase. Because the group II mice received multiple doses over a 24-hour period on each of 4 days, the presence of active drug was sustained. Hence, the chance of cancer cells being in S phase while active drug was present was greatly increased, thereby leading to enhanced cell kill with resultant cure.

The message from this experiment is this: Selection of the right drugs for cancer therapy is only one of the requirements for success; those drugs must also be administered according to schedules that maximize beneficial effects. Dosing sched-

MAJOR TOXICITIES OF CHEMOTHERAPEUTIC DRUGS

The agents used for cancer chemotherapy constitute our most toxic group of medicines. Serious injury occurs most often to tissues with a high growth fraction (bone marrow, GI epithelium, hair follicles, sperm-forming cells). In the discussion below, we consider the more common toxicities of the *cytotoxic* anticancer drugs along with steps that can be taken to minimize harm and discomfort.

Bone Marrow Suppression

Chemotherapeutic drugs are highly toxic to the bone marrow, a tissue with a high proportion of proliferating cells. Myelosuppression reduces the number of circulating neutrophils, platelets, and erythrocytes. Loss of these cells has three major consequences: (1) infection (from loss of neutrophils); (2) bleeding (from loss of platelets); and (3) anemia (from loss of erythrocytes).

Neutropenia

Neutrophils (neutrophilic granulocytes) are white blood cells that play a critical role in fighting infection. In patients with neutropenia (a reduction in circulating neutrophils), both the incidence and severity of infection are increased. Infections that are normally benign (eg, candidiasis) can become life threatening. Infection secondary to neutropenia is one of the most serious complications of chemotherapy.

Regional Drug Delivery

By using special techniques for drug delivery, we can increase drug access to tumors, thereby increasing cell kill and reducing systemic toxicity.

Intra-arterial Delivery. Local intra-arterial infusion can be used to treat solid tumors. This technique has the advantage of establishing a high concentration of drug in the vicinity of the tumor while minimizing toxicity to the rest of the body. Specific routes include carotid artery delivery (for brain tumors) and hepatic artery delivery (for liver metastases). Clearly, intra-arterial therapy is suitable only for localized disease.

Intrathecal Delivery. As noted, many anticancer agents are unable to cross the blood-brain barrier, and therefore cannot reach malignant cells in the CNS. To enhance therapy of CNS cancers, drugs can be administered intrathecally (by injection directly into the subarachnoid space). This technique bypasses the blood-brain barrier, thereby giving drugs better access to cells within the CNS.

Other Specialized Routes. Anticancer agents can be administered via the portal vein to treat liver metastases, and directly into the bladder to treat bladder cancer. Neoplasms located in the pleural and peritoneal cavities can be treated by direct intracavitary drug administration. As discussed in Chapter 102, carmustine, a drug for brain tumors, is available in a wafer that is implanted in the brain to kill cancer cells left behind following surgical removal of a tumor.

With most anticancer drugs, onset of neutropenia is rapid and recovery develops relatively quickly. Neutropenia begins to develop a few days after dosing, and the lowest neutrophil count, called the *nadir*, occurs between days 10 and 14. Neutrophil counts then recover a week or so later. Patients are at highest risk during the nadir. Accordingly, special care should be taken to prevent infection.

With some anticancer drugs, neutropenia is *delayed*. Neutrophil counts begin to fall in 1 to 2 weeks, and reach their nadir between weeks 3 and 4. Full recovery may not occur until after week 7.

Neutrophil counts must be monitored. Normal counts range from 2500 to 7000 cells/mm³. If neutropenia is substantial (absolute neutrophil count below 500/mm³), chemotherapy should be withheld until neutrophil counts return toward normal.

Lack of neutrophils confounds the diagnosis of infection. Why? Because the usual signs of infection (eg, pus, abscesses, infiltrates on the chest x-ray) depend on neutrophils being present. In the absence of neutrophils, *fever* is the principal early sign of infection.

Patients must be their own first line of defense against infection. They should be made aware of their elevated risk of infection and taught how to minimize contagion. They should be informed that fever may be the only indication of infection and instructed to report immediately if fever develops. Because infection is commonly acquired through contact with other people, hospitalized patients should be instructed to refuse direct contact with anyone who has not washed his or her hands in the patient's presence. This rule applies not only to visiting friends and relatives but also to nurses, physicians, and all other hospital staff. The normal flora of the body is a major source of infection; the risk of acquiring an infection with these microbes can be reduced by daily examination and cleansing of the skin and oral cavity.

Hospitalization of the infection-free neutropenic patient is controversial. Some clinicians feel that hospitalization *increases* the risk of acquiring a serious infection. Why? Because hospitals harbor drug-resistant microbes, which can make hospital-acquired (nosocomial) infections especially difficult to treat. Accordingly, these clinicians recommend that neutropenic patients stay at home as long as they remain infection free.

If neutropenic patients *are* hospitalized, every precaution must be taken to prevent nosocomial infection. Patients should be given an isolation room and monitored frequently for fever. Certain foods (eg, salads) abound in pathogenic bacteria and must be avoided.

When a neutropenic patient develops an infection, immediate and vigorous intervention is required. Specimens for culture should be taken to determine the identity and drug sensitivity of the infecting organism. While awaiting reports on the cultures, empiric therapy with IV antibiotics should be instituted. Initial therapy is usually done with a single drug active against *Pseudomonas* and other gram-negative bacteria. Options include ceftazidime, imipenem, and doripenem. If the patient develops sepsis, an aminoglycoside (eg, tobramycin, amikacin) is added. If the patient remains febrile, vancomycin is added (for gram-positive coverage).

Colony-stimulating factors can minimize neutropenia. Three preparations are available: *granulocyte colony-stimulating fac-*

tor (filgrastim), long-acting granulocyte colony-stimulating factor (pegfilgrastim), and *granulocyte-macrophage colony-stimulating factor* (sargramostim). All three drugs act on the bone marrow to enhance granulocyte (neutrophil) production. Colony-stimulating factors can decrease the incidence, magnitude, and duration of neutropenia. As a result, they can decrease the incidence and severity of infection as well as the need for IV antibiotics and hospitalization. The basic pharmacology of these drugs is discussed in Chapter 56.

Thrombocytopenia

Bone marrow suppression can cause thrombocytopenia (a reduction in circulating platelets), thereby increasing the risk of serious bleeding. Bleeding from the nose and gums is relatively common. Bleeding from the gums can be reduced by avoiding vigorous toothbrushing. Drugs that promote bleeding (eg, aspirin, anticoagulants) should not be used. When a mild analgesic is required, acetaminophen, which does not promote bleeding, is preferred to aspirin. For patients with severe thrombocytopenia, platelet infusions are the mainstay of treatment. As discussed in Chapter 56, platelet production can be stimulated with *oprelvekin* [Neumega]. However, owing to limited efficacy and flu-like reactions, oprelvekin is not often used.

Caution should be exercised when performing procedures that might promote bleeding. Intravenous needles should be inserted with special care, and intramuscular injections should be avoided. Blood pressure cuffs should be applied cautiously, because overinflation may cause bruising or bleeding.

Anemia

Anemia is defined as a reduction in the number of circulating erythrocytes (red blood cells). Although anticancer drugs can suppress erythrocyte production, anemia is much less common than neutropenia or thrombocytopenia. Why? Because circulating erythrocytes have a long life span (120 days), which usually allows erythrocyte production to recover before levels of existing erythrocytes fall too low.

If anemia does develop, it can be treated with a transfusion or with erythropoietin (*epoetin alfa* or *darbepoetin alfa*), a hormone that stimulates production of red blood cells. Because transfusions require hospitalization, whereas epoetin can be administered at home, epoetin therapy can spare the patient inconvenience. However, erythropoietin has two huge drawbacks. First, it cannot be used in patients with leukemias and other myeloid malignancies (because it can stimulate proliferation of these cancers). Second, it *shortens* survival in all cancer patients, and hence is indicated only when the treatment goal is *palliation*. Clearly, erythropoietin should not be used when the goal is cure or prolongation of life. The basic pharmacology of erythropoietin is discussed in Chapter 56.

Digestive Tract Injury

The epithelial lining of the GI tract has a very high growth fraction, and hence is exquisitely sensitive to cytotoxic drugs. Stomatitis and diarrhea are common. Severe GI injury can be life threatening.

Stomatitis. Stomatitis (inflammation of the oral mucosa) often develops a few days after the onset of chemotherapy and may persist for 2 or more weeks after treatment has ceased.

Hyperuricemia. Hyperuricemia is defined as an excessive level of uric acid in the blood. Uric acid, a compound with low solubility, is formed by the breakdown of DNA following cell death. Hyperuricemia is especially common following treatment for leukemias and lymphomas (because therapy results in massive cell kill). The major concern with hyperuricemia is injury to the kidneys secondary to deposition of uric acid crystals in renal tubules. The risk of crystal formation can be reduced by increasing fluid intake. In pa-

Reproductive Toxicity. The developing fetus and the germinal epithelium of the testes have high growth fractions. As a result, both are highly susceptible to injury by cytotoxic drugs, especially the alkylating agents. These drugs can interfere with embryogenesis, causing death of the early embryo. They may also cause fetal malformation. Risk is highest during the first trimester, and hence chemotherapy should generally be avoided during this time. However, after 18 weeks of gestation, risk appears to be very low; according to a 2012 report in *Lancet*, exposure during this time does not cause neurologic, cardiac, or any other fetal abnormalities. Drug effects on the ovaries may result in amenorrhea, menopausal symptoms, and atrophy of the vaginal epithelium.

Cytotoxic drugs can cause irreversible sterility in males. Men should be forewarned and counseled about sperm banking. **Allopecia.** Reversible alopecia (hair loss) results from injury to hair follicles. Alopecia can occur with most cytotoxic anticancer drugs. Hair loss begins 7 to 10 days after the onset of treatment and becomes maximal in 1 to 2 months. Regeneration begins 1 to 2 months after the last course of treatment. While alopecia is not dangerous, it is nonetheless very upsetting. In fact, for many cancer patients, alopecia is second only to vomiting as their greatest treatment-related fear. If drugs are expected to cause hair loss, the patient should be forewarned. For patients who choose to wear a hairpiece, one

TABLE 101-7 • Emetogenic Potential of Selected Intravenous Anticancer Drugs

Low	Moderate	Severe
Carmustine	Cisplatin	Cisplatin
Cyclophosphamide (high dose)	Dactinomycin	Dactinomycin
Dacarbazine	Doxorubicin	Doxorubicin
Etoposide	Epirubicin	Epirubicin
Fluorouracil	Idarubicin	Idarubicin
Gemtuzumab	Ifofosfamide	Ifofosfamide
Methotrexate (high dose)	Irinotecan	Irinotecan
Mitomycin	Oxaliplatin	Oxaliplatin
Mitoxantrone		
Paclitaxel		
Pemetrexed		
Topotecan		
Trastuzumab		
Minimal		
Bevacizumab		
Bleomycin		
Busulfan		
Cetuximab		
Fludarabine		
Palifermin		
Rituximab		
Vinorelbine		
Vincristine		
Vinorelbine		

Other Important Toxicities

Allopecia. Reversible alopecia (hair loss) results from injury to hair follicles. Alopecia can occur with most cytotoxic anticancer drugs. Hair loss begins 7 to 10 days after the onset of treatment and becomes maximal in 1 to 2 months. Regeneration begins 1 to 2 months after the last course of treatment. While alopecia is not dangerous, it is nonetheless very upsetting. In fact, for many cancer patients, alopecia is second only to vomiting as their greatest treatment-related fear. If drugs are expected to cause hair loss, the patient should be forewarned. For patients who choose to wear a hairpiece, one

Nausea and vomiting can be reduced by premedication with antiemetics. These drugs offer three benefits: (1) reduction of anticipatory nausea and vomiting, (2) prevention of dehydration and malnutrition secondary to frequent nausea and vomiting, and (3) promotion of compliance with chemotherapy by reducing highly emetogenic drugs consists of choice for patients taking single-drug therapy. The regimen of upregulation [Emend], dexmethasone, and a serotonin antagonist, such as ondansetron [Zofran]. The use of antiemetics for chemotherapy-induced nausea and vomiting is discussed at length in Chapter 80, and in a 2011 guideline titled *Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update*.

You should appreciate that nausea and vomiting associated with chemotherapy are much more severe than with other medications. Hence, whereas these reactions are generally unremarkable with most drugs, they must be considered major and characteristic toxicities of anticancer drugs. The emetogenic potential of several intravenous agents is indicated in Table 101-7.

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Nausea and Vomiting

Nausea and vomiting are common sequelae of cancer chemotherapy. These responses, which result in part from direct stimulation of the chemoreceptor trigger zone, can be both immediate and dramatic, and may persist for hours or even days. In some cases, discomfort is so great as to prompt refusal of further treatment.

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tients with leukemias and lymphomas, in whom hyperuricemia is likely, prophylaxis with *allopurinol* is the standard of care. (As discussed in Chapter 74, allopurinol prevents hyperuricemia by inhibiting xanthine oxidase, an enzyme involved in converting nucleic acids to uric acid.) If hyperuricemia develops despite use of allopurinol, it can be managed with *rasburicase*, an enzyme that catalyzes uric acid degradation (see Chapter 107).

Local Injury from Extravasation of Vesicants. Certain anticancer drugs, known as *vesicants*, are highly chemically reactive. These drugs can cause severe local injury if they make direct contact with tissues. Vesicants are administered IV, usually into a central line (because rapid dilution in venous blood minimizes the risk of injury). When a peripheral line is used, administration is by IV push through a sidearm in a freely flowing IV line. Sites of previous irradiation should be avoided. Extreme care must be exercised to prevent extravasation, because leakage can produce high local concentrations, resulting in prolonged pain, infection, and loss of mobility. Severe injury can lead to necrosis and sloughing, requiring surgical débridement and skin grafting. If extravasation occurs, the infusion should be stopped immediately. Vesicants should be administered only by clinicians specially trained to handle them safely.

Unique Toxicities. In addition to the toxicities discussed above, which generally apply to the cytotoxic drugs as a group, some agents produce unique toxicities. For example, daunorubicin can cause serious injury to the heart, cisplatin can injure the kidneys, and vincristine can injure peripheral nerves. Special toxicities of individual drugs are considered in Chapters 102 and 103.

Carcinogenesis. Along with their other adverse actions, anticancer drugs have one final and ironic toxicity: These drugs, which are used to treat cancer, have caused cancer in some patients. Cancer results from drug-induced damage to

DNA, and is most likely with alkylating agents. Cancers caused by anticancer drugs may take many years to appear and are hard to treat.

MAKING THE DECISION TO TREAT

From the preceding discussion of toxicities, it is clear that cytotoxic anticancer drugs can cause great harm. Given the known dangers of these drugs, we must ask why such toxic substances are given to sick people at all. The answer lies with the primary rule of therapeutics, which states that the benefits of treatment must outweigh the risks. For most patients undergoing chemotherapy, the conditions of this rule are met. That is, although the toxicities of the anticancer drugs can be significant, the potential benefits (cure, prolonged life, palliation) justify the risks. However, the desirability of treating cancer with drugs is not always obvious. There are patients whose chances of being helped by chemotherapy are remote, while the risk of serious toxicity is high. Because the potential benefits for some patients are small and the risks are large, the decision to institute chemotherapy must be made with care.

Before a decision to treat can be made, the patient must be given some idea of the benefits the proposed therapy might offer. Three basic benefits are possible: cure, prolongation of life, and palliation. For treatment to be justified, there should be reason to believe that at least one of these benefits will be forthcoming. If a patient cannot be offered some reasonable hope of cure, prolonged life, or palliation, it would be difficult to justify treatment.

The most important factors for predicting the outcome of chemotherapy are (1) the general health of the patient and (2) the responsiveness of the type of cancer the patient has. General health status is assessed by measuring performance status, frequently using the Karnofsky Performance Scale (Table 101-8). A Karnofsky score of less than 40 indicates the

TABLE 101-8 • Karnofsky Performance Scale

Definition	Percentage	Criteria
Able to carry on normal activity and work; no special care needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or do active work
	60	Requires occasional assistance; able to care for most needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death not imminent
	20	Very sick, hospitalization necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

patient is debilitated and not likely to tolerate the additional stress of chemotherapy. Accordingly, patients with a low Karnofsky rating should not receive anticancer drugs—unless their cancer is known to be especially responsive.

The responsiveness of specific cancers is not highly predictable: Some patients with a specific type of cancer may respond well, but others may not. Nonetheless, we should still try to assess whether treatment is likely to produce cure, palliation, or prolonged life. If a positive outcome is deemed likely, the patient should almost always be treated, even if his or her Karnofsky score is low. In contrast, if a positive outcome is deemed highly unlikely, the patient should be treated only after careful consideration, so as to avoid the discomforts of a course of treatment that has little to offer.

An important requirement for deciding in favor of chemotherapy is that the impact of treatment be measurable. That is, there must be some objective means of determining the cancer's response to drugs. For solid tumors, we should be able to measure a decrease in tumor size (or at least inhibition of further growth). For hematologic cancers, we should be able to measure a decrease in neoplastic cells in blood and bone marrow. If we have no way to measure the response of a cancer, then we have no way of knowing if treatment has done any good. If we cannot determine that drugs are doing something beneficial, there is little justification for giving them.

Clearly, not all patients are candidates for chemotherapy. The decision to institute treatment must be individualized. Patients should be informed as accurately as possible about the potential risks and benefits of the proposed therapy. When the decision to treat is made, it should be the result of collaboration between the patient, family, and physician, and should reflect a conviction on the part of the patient that, within his or her set of values, the potential benefits outweigh the inherent risks.

LOOKING AHEAD

Does the future offer hope of developing drugs that can cure people who can't be cured today? This question can be cautiously answered in the affirmative. There is no theoretical reason to believe that cancers are inherently incapable of cure. On the contrary, there is good reason to believe that cancers are, in fact, curable. New insights into tumor biology are suggesting many new ways to attack cancer cells. Three approaches are especially exciting: cancer vaccines, angiogenesis inhibitors, and telomerase inhibitors. Custom-made vaccines using the patient's own cancer cells can intensify immune attack against the cancer. Angiogenesis inhibitors can block the growth of new blood vessels into solid tumors, thereby starving the tumor. Telomerase inhibitors offer the possibility of a "magic bullet" that can block the endless proliferation of cancer cells, while leaving normal cells unharmed. Other important approaches include inhibition of epidermal growth factor, inhibition of various cellular kinases, and inhibition of oncogenes. These areas of research and others may finally lead to drugs that have the same degree of selective toxicity for cancer as, for example, penicillin G has for gram-positive bacteria. Drugs with this degree of selectivity will offer a cure for neoplastic diseases—and will provide that cure without the toxicities associated with most of today's drugs. It is not completely naïve to believe that such drugs will eventually be available. In the meantime, we can take heart in the progress achieved so far: Drugs like trastuzumab [Herceptin] (for breast cancer) and imatinib [Gleevec] (for chronic myeloid leukemia and GI stromal tumors) are both highly effective and much less toxic than traditional chemotherapeutic agents.

KEY POINTS

- The term *cancer* refers not to a single disorder, but rather to a large group of disorders that differ with respect to clinical presentation, aggressiveness, drug sensitivity, and prognosis.
- Cancer cells are characterized by immortality, persistent proliferation, invasive growth, and the ability to form metastases.
- Cancer can be treated with three basic modalities: surgery, radiation therapy, and drug therapy.
- Agents used for drug therapy fall into two main groups (1) cytotoxic agents and (2) noncytotoxic agents, such as hormones, immunomodulators, and targeted drugs.
- Surgery and/or irradiation are the treatments of choice for most solid tumors.
- Drugs are the treatment of choice for disseminated cancers (leukemias, disseminated lymphomas, widespread metastases). Drugs are also used as adjuvants to surgery and irradiation to kill malignant cells that surgery and irradiation leave behind.
- The cell cycle has four major phases: G_1 , in which cells prepare to synthesize DNA; S, in which cells synthesize DNA; G_2 , in which cells prepare for mitosis (division); and M, in which cells actually divide. Following mitosis, the resulting daughter cells may either enter G_1 and repeat the cycle, or enter G_0 and become mitotically dormant.
- The growth fraction of a tissue is defined as the ratio of proliferating cells to cells in G_0 .
- Tissues with a large percentage of proliferating cells and few cells in G_0 have a high growth fraction. Conversely, tissues composed mostly of G_0 cells have a low growth fraction.
- Cytotoxic anticancer drugs are more toxic to cancers that have a high growth fraction than to cancers that have a low growth fraction. Why? Because cytotoxic anticancer drugs are more active against proliferating cells than against cells in G_0 .
- The most common cancers—solid tumors of the breast, lung, prostate, colon, and rectum—have a low growth fraction, and hence respond poorly to drugs. In contrast, only some rarer cancers—such as acute lymphocytic leukemia, Hodgkin's disease, and certain testicular cancers—have a high growth fraction, and hence tend to respond well.

- To cure a patient of cancer, we must produce 100% cell kill, which is rare with chemotherapy alone.
- Killing of cancer cells follows first-order kinetics. That is, at any given dose, drugs kill a constant *percentage* of malignant cells, regardless of how many cells are present.
- Over the course of chemotherapy, cancer cells often become drug resistant, thereby decreasing the chance of success.
- The purpose of intermittent chemotherapy is to allow normal cells to repopulate between rounds of treatment. However, if the cancer cells repopulate as fast as (or faster than) normal cells, there will be no reduction in tumor burden with each round of treatment, and hence treatment will fail.
- Multidrug chemotherapy is generally much more effective than single-drug therapy. Why? Because combination therapy can (1) suppress drug resistance, (2) increase cell kill, and (3) reduce injury to normal cells (at any given level of anticancer effect).
- Ideally, the drugs used in combination therapy should have (1) different mechanisms of action, (2) minimally overlapping toxicities, and (3) good efficacy when used alone.
- For drugs that act during a specific phase of the cell cycle, selecting the right dosing schedule is critical to success.
- Toxicity to normal tissues is the major obstacle to successful therapy with cytotoxic anticancer drugs.
- Cytotoxic anticancer drugs injure normal tissue because these drugs lack selective toxicity.
- As a rule, serious toxicity occurs to normal tissues that have a high growth fraction (ie, bone marrow, GI epithelium, hair follicles, sperm-forming cells).
- Myelosuppression (toxicity to bone marrow) can reduce the number of neutrophils, platelets, and erythrocytes, thereby posing a risk of infection (from loss of neutrophils), bleeding (from loss of platelets), and anemia (from loss of erythrocytes).
- Loss of neutrophils and platelets during chemotherapy is common; significant loss of erythrocytes is relatively rare, but can happen with certain drugs (eg, cisplatin).
- In patients taking myelosuppressive drugs, neutrophil counts must be monitored. If neutropenia is substantial (absolute neutrophil count below $500/\text{mm}^3$), the next round of chemotherapy should be delayed.
- When a neutropenic patient develops an infection, immediate and vigorous intervention is required. Until lab reports on the identity and drug sensitivity of the infecting organism are available, empiric therapy with IV antibiotics should be instituted.
- Neutropenia can be minimized by treatment with granulocyte colony-stimulating factor (short-acting and long-acting forms) and granulocyte-macrophage colony-stimulating factor—drugs that act on bone marrow to increase neutrophil production.
- Anemia can be managed with erythropoietin, but only in patients who do *not* have myeloid malignancies (eg, leukemia), and then only when the goal is palliation (erythropoietin *shortens* life in all cancer patients, and hence must not be used when the goal is cure or prolongation of life).
- By injuring the epithelial lining of the GI tract, anticancer drugs often cause stomatitis and diarrhea.
- Many anticancer drugs cause moderate to severe nausea and vomiting, in part by stimulating the chemoreceptor trigger zone.
- Nausea and vomiting can be reduced by premedication with antiemetics. The combination of aprepitant, dexamethasone, and ondansetron is especially effective.
- Anticancer drugs often injure hair follicles, thereby causing alopecia (hair loss). Patients who want to wear a hairpiece should select one before hair loss occurs.
- Anticancer drugs can cause fetal malformation and death, primarily in the first trimester. However, after 18 weeks of gestation, risk appears to be very low.
- Anticancer drugs can cause irreversible male sterility. Accordingly, men undergoing chemotherapy should be counseled about possible sperm banking.
- Chemotherapy can cause hyperuricemia as a result of DNA degradation secondary to massive cell death.
- Renal injury from hyperuricemia can be minimized by giving (1) fluids, (2) prophylactic allopurinol (a drug that blocks uric acid formation), and (3) rasburicase (an enzyme that catalyzes uric acid degradation).
- Anticancer drugs with vesicant properties can cause severe local injury if the IV line through which they are being administered becomes extravasated.
- Cancer chemotherapy has three possible benefits: cure, palliation, and prolongation of useful life. For treatment to be justified, at least one of these benefits should be likely.

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Anticancer Drugs I: Cytotoxic Agents

Introduction to the Cytotoxic Anticancer Drugs

Mechanisms of Cytotoxic Action

Cell-Cycle Phase Specificity

Toxicity

Dosage, Handling, and Administration

Alkylating Agents

Shared Properties

Properties of Individual Alkylating Agents

Platinum Compounds

Antimetabolites

Folic Acid Analogs

Pyrimidine Analogs

Purine Analogs

Hypomethylating Agents

Antitumor Antibiotics

Anthracyclines

Nonanthracyclines

Mitotic Inhibitors

Vinca Alkaloids

Taxanes

Other Mitotic Inhibitors

Topoisomerase Inhibitors

Miscellaneous Cytotoxic Drugs

INTRODUCTION TO THE CYTOTOXIC ANTICANCER DRUGS

The cytotoxic agents constitute the largest class of anticancer drugs. As their name implies, these agents act directly on cancer cells to cause their death. The cytotoxic drugs can be subdivided into eight major groups: (1) alkylating agents, (2) platinum compounds, (3) antimetabolites, (4) hypomethylating agents, (5) antitumor antibiotics, (6) mitotic inhibitors, (7) topoisomerase inhibitors, and (8) miscellaneous cytotoxic drugs. I don't discuss each drug in detail. Rather, I focus on selected representative agents. Individual cytotoxic agents are listed in Table 102-1.

Mechanisms of Cytotoxic Action

Table 102-2 summarizes the principal mechanisms by which the cytotoxic anticancer drugs act. As the table shows, most cytotoxic agents disrupt processes related to synthesis of

DNA or its precursors. In addition, some agents (eg, vinblastine, vincristine) act specifically to block mitosis, and one drug—asparaginase—disrupts synthesis of proteins. Note that, with the exception of asparaginase, all of the cytotoxic drugs disrupt processes carried out exclusively by cells that are undergoing replication. As a result, these drugs are most toxic to tissues that have a high growth fraction (ie, a high proportion of proliferating cells).

Cell-Cycle Phase Specificity

As discussed in Chapter 101, the cell cycle is the sequence of events that a cell goes through from one mitotic division to the next. Some anticancer agents, known as *cell-cycle phase-specific drugs*, are effective only during a specific phase of the cell cycle. Other anticancer agents, known as *cell-cycle phase-nonspecific drugs*, can affect cells during any phase of the cell cycle. About half of the cytotoxic anticancer drugs are phase specific, and the other half are phase nonspecific. The phase specificity of individual cytotoxic agents is summarized in Table 102-1.

Cell-Cycle Phase-Specific Drugs. Phase-specific agents are toxic only to cells that are passing through a particular phase of the cell cycle. Vincristine, for example, acts by causing mitotic arrest, and hence is effective only during M phase. Other agents act by disrupting DNA synthesis, and hence are effective only during S phase. Because of their phase specificity, these drugs are toxic only to cells that are active participants in the cell cycle; cells that are “resting” in G_0 will not be harmed. Obviously, if these drugs are to be effective, they must be present as neoplastic cells cycle through the specific phase in which they act. Accordingly, these drugs must be present for an extended time. To accomplish this, phase-specific drugs are often administered by prolonged infusion. Alternatively, they can be given in multiple doses at short intervals over an extended time. Because the dosing schedule is so critical to therapeutic response, phase-specific drugs are also known as *schedule-dependent drugs*.

Cell-Cycle Phase-Nonspecific Drugs. The phase-nonspecific drugs can act during any phase of the cell cycle, including G_0 . Among the phase-nonspecific drugs are the alkylating agents and most antitumor antibiotics. Because phase-nonspecific drugs can injure cells throughout the cell cycle, whereas phase-specific drugs cannot, phase-nonspecific drugs can increase cell kill when combined with phase-specific drugs.

Although the phase-nonspecific drugs can cause biochemical lesions at any time during the cell cycle, *as a rule these drugs are more toxic to proliferating cells than to cells in G_0 .*

TABLE 102-1 ■ Cytotoxic Anticancer Drugs

Generic Name	Trade Name	Cell-Cycle Phase Specificity	Route	Dose-Limiting Toxicity
Alkylating Agents				
Nitrogen Mustards				
Bendamustine	Treanda	Phase nonspecific	IV	Bone marrow suppression, infusion reactions
Chlorambucil	Leukeran	Phase nonspecific	PO	Bone marrow suppression
Cyclophosphamide	generic only	Phase nonspecific	PO, IV	Bone marrow suppression
Ifosfamide	Ifex	Phase nonspecific	IV	Bone marrow suppression and hemorrhagic cystitis
Mechlorethamine	Mustargen	Phase nonspecific	IV, IC, IP	Bone marrow suppression
Melphalan	Alkeran	Phase nonspecific	PO, IV	Bone marrow suppression
Nitrosoureas				
Carmustine	BiCNU, Gliadel	Phase nonspecific	IV, CNS implant	Bone marrow suppression
Lomustine	CeeNU	Phase nonspecific	PO	Bone marrow suppression
Streptozocin	Zanosar	Phase nonspecific	IV	Nephrotoxicity
Others				
Busulfan	Myleran, Busulfex	Phase nonspecific	PO, IV	Bone marrow suppression, pulmonary fibrosis
Temozolomide	Temodar, Temodal ✱	Phase nonspecific	PO	Bone marrow suppression
Platinum Compounds				
Carboplatin	generic only	Phase nonspecific	IV	Bone marrow suppression
Cisplatin	generic only	Phase nonspecific	IV	Nephrotoxicity
Oxaliplatin	Eloxatin	Phase nonspecific	IV	Peripheral neuropathy
Antimetabolites				
Folic Acid Analogs				
Methotrexate	Rheumatrex, Trexall	S-phase specific	IV, IM, PO, IT	Bone marrow suppression, mucositis
Pemetrexed	Alimta	S-phase specific	IV	Bone marrow suppression
Pralatrexate	Folotyn	S-phase specific	IV	Bone marrow suppression, mucositis
Pyrimidine Analogs				
Capecitabine	Xeloda	Kills dividing cells only, mainly in S phase	PO	Bone marrow suppression, diarrhea, hand-and-foot syndrome
Cytarabine	DepoCyt, Tarabine PFS	S-phase specific	IV, subQ, IT	Bone marrow suppression
Floxuridine	FUDR	Kills dividing cells only, mainly in S phase	IA	Bone marrow suppression, oral and GI ulceration
Fluorouracil	Adrucil	Kills dividing cells only, mainly in S phase	IV	Bone marrow suppression, oral and GI ulceration
Gemcitabine	Gemzar	S-phase specific	IV	Bone marrow suppression
Purine Analogs				
Cladribine	Leustatin	Kills dividing cells only, mainly in S phase	IV	Bone marrow suppression
Clofarabine	Clolar	S-phase specific	IV	Bone marrow suppression
Fludarabine	Fludara, Oforta	S-phase specific	PO, IV	Bone marrow suppression
Mercaptopurine	Purinethol	S-phase specific	PO	Bone marrow suppression
Nelarabine	Arranon, Atriance ✱	S-phase specific	IV	Neurotoxicity
Pentostatin	Nipent	S-phase specific	IV	Bone marrow suppression
Thioguanine	Tabloid, Lanvis ✱	S-phase specific	PO, IV	Bone marrow suppression
Hypomethylating Agents				
Azacitidine	Vidaza	S-phase specific	subQ	Bone marrow suppression
Decitabine	Dacogen	S-phase specific	IV	Bone marrow suppression
Antitumor Antibiotics				
Anthracyclines				
Daunorubicin (liposomal)	DaunoXome	Phase nonspecific	IV	Bone marrow suppression, cardiotoxicity
Doxorubicin	Adriamycin, Doxil, Caelyx ✱	Phase nonspecific	IV	Bone marrow suppression, cardiotoxicity

IA = intra-arterial, IC = intracavitary, IM = intramuscular, IP = intrapleural, IT = intrathecal, IV = intravenous, PO = oral, subQ = subcutaneous.

TABLE 102-1 ■ Cytotoxic Anticancer Drugs—cont'd

Generic Name	Trade Name	Cell-Cycle Phase Specificity	Route	Dose-Limiting Toxicity
Antitumor Antibiotics—cont'd				
Anthracyclines—cont'd				
Epirubicin	Ellence	Phase nonspecific, but S and G ₂ most sensitive	IV	Bone marrow suppression, cardiotoxicity
Idarubicin	Idamycin	Phase nonspecific, but S most sensitive	IV	Bone marrow suppression, cardiotoxicity
Mitoxantrone*	Novantrone	Phase nonspecific	IV	Bone marrow suppression, cardiotoxicity
Nonanthracyclines				
Bleomycin	generic only	G ₂ -phase specific	IV, IM, subQ, IP	Pneumonitis and pulmonary fibrosis
Dactinomycin	Cosmegen	Phase nonspecific	IV	Bone marrow suppression, mucositis
Mitomycin	generic only	Phase nonspecific, but G ₁ and S most sensitive	IV	Bone marrow suppression
Mitotic Inhibitors				
Vinca Alkaloids				
Vinblastine	Velban	M-phase specific	IV	Bone marrow suppression
Vincristine	Oncovin, Vincasar PFS	M-phase specific	IV	Peripheral neuropathy
Vinorelbine	Navelbine	M-phase specific	IV	Bone marrow suppression
Taxanes				
Cabazitaxel	Jevtana	G ₂ /M-phase specific	IV	Bone marrow suppression, diarrhea
Docetaxel	Taxotere	G ₂ /M-phase specific	IV	Bone marrow suppression
Paclitaxel	Abraxane, Onxol, Taxol [®]	G ₂ /M-phase specific	IV	Bone marrow suppression
Others				
Eribulin	Halaven	G ₂ /M-phase specific	IV	Bone marrow suppression, peripheral neuropathy
Estramustine	Emcyt	M-phase specific	PO	Nausea and vomiting
Ixabepilone	Ixempra	G ₂ /M-phase specific	IV	Bone marrow suppression, neurotoxicity
Topoisomerase Inhibitors				
Etoposide	Etopophos, Toposar	S and G ₂ most sensitive	IV, PO	Bone marrow suppression
Irinotecan	Camptosar	S-phase specific	IV	Bone marrow suppression and late diarrhea
Teniposide	Vumon	S and G ₂ most sensitive	IV	Bone marrow suppression
Topotecan	Hycamtin	S-phase specific	IV	Bone marrow suppression
Miscellaneous				
Altretamine	Hexalen	Specificity unknown	PO	Bone marrow suppression
Asparaginase	Elspar, Erwinase [®] , Kidrolase [®]	G ₁ -phase specific	IV, IM	None
Dacarbazine	DTIC-Dome	Phase nonspecific	IV	Bone marrow suppression
Hydroxyurea	Hydrea, Droxia	S-phase specific	PO	Bone marrow suppression
Mitotane	Lysodren	Phase nonspecific	PO	CNS depression
Pegaspargase	Oncaspar	G ₁ -phase specific	IV, IM	None
Procarbazine	Matulane	Phase nonspecific	PO	Bone marrow suppression

*Mitoxantrone is classified chemically as an anthracenedione, which is very similar to an anthracycline.

There are two reasons why this is so. First, cells in G₀ have time to repair drug-induced damage before it can result in significant harm. In contrast, proliferating cells often lack time for repair. Second, toxicity may not become manifest until the cells attempt to proliferate. For example, many alkylating agents act by producing cross-links between DNA strands. Although these biochemical lesions can be made at any time, they are largely without effect until cells attempt to replicate DNA. This is much like inflicting a flat tire on an

automobile: The tire can be deflated at any time; however, loss of air is consequential only if the car is moving. Carrying the analogy further, if the flat occurs while the car is stopped, and is repaired before travel is attempted, the flat will have no functional impact at all.

It should be noted that some dividing cells are more vulnerable than others. Specifically, cells that divide quickly are harmed more readily than cells that divide slowly. Why? Because quickly dividing cells have less time for repair.

TABLE 102-2 ■ Actions of Representative Cytotoxic Anticancer Drugs

Drug	Drug Action	Cellular Process Disrupted
Cyclophosphamide	Alkylates DNA, causing cross-links and strand breakage	DNA and RNA synthesis
Methotrexate	Inhibits 1-carbon transfer reactions	Synthesis of DNA precursors (purines, dTMP)
Hydroxyurea	Inhibits ribonucleotide reductase	Synthesis of DNA precursors (blocks conversion of ribonucleotides into deoxyribonucleotides)
Thioguanine, mercaptopurine	Inhibit purine ring synthesis and nucleotide interconversion	Synthesis of DNA precursors (purines, pyrimidines, ribonucleotides, and deoxyribonucleotides)
Fluorouracil	Inhibits thymidylate synthetase	Synthesis of dTMP, a DNA precursor
Cytarabine	Inhibits DNA polymerase	DNA synthesis
Bleomycin	Breaks DNA strands and prevents their repair	DNA synthesis
Doxorubicin	Intercalates between base pairs of DNA and inhibits topoisomerase II	DNA and RNA synthesis
Vinblastine, vincristine	Block microtubule assembly	Mitosis
Asparaginase	Deaminates asparagine, depriving cells of this amino acid	Protein synthesis
Topotecan	Inhibits topoisomerase I and thereby prevents resealing of DNA strand breaks	Impairs DNA replication

Toxicity

As discussed in Chapter 101, many anticancer drugs are toxic to normal tissues—especially tissues that have a high percentage of proliferating cells (bone marrow, hair follicles, GI epithelium, germinal epithelium). The common major toxicities of the cytotoxic anticancer drugs, together with management procedures, are discussed at length in Chapter 101. Therefore, as we consider individual anticancer agents in this chapter, discussion of most toxicities is brief.

Dosage, Handling, and Administration

Cancer chemotherapy is a highly specialized field. Accordingly, in a general text such as this, presentation of detailed information on dosage and administration of specific agents seems inappropriate. However, be aware that dosages for anticancer agents must be individualized and that timing of administration may vary with the particular protocol being followed. Also, because of the complex and hazardous nature of cancer chemotherapy, anticancer drugs should be administered under the direct supervision of a clinician experienced in their use.

Handling Cytotoxic Drugs. Antineoplastic drugs are often mutagenic, teratogenic, and carcinogenic. In addition, direct contact with the skin, eyes, and mucous membranes can result in local injury (and can increase cancer risk if enough drug is absorbed). Accordingly, it is imperative that healthcare personnel involved in preparing and giving these drugs follow safe handling procedures. Risk of injury from contact with

parenteral chemotherapeutic drugs can be minimized by using biologic safety cabinets and by following approved procedures for compounding and administration.

Administering Vesicants. As discussed in Chapter 101, extravasation of vesicants can cause severe local injury, sometimes requiring surgical débridement and skin grafting. Drugs with strong vesicant properties include carmustine, dacarbazine, dactinomycin, daunorubicin, doxorubicin, mechlorethamine, mitomycin, plicamycin, streptozocin, vinblastine, and vincristine. To minimize the risk of injury, IV administration should be performed only into a vein with good flow. Sites of previous irradiation should be avoided. If extravasation occurs, the infusion should be discontinued immediately.

ALKYLATING AGENTS

The family of alkylating agents consists of nitrogen mustards, nitrosoureas, and other compounds. Before considering the properties of individual alkylating agents, we discuss the characteristics of the group as a whole. The alkylating agents are listed in Table 102-1.

Shared Properties

Mechanism of Action. The alkylating agents are highly reactive compounds that can transfer an alkyl group to various cell constituents. Cell kill results primarily from alkylation of DNA. As a rule, alkylating agents interact with DNA by

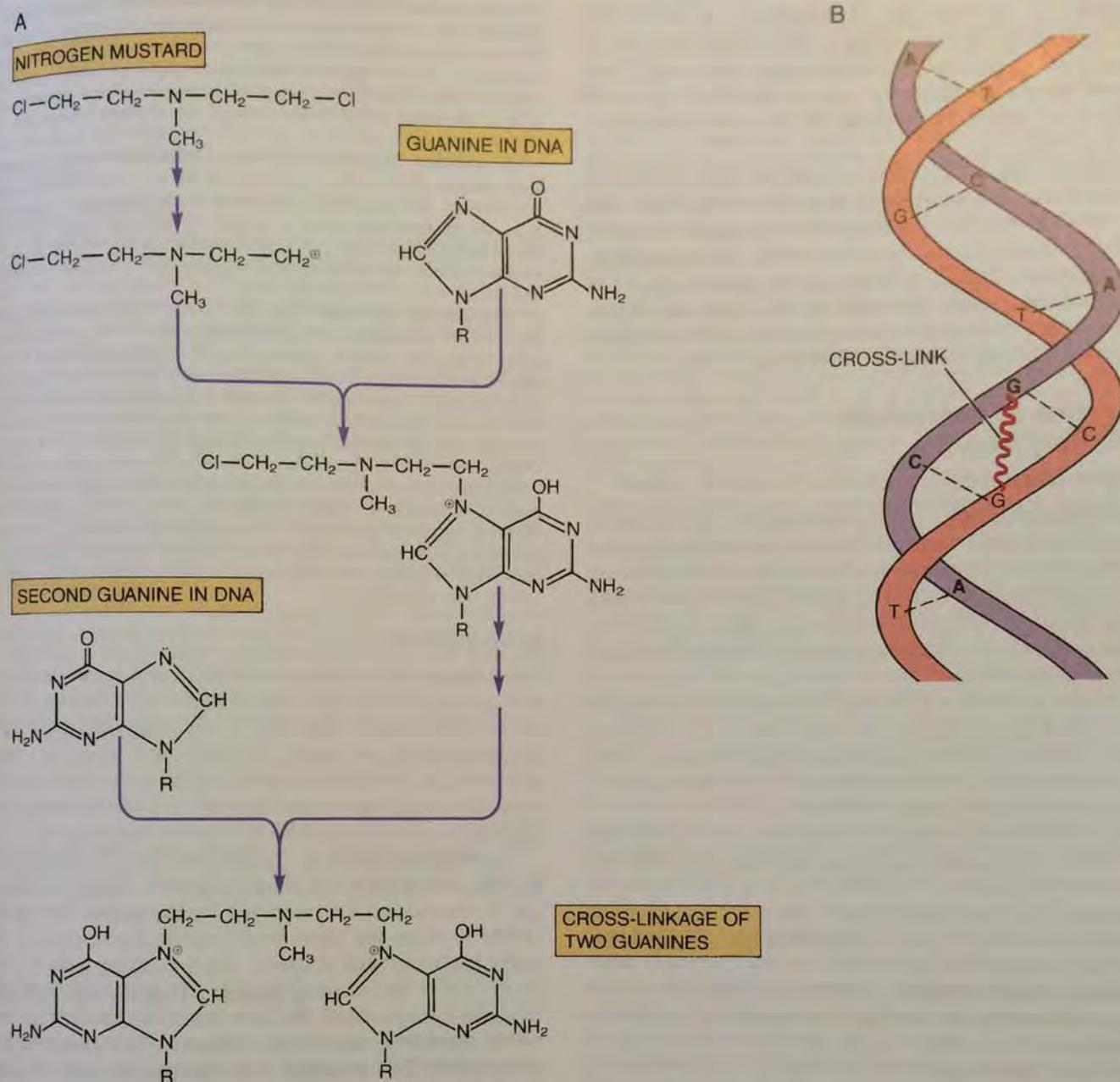


Figure 102-1 • Cross-linking of DNA by an alkylating agent.

A, Reactions leading to cross-linkage between guanine moieties in DNA. **B**, Schematic representation of interstrand cross-linking within the DNA double helix. (A = adenine, C = cytosine, G = guanine, T = thymine.)

forming a covalent bond with a specific nitrogen atom in guanine (Fig. 102-1).

Some alkylating agents have two reactive sites, whereas others have only one. Alkylating agents with two reactive sites (*bifunctional* agents) are able to bind DNA in two places to form *cross-links*. These bridges may be formed within a single DNA strand or between parallel DNA strands. Figure 102-1 illustrates the production of interstrand cross-links by nitrogen mustard. Alkylating agents with only one reactive site (*monofunctional* agents) lack the ability to form cross-links, but can still bind to a single guanine in DNA.

The consequences of guanine alkylation are miscoding, scission of DNA strands, and, if cross-links have been formed, inhibition of DNA replication. Because cross-linking of DNA

is especially injurious, cell death is more likely with bifunctional agents than with monofunctional agents.

Because alkylation reactions can take place at any time during the cell cycle, alkylating agents are considered *cell-cycle phase nonspecific*. However, *most of these drugs are more toxic to dividing cells—especially cells that divide rapidly—than they are to cells in G₀*. Why? Because (1) alkylation of DNA produces its most detrimental effects when cells attempt to replicate DNA, and (2) quiescent cells are often able to repair damage to DNA before it can affect cell function. Because alkylating agents are phase nonspecific, they needn't be present over an extended time. Accordingly, they can be administered by bolus dosing, rather than by prolonged infusion.

Resistance. Development of resistance to alkylating agents is common. A major cause is increased production of enzymes that repair DNA. Resistance may also result from decreased uptake of alkylating agents and from increased production of nucleophiles (compounds that act as decoy targets for alkylation).

Toxicities. Alkylating agents are toxic to tissues that have a high growth fraction. Accordingly, these drugs may injure cells of the bone marrow, hair follicles, GI mucosa, and germinal epithelium. Blood dyscrasias—neutropenia, thrombocytopenia, and anemia—caused by bone marrow suppression are of greatest concern. Nausea and vomiting occur with all alkylating agents. Also, several of these drugs are vesicants, and hence must be administered through a free-flowing IV line.

Properties of Individual Alkylating Agents

Nitrogen Mustards

Cyclophosphamide. Cyclophosphamide, formerly available as Cytoxan and Neosar, is a bifunctional alkylating agent active against a *broad spectrum* of neoplastic diseases. Indications include *Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma, and solid tumors of the head, neck, ovary, and breast.* Of all the alkylating agents, cyclophosphamide is employed most widely.

Cyclophosphamide is a prodrug that undergoes conversion to its active form in the liver. Because activation is required, onset of effects is delayed. Cyclophosphamide is not a vesicant, and hence can be administered PO as well as IV. Oral doses should be administered with food.

The major dose-limiting toxicity is bone marrow suppression. Severe nausea, vomiting, and alopecia are also common, especially at high doses. In addition, the drug can cause acute hemorrhagic cystitis; bladder injury and associated bleeding can be minimized by (1) maintaining adequate hydration, and (2) giving a protective agent called *mesna* [Mesnex] when high-dose cyclophosphamide is employed. Other adverse effects include sterility, immunosuppression, and hypersensitivity reactions.

Mechlorethamine. Mechlorethamine [Mustargen], a bifunctional compound, was the first alkylating agent employed clinically. Indications include *bronchogenic carcinoma, Hodgkin's disease, leukemias, and mycosis fungoides.* Mechlorethamine is a powerful vesicant and can cause severe local injury. Accordingly, for systemic therapy, the drug must be administered IV. Caution must be exercised to avoid both extravasation and direct contact with the skin. Once in the bloodstream, mechlorethamine undergoes rapid conversion to active metabolites. The dose-limiting toxicity is bone marrow suppression. Other major toxicities include severe nausea and vomiting, alopecia, diarrhea, stomatitis, amenorrhea, and sterility.

Bendamustine. Bendamustine [Treanda], approved in 2008, is a derivative of mechlorethamine, and may be better tolerated. The drug has two indications: *chronic lymphocytic leukemia and non-Hodgkin's lymphoma.* Administration is IV. As with mechlorethamine, the dose-limiting toxicity is bone marrow suppression. Nausea and vomiting are common. Some patients experience an infusion reaction, characterized by fever, hypotension, chills, rigors, and myalgias. There have been postmarketing reports of serious skin reactions, including bullous exanthema and toxic epidermal necrolysis. However, a causal relationship has not been established. Nonetheless, if a severe skin reaction occurs, bendamustine should be withheld or discontinued. Fluvoxamine [Luvox] and other drugs that inhibit CYP1A2 (the 1A2 isozyme of cytochrome P450) may raise bendamustine levels, whereas carbamazepine [Tegretol] and other drugs that induce CYP1A2 may reduce bendamustine levels.

Chlorambucil. Chlorambucil [Leukeran], an oral nitrogen mustard, is generally well tolerated. Bone marrow suppression is the major dose-limiting toxicity. Other adverse effects include hepatotoxicity, sterility, and rarely, pulmonary fibrosis. Nausea and vomiting are usually mild. Chlorambucil is a drug of choice for palliative therapy of *chronic lymphocytic leukemia.* The drug is also used for *Hodgkin's disease, non-Hodgkin's lymphomas, and multiple myeloma.*

Melphalan. Melphalan [Alkeran], a bifunctional agent, is generally well tolerated. Bone marrow suppression is the major dose-limiting toxicity. The drug can cause secondary malignancy and is mutagenic like other alkylating agents. Melphalan is not a vesicant. Severe nausea and vomiting are rare. Administration is PO and IV. Melphalan is a preferred drug for *multiple myeloma, and is also active against lymphoma and carcinoma of the ovary and breast.*

Ifosfamide. Ifosfamide [Ifex], a derivative of cyclophosphamide, is approved for refractory *germ cell testicular cancer, and is used off-label against many other tumors, including Hodgkin's and non-Hodgkin's lymphomas, non-small cell and small cell lung cancer, and head and neck cancer.* Dose-limiting toxicities are bone marrow suppression and hemorrhagic cystitis. The risk of cystitis is minimized by concurrent therapy with *mesna* [Mesnex] and by extensive hydration (at least 2 L of oral or IV fluid daily). Owing to the risk of cystitis, urinalysis should be performed before each dose. If the analysis reveals microscopic hematuria, dosing should be postponed until hematuria resolves. Additional adverse effects include nausea, vomiting, metabolic acidosis, and central nervous system (CNS) toxicity (confusion, hallucinations, blurred vision, coma). Severe adverse effects are most likely in patients receiving high-dose therapy and in those with renal failure. Administration is IV.

Nitrosoureas

The nitrosoureas are bifunctional alkylating agents, and are active against a broad spectrum of neoplastic diseases. Cell kill results from cross-linking DNA. Unlike many anticancer drugs, the nitrosoureas are highly lipophilic, and hence can readily penetrate the blood-brain barrier. As a result, these drugs are especially useful against *cancers of the CNS.* The major dose-limiting toxicity is *delayed bone marrow suppression.*

Carmustine (BCNU). Carmustine [BiCNU, Gliadel] was the first nitrosourea to undergo extensive clinical testing and can be considered the prototype for the group. Owing to its ability to cross the blood-brain barrier, carmustine is especially useful against *primary and metastatic tumors of the brain.* Other indications include *Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma, malignant melanoma, hepatoma, and adenocarcinoma of the stomach, colon, and rectum.* The principal dose-limiting toxicity is delayed bone marrow suppression; leukocyte and platelet nadirs occur 4 to 6 weeks after treatment. Nausea and vomiting can be severe. Injury to the liver and kidneys has been reported. High cumulative doses may cause pulmonary fibrosis. Accordingly, if pulmonary function begins to decline, corticosteroids should be given to prevent fibrosis.

Administration may be topical or IV. Topical administration is done by implanting a biodegradable, carmustine-impregnated wafer [Gliadel] into the cavity created by surgical removal of a brain tumor. This technique has the obvious benefit of concentrating the drug where it is most needed. When administered IV, carmustine can cause local phlebitis and extravasation injury, even though it is not a vesicant.

Lomustine (CCNU). Lomustine [CeeNU] is similar to carmustine in actions and uses. Like carmustine, lomustine crosses the blood-brain barrier and is approved for *brain cancer.* The drug is also approved for *Hodgkin's disease.* As with carmustine, the major dose-limiting toxicity is delayed bone marrow suppression. Additional toxicities include nausea and vomiting, renal and hepatic toxicity, pulmonary fibrosis, and neurologic reactions. Dosing is oral.

Streptozocin. Streptozocin [Zanosar] differs significantly from other nitrosoureas. The drug contains a glucose moiety that causes selective uptake by islet cells of the pancreas. This property underlies the drug's only approved indication: *metastatic islet cell tumors*. The major dose-limiting toxicity is kidney damage. Accordingly, renal function should be monitored in all patients. Nausea and vomiting can be severe. Additional toxicities include hypoglycemia, hyperglycemia, diarrhea, chills, and fever. In contrast to other nitrosoureas, streptozocin causes minimal bone marrow suppression. The drug is given IV.

Other Alkylating Agents

Busulfan. Busulfan [Myleran, Busulfex] is a bifunctional agent with just one approved use: *chronic myelogenous leukemia*. Dose-limiting toxicities are bone marrow suppression, pulmonary infiltrates, and pulmonary fibrosis. Other toxicities include nausea, vomiting, alopecia, gynecomastia, male and female sterility, skin hyperpigmentation, cataracts, seizures, and liver injury. Dosing is oral and IV.

Temozolomide. Therapeutic Uses. Temozolomide [Temodar, Temodal[®]], is indicated for oral therapy of adults with *anaplastic astrocytoma* that has relapsed after treatment with preferred agents: procarbazine and a nitrosourea (lomustine or carmustine). Temozolomide can also benefit patients with recurrent *glioblastoma multiforme*. Both of these cancers arise from glial cells in the brain, and both eventually recur despite aggressive treatment. However, even though temozolomide cannot offer cure, it can increase health-related quality of life. The initial dosage is 150 mg/m² once daily for 5 consecutive days, repeated every 28 days. In clinical trials, temozolomide produced partial tumor shrinkage in 27% of patients, and complete shrinkage in 8%.

Pharmacokinetics and Mechanism of Action. Temozolomide undergoes nearly complete absorption after oral dosing. Food reduces both the rate and extent of absorption. Once in the body, temozolomide undergoes rapid, nonenzymatic conversion to its active form, an alkylating agent known as MTIC. As MTIC, the drug alkylates DNA, and thereby causes cell death. Temozolomide readily crosses the blood-brain barrier to reach its site of action. The elimination half-life is 1.8 hours.

Adverse Effects. The major dose-limiting toxicity is myelosuppression, manifesting as neutropenia and thrombocytopenia. The most common adverse effects are nausea (53%) and vomiting (42%). Both respond well to antiemetic drugs. Other common reactions include headache (41%), fatigue (34%), constipation (33%), and diarrhea (16%). Convulsions may also occur. Patients must not open temozolomide capsules; the drug can cause local injury following inhalation or contact with the skin or mucous membranes.

PLATINUM COMPOUNDS

The platinum-containing anticancer drugs—cisplatin, carboplatin, and oxaliplatin—are similar to the alkylating agents, and often classified as such. Like the bifunctional alkylating agents, the platinum compounds produce cross-links in DNA, and hence are cell-cycle phase nonspecific.

Cisplatin

Cisplatin, formerly available as Platinol-AQ, kills cells primarily by forming cross-links between and within strands of DNA. The drug is approved only for *metastatic testicular and ovarian cancers* and *advanced bladder cancer*. Nonetheless, it is used off-label as a component in standard-of-care regimens for *lung cancer* and *head and neck cancer*. The major dose-limiting toxicity is kidney damage, which can be minimized by extensive hydration coupled with diuretic therapy and *amifostine* [Ethyol]. Cisplatin is highly emetogenic; nausea and vomiting begin about 1 hour after dosing and can persist for several days. Other adverse effects include clinically important peripheral neuropathy, mild to moderate bone marrow suppression, kidney damage, and ototoxicity, which manifests as tinnitus and high-frequency hearing loss. The drug is given by IV infusion.

Carboplatin

Carboplatin, formerly available as Paroplatin, is an analog of cisplatin. Cell kill appears to result from cross-linking DNA. The drug's only approved indications are initial and palliative therapy of *advanced ovarian cancer*. Labeled uses include *small cell cancer of the lung*, *squamous cell cancer of the head and neck*, and *endometrial cancer*. The major dose-limiting toxicity is bone marrow suppression. Nausea and vomiting occur, but are less severe than with cisplatin. Similarly, nephrotoxicity, neurotoxicity, and hearing loss are less frequent than with cisplatin. Carboplatin is administered by IV infusion. Anaphylactic reactions have occurred minutes after dosing; symptoms can be managed with epinephrine, glucocorticoids, and antihistamines.

Oxaliplatin

Actions and Uses. Oxaliplatin [Eloxatin], approved in 2002, is similar to carboplatin. Like carboplatin, oxaliplatin produces intra- and interstrand cross-links in DNA. Oxaliplatin is approved only for *colorectal cancer*, and only in combination with fluorouracil/leucovorin (leucovorin potentiates the activity of fluorouracil). This regimen may be used for adjuvant therapy following complete tumor resection, or in patients with advanced colorectal cancer. Investigational uses include *mesothelioma*, *non-Hodgkin's lymphoma*, and *cancers of the breast, ovary, pancreas, prostate, and lung*. Administration is by IV infusion.

Toxicity. Peripheral Sensory Neuropathy. The major dose-limiting toxicity is peripheral sensory neuropathy, manifesting as numbness or tingling in the fingers and toes and around the mouth and throat. Neuropathy develops in most patients, either early in treatment or after several courses. Neuropathy may impede activities of daily living, such as buttoning clothing, writing, or just holding things. Symptoms are often intensified by exposure to cold. Accordingly, patients should be warned to cover exposed skin before touching cold objects or entering a cold environment. Also, patients should avoid cold liquids and use of ice. Oxaliplatin-induced neuropathy typically resolves after treatment stops, although complete recovery may take several months. Oral gabapentin may reduce or prevent neuropathy.

Other Toxicities. Damage to bone marrow can cause anemia (64%), neutropenia (15% with oxaliplatin alone, 66% when combined with fluorouracil), and thrombocytopenia (41% with oxaliplatin alone, 76% when combined with fluorouracil). Other common reactions are nausea and vomiting (70%), liver abnormalities (46%), diarrhea (41%), fever (36%), abdominal pain (31%), and infection (23%). Alopecia occurs in 2% of patients. Life-threatening anaphylactoid reactions may develop, but are uncommon; epinephrine, glucocorticoids, and antihistamines have been employed for treatment.

ANTIMETABOLITES

Antimetabolites are structural analogs of important natural metabolites. Because they resemble natural metabolites, these drugs are able to disrupt critical metabolic processes. Some antimetabolites inhibit enzymes that synthesize essential cellular constituents. Others undergo incorporation into DNA, and thereby disrupt DNA replication and function.

Antimetabolites are effective only against cells that are active participants in the cell cycle. Most antimetabolites are S-phase specific, although some can act during any phase of the cycle, except G₀. To be effective, agents that are S-phase specific must be present for an extended time.

There are three classes of antimetabolites: (1) folic acid analogs, (2) pyrimidine analogs, and (3) purine analogs. Members of each class are listed in Table 102-1.

Folic Acid Analogs

Folic acid, in its active form, is needed for several essential biochemical reactions. The folic acid analogs block the conversion of folic acid to its active form. At this time, three analogs of folic acid are used against cancer: methotrexate, pemetrexed, and pralatrexate. Other folate analogs are used to treat bacterial infections (trimethoprim), malaria (pyrimethamine), and *Pneumocystis jirovecii* pneumonia (trimetrexate).

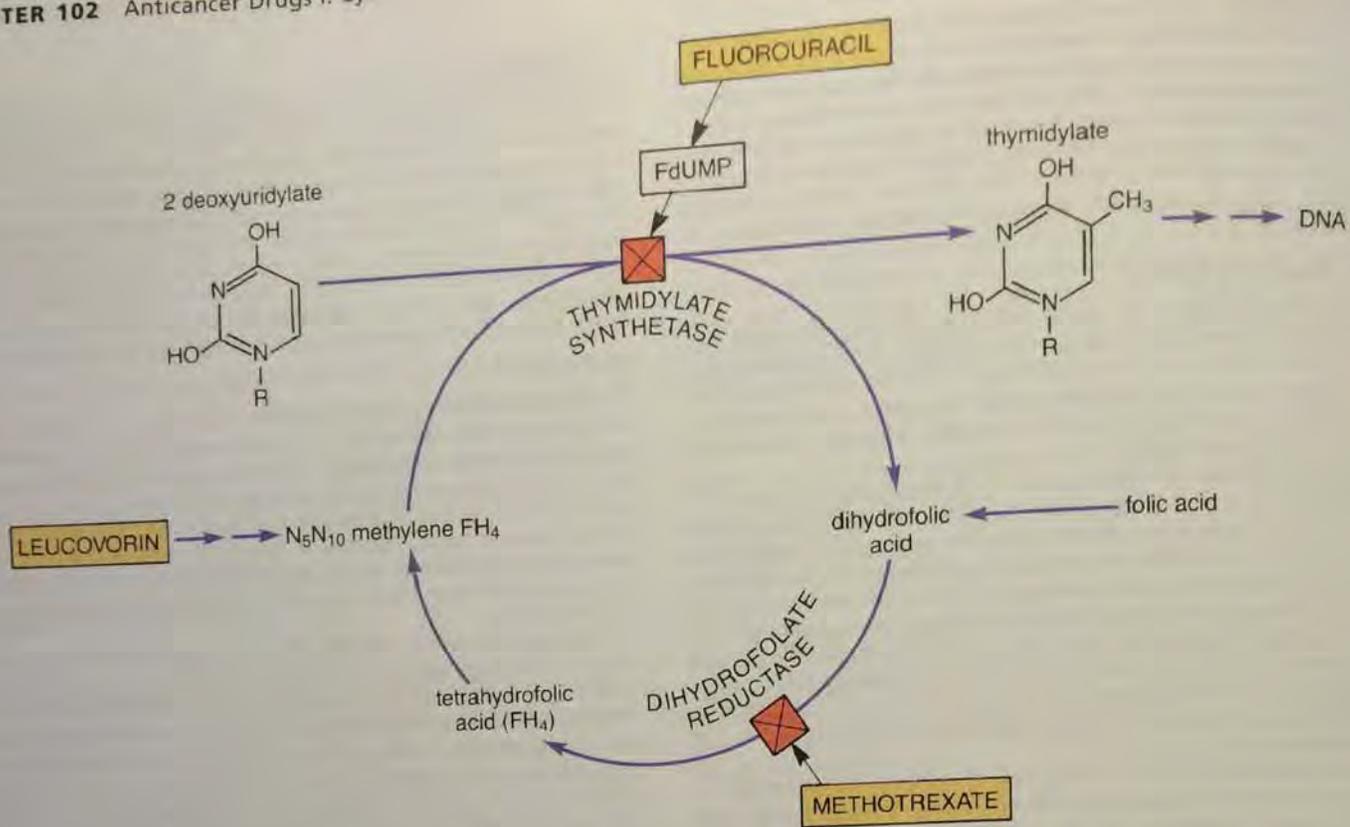


Figure 102-2 • Actions of methotrexate, leucovorin, and fluorouracil. (FdUMP = 5-fluoro-2'-deoxyuridine-5'-monophosphate, X = blockade of reaction.)

Methotrexate

Mechanism of Action. As shown in Figure 102-2, methotrexate [Rheumatrex, Trexall] *inhibits dihydrofolate reductase*, the enzyme that converts dihydrofolic acid (FH₂) into tetrahydrofolic acid (FH₄). Since production of FH₄ is a necessary step in the activation of folic acid, and since activated folic acid is required for biosynthesis of essential cellular constituents (DNA, RNA, proteins), inhibition of FH₄ production has multiple effects on the cell. Of all the processes that are suppressed by reduced FH₄ availability, biosynthesis of thymidylate appears most critical. Why? Because, in the absence of thymidylate, cells are unable to make DNA. Because cell kill results primarily from disrupting DNA synthesis, methotrexate is considered *S-phase specific*. Please note, however, that in addition to its S-phase effect, methotrexate has another beneficial action: the fall in thymidine levels caused by methotrexate is a potent signal for inducing apoptosis (programmed cell death).

A technique known as *leucovorin rescue* can be employed to enhance the effects of methotrexate. Some neoplastic cells are unresponsive to methotrexate because they lack the transport system required for active uptake of the drug. By giving massive doses of methotrexate, we can force the drug into these cells by passive diffusion. However, because this process also exposes normal cells to extremely high concentrations of methotrexate, normal cells are also at risk. To save them, leucovorin (citrovorum factor, folinic acid) is given. As shown in Figure 102-2, leucovorin bypasses the metabolic block caused by methotrexate, thereby permitting normal cells to synthesize thymidylate and other compounds. Malignant cells are not saved to the same extent because leucovorin uptake requires the same transport system employed for

methotrexate uptake, a transport system these cells lack. It should be noted that leucovorin rescue is potentially dangerous: *Failure to administer leucovorin in the right dose at the right time can be fatal.*

Pharmacokinetics. Methotrexate can be administered PO, IM, IV, and intrathecally. The drug is highly polar, and hence a transport system is needed to enter mammalian cells. In cancer cells and normal cells, methotrexate undergoes enzymatic activation to a polyglutamated form. Elimination is primarily renal. Hence, in patients with renal impairment, dosage must be reduced to prevent the drug from accumulating to toxic levels.

Because methotrexate is highly polar, it crosses the blood-brain barrier poorly, except when given in very high doses. To ensure effective levels, intrathecal administration is employed for most CNS cancers.

Resistance. Cancer cells can acquire resistance to methotrexate through five mechanisms: (1) decreased uptake of methotrexate, (2) increased synthesis of dihydrofolate reductase (the target enzyme for methotrexate), (3) synthesis of a modified form of dihydrofolate reductase that has a reduced affinity for methotrexate, (4) increased production of a transporter that pumps methotrexate out of cells, and (5) reduced production of enzymes needed to convert methotrexate to its active (polyglutamated) form.

Therapeutic Uses. Methotrexate is curative for women with *choriocarcinoma*. The drug is also active against *non-Hodgkin's lymphomas* and *acute lymphocytic leukemia of childhood*. Very large doses coupled with leucovorin rescue have been employed to treat *head and neck sarcomas* and *osteogenic sarcoma*. Noncancer applications include *rheumatoid arthritis* (see Chapter 73), *Crohn's disease* (see Chapter 80), *psoriasis* (see Chapter 105), and *abortion* (see Chapter 62).

Toxicity. The usual dose-limiting toxicities are bone marrow suppression, pulmonary infiltrates and fibrosis, and oral and GI ulceration. Death may result from intestinal perforation and hemorrhagic enteritis. Nausea and vomiting may occur shortly after administration. High doses can directly injure the kidneys. To promote drug excretion, and thereby minimize renal damage, the urine should be alkalized and

adequate hydration maintained. Methotrexate has been associated with fetal malformation and death. Accordingly, pregnancy should be avoided until at least 6 months after completing treatment.

Pemetrexed

Mechanism of Action. Pemetrexed [Alimta], approved in 2004, is an antifolate compound with actions similar to those of methotrexate. Like methotrexate, pemetrexed inhibits dihydrofolate reductase. However, unlike methotrexate, pemetrexed also inhibits two other enzymes: thymidylate synthase and glycinamide ribonucleotide formyltransferase. All three enzymes are involved in the *de novo* synthesis of thymidine and purine nucleotides. By inhibiting these enzymes, pemetrexed can suppress synthesis of DNA, RNA, and proteins. Cell death results primarily from disrupting DNA synthesis and function. Pemetrexed is considered S-phase specific.

Therapeutic Uses. Pemetrexed, in combination with cisplatin, is approved for IV therapy of unresectable *malignant pleural mesothelioma*, a rare cancer usually associated with asbestos exposure. The drug is also approved for monotherapy of *non-small cell lung cancer* following prior chemotherapy, and for initial therapy of this cancer when combined with cisplatin. Investigational uses include *gastric, pancreatic, and breast cancer*.

Pharmacokinetics. Pemetrexed is administered IV and, like methotrexate, undergoes conversion to active polyglutamates within cells. (Compared with normal cells, cancer cells are more efficient at polyglutamation, and hence cancer cells are more likely to be harmed.) Pemetrexed is eliminated by renal excretion. In patients with normal renal function, the elimination half-life is 3.5 hours. In patients with renal impairment, elimination is delayed.

Toxicity. The most common adverse effects are bone marrow suppression (the usual dose-limiting toxicity), GI disturbances (nausea, diarrhea, and sores of the lips, mouth, and throat), skin rash, and fatigue. To reduce bone marrow and GI toxicity, patients should receive prophylactic doses of vitamin B₁₂ and folic acid, starting 1 week prior to dosing. To reduce skin rash, patients should receive prophylactic glucocorticoids (eg, dexamethasone). Pemetrexed can cause fetal malformation and death, and hence should not be used during pregnancy. The drug is not a vesicant, and hence extravasation is managed as it would for other nonvesicants.

Pralatrexate

Mechanism of Action. Pralatrexate [Folotyn], approved in 2009, is a folate analog with a structure similar to that of methotrexate. Like methotrexate, pralatrexate inhibits dihydrofolate reductase, and thereby disrupts synthesis of DNA and other essential cellular components. The result is cell death. Pralatrexate can be considered S-phase specific.

Therapeutic Use. Pralatrexate has only one indication: intravenous treatment of relapsed or refractory *peripheral T-cell lymphoma*, a relatively rare and often aggressive form of non-Hodgkin's lymphoma. In clinical trials, only a minority of patients responded. However, in some patients who did respond, the response duration was substantial.

Pharmacokinetics. Pralatrexate is administered by IV push and becomes 67% bound to plasma proteins. Like methotrexate, the drug undergoes metabolic conversion to active polyglutamates within cells. Elimination is primarily renal. Accordingly, in patients with significant renal impairment, dosage must be reduced to avoid toxicity from drug accumulation.

Toxicity. The major dose-limiting toxicities are GI mucositis (70%) and bone marrow suppression, manifesting as thrombocytopenia (41%), anemia (34%), and neutropenia (24%). To reduce toxicity to the GI mucosa and bone marrow, patients should receive prophylactic doses of folic acid (starting 10 days before treatment) and vitamin B₁₂ (starting 10 weeks before treatment). Other common toxicities include fatigue (36%), nausea (40%), vomiting (25%), constipation (33%), edema (30%), fever (32%), and cough (28%). Pralatrexate is embryotoxic, and hence is classified in Food and Drug Administration Pregnancy Risk Category D: the drug should be avoided during pregnancy unless benefits to the mother are deemed to outweigh risks to the fetus. Women receiving the drug should be warned not to get pregnant.

Pyrimidine Analogs

Pyrimidines—cytosine, thymine, and uracil—are bases employed in the biosynthesis of DNA and RNA. The pyrimidine analogs, because of their structural similarity to naturally occurring pyrimidines, can act in several ways: (1) they can inhibit biosynthesis of pyrimidines, (2) they can inhibit biosynthesis of

DNA and RNA, and (3) they can undergo incorporation into DNA and RNA, and thereby disrupt nucleic acid function. All of the pyrimidine analogs are prodrugs that must be converted to their active forms in the body.

Cytarabine

Cytarabine, also known as *cytosine arabinoside* and *Ara-C*, is an analog of deoxycytidine. The drug has an established role in treating *acute myelogenous leukemia*. Cytarabine is available in two formulations: (1) conventional [Tarabine PFS], for IV and subQ dosing, and (2) liposomal [DepoCyt], for intrathecal dosing.

Mechanism of Action. Cytarabine is converted to its active form—Ara-CTP—within the body. As Ara-CTP, the drug undergoes incorporation into DNA. By a mechanism that is not fully understood, incorporation suppresses further DNA synthesis. Ara-CTP may also impede DNA synthesis by a second mechanism: inhibition of DNA polymerase. Cytarabine is S-phase specific.

Resistance. Decreased conversion of cytarabine to Ara-CTP is a major cause of resistance. Other mechanisms include decreased uptake of cytarabine, increased conversion of cytarabine to an inactive product, and increased production of dCTP (the natural metabolite that Ara-CTP competes with for incorporation into DNA).

Pharmacokinetics. Administration may be IV, subQ, or intrathecal. Cytarabine is not active orally. Drug that is not taken up by cells undergoes rapid deamination in the liver. Metabolites are excreted in the urine.

Therapeutic Uses. The principal indication for cytarabine is *acute myelogenous leukemia*. To induce remission, the drug is combined with idarubicin as part of the so-called 7 + 3 regimen (7 days of cytarabine + 3 days of idarubicin). Other applications include *acute lymphocytic leukemia, non-Hodgkin's lymphomas, and lymphomatous meningitis*.

Toxicity. Bone marrow suppression (neutropenia, thrombocytopenia) is the usual dose-limiting toxicity. Nausea, vomiting, and fever may develop, especially after bolus IV injection. Other toxicities include stomatitis, liver injury, and conjunctivitis. High doses may cause pulmonary edema and cerebellar toxicity.

The liposomal formulation can cause chemical arachnoiditis, manifesting as nausea, vomiting, headache, and fever. Left untreated, the condition can be fatal. The incidence and severity of the reaction can be reduced by coadministration of dexamethasone, an anti-inflammatory glucocorticoid.

Fluorouracil

Fluorouracil [Acrucil] is a fluorinated derivative of uracil. The drug is employed extensively to treat solid tumors.

Mechanism of Action. In order to exert cytotoxic effects, fluorouracil must be converted to its active form, 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP). As shown in Figure 102-2, FdUMP inhibits thymidylate synthetase, thereby depriving cells of thymidylate needed to make DNA. Fluorouracil is only active against cells that are going through the cell cycle, and shows some S-phase specificity.

Resistance. Potential mechanisms for resistance are decreased activation of fluorouracil and production of altered thymidylate synthetase that has a low affinity for FdUMP. The clinical significance of these mechanisms has not been established.

Therapeutic Uses. Chemotherapeutic use of fluorouracil is limited to solid tumors. The drug is employed, together with other drugs, in the adjuvant treatment of *breast and colorectal cancer*, and in palliative therapy of *carcinomas of the colon, rectum, breast, stomach, and pancreas*. As discussed in Chapter 105, fluorouracil can be used topically to treat *pre-malignant keratoses*.

Pharmacokinetics. Administration is IV. Continuous infusion is more effective and less toxic than bolus administration. Fluorouracil is distributed widely and enters the CNS with ease. Elimination is by rapid hepatic metabolism.

Toxicity. The usual dose-limiting toxicities are bone marrow suppression (neutropenia) and oral and GI ulceration. To minimize GI injury (eg, ulceration of the oropharynx or bowel), fluorouracil should be discontinued as soon as mild reactions (stomatitis, diarrhea) occur. Dosage can also be limited by palmar-plantar erythrodysesthesia (hand-and-foot syndrome), characterized by tingling, burning, redness, flaking, swelling, and blistering of the palms and soles. Other adverse effects include alopecia, hyperpigmentation, and neurologic deficits.

In patients given a fluorouracil overdose, treatment with an investigational antidote—*vistonuridine*—can be lifesaving. Vistonuridine is a prodrug that undergoes conversion to uridine, which then dampens the effects of fluorouracil on cellular metabolism.

Capecitabine

Capecitabine [Xeloda], a prodrug form of fluorouracil, is indicated for oral therapy of metastatic *breast cancer* as well as *colorectal cancer* in both the adjuvant and metastatic settings. Once in the body, capecitabine undergoes metabolic conversion to fluorouracil and then to FdUMP, its active form. Consequently, the pharmacology of capecitabine is much like that of fluorouracil itself. Cell kill results from inhibition of thymidylate synthetase. Capecitabine is active only against dividing cells, and like fluorouracil, shows some S-phase specificity. In clinical trials, 20% of patients with breast cancer experienced at least a 50% decrease in tumor size. Severe diarrhea is common and can be dose limiting. Other common side effects include nausea, vomiting, stomatitis, and hand-and-foot syndrome, characterized by local tingling, numbness, pain, swelling, and erythema of the palms and soles. Capecitabine is a teratogen and hence must not be used during pregnancy. The drug can cause leukopenia, but severe myelosuppression is uncommon. Alopecia has not been reported. Postmarketing surveillance has shown that capecitabine enhances the effects of warfarin; to reduce the risk of bleeding, anticoagulant effects should be monitored closely, and warfarin dosage reduced as indicated. The recommended dosage for capecitabine is 1250 mg/m² taken twice a day (after eating) for 14 days, followed by 7 days off. This sequence is repeated as appropriate. In patients with renal impairment, capecitabine can accumulate to toxic levels. If renal impairment is *moderate*, dosage should be reduced by 75%; if impairment is *severe*, the drug should not be used.

Floxuridine

Floxuridine [FUDR], like fluorouracil, is converted to FdUMP in the body. Hence, the effects of floxuridine and fluorouracil are nearly identical. Floxuridine is indicated only for *GI adenoma metastatic to the liver*. For this cancer, the drug is administered by infusion directly into the hepatic artery. The major dose-limiting toxicities are bone marrow suppression and oral and GI ulceration.

Gemcitabine

Mechanism of Action. Gemcitabine [Gemzar] is a nucleoside analog that inhibits DNA synthesis. Hence, the drug is S-phase specific. Following uptake by cells, gemcitabine is converted to two active forms: gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme needed to form deoxynucleoside triphosphates, which are required for DNA synthesis. Gemcitabine triphosphate undergoes incorporation into DNA, where it inhibits strand elongation.

Therapeutic Uses. Gemcitabine is indicated for *adenocarcinoma of the pancreas* and *non-small cell cancer of the lung*. For pancreatic cancer, the drug may be used as first-line therapy in patients with locally advanced or metastatic disease, and in patients previously treated with fluorouracil. In clinical trials, gemcitabine reduced pain, improved functional status, and prolonged life slightly. The recommended dosage is 1000 mg/m² infused IV over 30 minutes once a week for up to 7 weeks. After a 1-week hiatus, treatment is resumed, but dosing is reduced to one infusion every 3 to 4 weeks.

Toxicity. Although gemcitabine can cause a wide variety of adverse effects, it is fairly well tolerated. Myelosuppression is dose limiting. Nausea

and vomiting are common (70%) but usually mild to moderate. Other common reactions include elevation of serum transaminases (75%), proteinuria (45%), hematuria (35%), pain (45%), fever (41%), rash (30%), and a flu-like syndrome (19%). Less common reactions include diarrhea, constipation, stomatitis, dyspnea, paresthesias, edema, and alopecia. Infusion reactions (eg, hypotension, flushing) may occur, and can be managed by slowing the infusion.

Purine Analogs

Like the pyrimidines, the purines—adenine, guanine, and hypoxanthine—are bases employed for biosynthesis of nucleic acids. The purine analogs discussed in this chapter are used primarily in the treatment of cancer. Purine analogs discussed in other chapters are used for immunosuppression, antiviral therapy, and gout.

Mercaptopurine

Mechanisms of Action and Resistance. Mercaptopurine [Purinethol] is a prodrug that undergoes conversion to its active form within cells. Following activation, the drug can disrupt multiple biochemical processes, including purine biosynthesis, nucleotide interconversion, and biosynthesis of nucleic acids. All of these actions probably contribute to cytotoxic effects. Mercaptopurine is S-phase specific. Mechanisms of resistance include reduced activation of the drug and accelerated deactivation.

Pharmacokinetics. Mercaptopurine is administered orally and undergoes erratic absorption. Absorbed drug is distributed widely, but not to the CNS. Extensive metabolism occurs in the liver; an important reaction is catalyzed by xanthine oxidase. Accordingly, for patients receiving a xanthine oxidase inhibitor (eg, allopurinol), mercaptopurine dosage should be reduced.

Therapeutic Uses. The principal indication for mercaptopurine is maintenance therapy of *acute lymphocytic leukemia* in children and adults.

Toxicity. Bone marrow suppression (neutropenia, thrombocytopenia, anemia) is the principal dose-limiting toxicity. Mild hepatotoxicity, manifesting as elevations in bilirubin and liver transaminases, is relatively common; rarely, hepatic injury progresses to fatal liver failure. Other adverse effects include nausea, vomiting, and oral and intestinal ulceration. Concurrent use of a xanthine oxidase inhibitor increases the overall toxicity. Mercaptopurine is mutagenic, and hence must not be used during pregnancy.

Thioguanine

Actions and Uses. Thioguanine [Tabloid, Lanvis[®]] acts much like mercaptopurine. Following conversion to its active form, thioguanine inhibits purine synthesis and the interconversion of nucleotides. DNA synthesis is also inhibited. Like mercaptopurine, thioguanine is S-phase specific. The drug is used primarily for *acute nonlymphocytic leukemias*.

Pharmacokinetics. Administration is oral. Absorption is erratic and incomplete. Thioguanine does not distribute to the CNS. Inactivation is by hepatic metabolism. In contrast to mercaptopurine, thioguanine is not degraded by xanthine oxidase, and hence no dosage reduction is required if a xanthine oxidase inhibitor is being used.

Toxicity. The usual dose-limiting toxicity is bone marrow suppression. Gastrointestinal reactions (nausea, vomiting, diarrhea) may develop, but these are less severe than with mercaptopurine. Liver injury, manifesting as cholestatic jaundice, may occur.

Pentostatin

Pentostatin [Nipent] is an analog of adenosine. The drug acts in two major ways. First, it inhibits adenosine deaminase, causing accumulation of adenosine and deoxyadenosine nucleotides, compounds that inhibit ribonucleotide reductase and thereby block DNA synthesis. Second, pentostatin promotes accumulation of S-adenosyl homocysteine, a compound that is especially

toxic to lymphocytes. The drug has only one approved indication: *hairy cell leukemia* that has not responded to interferon alfa. The major dose-limiting toxicities are bone marrow suppression and CNS depression. Other toxicities include nausea, vomiting, rash, and fever. Combined use with fludarabine has caused fatal pulmonary toxicity, and hence is not recommended. Administration is by IV bolus or IV infusion.

Fludarabine

Fludarabine [Fludara, Oforta] is an analog of adenosine. The drug is used primarily for *chronic lymphocytic leukemia*, *low-grade non-Hodgkin's lymphoma*, and *acute myelogenous leukemia*. Administration is IV or PO. Once in the body, fludarabine undergoes rapid conversion to its active form, 2-fluoro-ara-ATP. Cell kill appears to result from several mechanisms, including inhibition of DNA replication, impairment of RNA function, and promotion of apoptosis. Thus the drug is probably S-phase specific. The major dose-limiting toxicity is bone marrow suppression (neutropenia, thrombocytopenia, anemia). Other common toxicities include nausea, vomiting, and chills. Life-threatening autoimmune hemolytic anemia has been reported. When used in normal doses, and especially in excessive doses, fludarabine can cause severe CNS effects, including blindness, seizures, coma, agitation, confusion, and death. Combined use with pentostatin has been associated with fatal pulmonary toxicity, and hence is not recommended.

Cladribine

Cladribine [Leustatin] is an adenosine analog with a unique combination of actions. Unlike other purine analogs, which inhibit DNA synthesis only, cladribine inhibits both DNA synthesis and repair. As a result, the drug is active against quiescent cells as well as cells that are actively dividing. Cladribine is highly active against *hairy cell leukemia* and is considered a drug of choice for this cancer. The drug is also active against *chronic lymphocytic leukemia*, *low-grade non-Hodgkin's lymphomas*, *acute myeloid leukemia*, and *mycosis fungoides*. The major dose-limiting toxicity is myelosuppression. Very high doses (4 to 9 times normal) have caused acute nephrotoxicity and delayed-onset neurotoxicity. For patients with hairy cell leukemia, cladribine is administered by continuous IV infusion over 7 consecutive days.

Nelarabine

Nelarabine [Arranon, Atriance[®]], approved in 2005, is an analog of guanosine. The drug is used for patients with *T-cell acute lymphoblastic leukemia* or *T-cell lymphoblastic lymphoma* that has not responded to (or has stopped responding to) at least two chemotherapy regimens. Monotherapy with nelarabine can produce a complete response in some of these patients. The drug is administered IV and undergoes conversion to its active form—ara-GTP—within cells. Incorporation of ara-GTP into DNA then causes DNA fragmentation and subsequent apoptosis. The most common side effects are anemia, leukopenia, neutropenia, and thrombocytopenia. Potentially fatal neurotoxicity—manifesting as paresthesias, ataxia, confusion, convulsions, severe somnolence, and coma—is dose limiting. The recommended adult dosage is 1500 mg/m² infused over 2 hours on days 1 and 5, repeated every 21 days.

Clofarabine

Clofarabine [Clolar], approved in 2004, is a purine nucleoside analog indicated for relapsed or refractory *acute lymphoblastic leukemia* after at least two prior regimens have failed. The drug is administered IV and undergoes intracellular conversion to its active form, clofarabine 5'-triphosphate. Cell kill results from several mechanisms, including termination of DNA elongation, inhibition of DNA repair, and promotion of apoptosis. In vitro, clofarabine is toxic to proliferating and quiescent cells. However, given its mechanism, the drug is probably most effective during S phase. The major dose-limiting toxicity is bone marrow suppression (neutropenia, thrombocytopenia, and anemia). Hyperuricemia may result from massive tumor lysis. Other common reactions include tachycardia, fatigue, chills, fever, headache, rash, diarrhea, abdominal pain, and pain in the extremities. Two life-threatening syndromes—systemic inflammatory syndrome and capillary leak syndrome—may also occur. Clofarabine is teratogenic in rats and rabbits, and should not be used during pregnancy.

HYPOMETHYLATING AGENTS

Azacitidine

Azacitidine [Vidaza], approved in 2004, is the first representative of a new class of anticancer drugs: the hypomethylating agents. Azacitidine, an analog of cytosine, becomes incorporated into DNA and then inhibits DNA methyltransferase, an enzyme that puts methyl groups onto DNA components. The

resultant hypomethylation of DNA is believed to induce apoptosis and restore normal function to genes critical to cell differentiation and proliferation. In vitro, drug concentrations that cause maximal inhibition of DNA methyltransferase do not cause significant inhibition of DNA synthesis. Azacitidine has one indication: *myelodysplastic syndrome*, a bone marrow disorder characterized by reduced blood cell counts and the potential to progress to acute myelogenous leukemia. Toxicities include myelosuppression, nausea and vomiting, and CNS depression. The starting dosage is 75 mg/m² (subQ or IV) once a day for 7 days repeated every 4 weeks.

Decitabine

Decitabine [Dacogen], like azacitidine, is an analog of cytosine that inhibits DNA methyltransferase, and thereby suppresses DNA methylation, leading to apoptosis and/or normalization of differentiation and proliferation. Like azacitidine, decitabine is used only for *myelodysplastic syndrome*. Toxicities include myelosuppression, nausea and vomiting, and a flu-like syndrome. A single dose consists of 15 mg/m² infused IV over 3 hours. The regimen consists of one dose every 8 hours for 72 hours, repeated every 6 weeks.

ANTITUMOR ANTIBIOTICS

The antitumor antibiotics are cytotoxic drugs originally isolated from cultures of *Streptomyces*. In this section, we consider five antitumor antibiotics and three of their derivatives. The antitumor antibiotics and their derivatives are used only to treat cancer; they are not used to treat infections. All of these drugs injure cells through direct interaction with DNA. Because of poor GI absorption, they are all administered parenterally, almost always IV. The antitumor antibiotics fall into two major groups: anthracyclines and nonanthracyclines.

Anthracyclines

Five of the antitumor antibiotics are derivatives of anthracycline. All five cause severe bone marrow suppression, and all five can damage the heart. In some patients, cardiotoxicity has led to fatal heart failure. Treatment with dexrazoxane [Zincard] offers some protection against cardiac damage.

Doxorubicin, Conventional

Doxorubicin, a derivative of anthracycline, is active against a broad spectrum of neoplastic diseases. Unfortunately, cardiotoxicity limits its utility. Doxorubicin is available in two formulations: conventional [Adriamycin] and liposomal [Doxil, Caelyx[®]]. The conventional preparation is discussed here. The liposomal preparation is discussed immediately below.

Mechanism of Action. Doxorubicin is a planar (flat) molecule that kills cells by two related mechanisms: *intercalation with DNA* and *inhibition of topoisomerase II*. We can understand intercalation by envisioning the stacked base pairs of DNA as having a structure like that of a stack of coins. Having a coin-like shape itself, doxorubicin is able to slip between base pairs of DNA, after which it becomes bound to DNA. This process (intercalation) distorts DNA structure. As a result, DNA polymerase and RNA polymerase are unable to use DNA as a template, and hence synthesis of DNA and RNA is inhibited.

While bound to DNA, doxorubicin forms a complex with topoisomerase II, an enzyme that cleaves and then repairs DNA strands. Doxorubicin allows topoisomerase II to cleave DNA, but prevents subsequent DNA repair. In the absence of DNA repair, apoptosis results. Topoisomerase is discussed further below, under *Topoisomerase Inhibitors*. Doxorubicin is *cell-cycle phase nonspecific*.

Pharmacokinetics. Doxorubicin is administered by IV infusion and undergoes rapid uptake by tissues, but does not cross the blood-brain barrier. Much of each dose is metabolized in the liver. Accordingly, dosage must be reduced in patients with hepatic impairment. Doxorubicin and its metabolites are eliminated primarily in the bile.

Therapeutic Uses. Doxorubicin is active against many neoplastic diseases. The drug is employed to treat solid tumors and disseminated cancers. Specific indications include *Hodgkin's and non-Hodgkin's lymphomas, sarcomas of soft tissue and bone, and various carcinomas, including carcinoma of the lung, stomach, breast, ovary, testes, and thyroid.*

Cardiotoxicity. Doxorubicin can cause acute and delayed injury to the heart. Acute effects (dysrhythmias, electrocardiographic changes) can develop within minutes of dosing. In most cases these reactions are transient, lasting no more than 2 weeks.

Delayed cardiotoxicity develops months to years after doxorubicin therapy, and manifests as heart failure secondary to diffuse cardiomyopathy (myofibril degeneration). The condition is often unresponsive to treatment. Delayed cardiac injury is directly related to the total cumulative dose: The risk of heart failure increases significantly as the cumulative lifetime dose rises above 550 mg/m². Accordingly, the total dose should not exceed this amount.

Dexrazoxane [Zinecard] can protect the heart from doxorubicin, but at the expense of additional myelosuppression and possible reduction of antitumor activity. To protect the heart, dexrazoxane must first undergo conversion to a chelating agent. In this active form, the drug binds intracellular iron. Just how chelation of iron protects against cardiotoxicity is unclear. In clinical trials, dexrazoxane significantly decreased the incidence of doxorubicin-induced heart failure. However, treatment did have two complications: (1) the drug appeared to intensify myelosuppression, and (2) it may have reduced the anticancer effects of doxorubicin. To ensure that the benefits of chemotherapy are not compromised, dexrazoxane is approved only for patients who have already received 300 mg/m² of doxorubicin. Furthermore, the drug is approved only for patients receiving doxorubicin for *breast cancer* (even though doxorubicin is used to treat other malignancies). Why the restriction? Because intensification of myelosuppression may be greater in patients with tumors other than breast cancer.

Angiotensin-converting enzyme (ACE) inhibitors, such as ramipril, can improve symptoms of cardiomyopathy. Furthermore, if given early, ACE inhibitors may be able to prevent cardiac damage.

Other Toxicities. Acute toxicity usually manifests as nausea and vomiting. Because of its vesicant properties, doxorubicin can cause severe local injury if extravasation occurs. In addition, the drug imparts a harmless red color to urine and sweat; patients should be forewarned. The usual dose-limiting toxicity is bone marrow suppression. Neutropenia develops in about 70% of patients. Thrombocytopenia and anemia may also occur. Additional delayed toxicities include alopecia, stomatitis, anorexia, conjunctivitis, and pigmentation in the extremities.

Doxorubicin, Liposomal

Liposomal doxorubicin [Doxil, Caelyx]—a reformulation of conventional doxorubicin—was created to increase delivery of the drug to tumor cells, and decrease its uptake by normal cells. The preparation consists of doxorubicin encapsulated within lipid vesicles (liposomes), which are coated with polyethylene glycol to avoid immune removal, and

thereby prolong their stay in the bloodstream. While in the vicinity of tumor cells and normal cells, the liposomes slowly release doxorubicin. However, because capillaries in tumors are more leaky than capillaries in healthy tissue, the liposomes have better access to tumor cells, and hence show some tumor selectivity. Liposomal doxorubicin is administered as a 30-minute IV infusion.

The preparation has four indications: *AIDS-related Kaposi's sarcoma, metastatic ovarian cancer, metastatic breast cancer, and multiple myeloma.*

Major dose-limiting toxicities are bone marrow suppression and heart failure. In addition, liposomal doxorubicin can cause hand-and-foot syndrome and infusion-related symptoms (back pain, flushing, and chest tightness), which are seen in 5% to 10% of patients. As a rule, the infusion symptoms begin within 5 minutes of infusion onset, subside when the infusion is interrupted, and don't return when the infusion is resumed at a slower rate.

Daunorubicin

Daunorubicin is nearly identical in structure to doxorubicin, and shares many of its properties. Like doxorubicin, daunorubicin intercalates with DNA and thereby inhibits DNA and RNA synthesis. The drug can act during all phases of the cell cycle, but cytotoxicity is greatest during S phase.

Like doxorubicin, daunorubicin is available in two formulations: conventional [Cerubidine] and liposomal [DaunoXome]. The conventional formulation is used for induction therapy of *leukemia*. The liposomal formulation is used for *HIV-associated Kaposi's sarcoma*.

As with doxorubicin, the major dose-limiting toxicities are bone marrow suppression and heart failure. In addition, daunorubicin may cause nausea, vomiting, stomatitis, and alopecia. Like doxorubicin, daunorubicin imparts a harmless red color to urine and tears.

Epirubicin

Mechanism of Action and Therapeutic Use. Epirubicin [Ellence], an analog of doxorubicin, is indicated for IV adjuvant therapy of *breast cancer*, following surgical removal of the primary tumor in patients who have axillary node involvement. Combined therapy with cyclophosphamide and fluorouracil is usually employed. Epirubicin is given in repeated 21-day cycles consisting of either (1) 100 mg/m² on day 1 only, or (2) 60 mg/m² on days 1 and 8. For most patients, epirubicin offers no advantages over doxorubicin.

Like doxorubicin, epirubicin (1) intercalates DNA and thereby inhibits synthesis of DNA, RNA, and proteins; and (2) causes DNA strand breaks by disrupting function of topoisomerase II. Epirubicin is considered cell-cycle phase nonspecific. However, cytotoxicity is maximal during S phase and G₂.

Pharmacokinetics. Epirubicin is widely distributed following IV infusion. The drug undergoes hepatic metabolism followed by excretion in the bile and urine. Elimination is slowed in patients with liver dysfunction secondary to hepatic metastases or other causes.

Adverse Effects. Epirubicin can cause a variety of serious adverse effects. As with doxorubicin, bone marrow suppression and cardiotoxicity are dose limiting. To reduce the risk of severe cardiac damage, the total cumulative dose should not exceed 900 mg/m² (compared with 550 mg/m² for doxorubicin). Fortunately, when epirubicin is used for adjuvant therapy, the cumulative dose should be well below the safe limit. Extravasation can result in severe local tissue necrosis. Additional adverse effects include alopecia, nausea, vomiting, mucositis, and red discoloration of urine. In animals, epirubicin is embryotoxic and teratogenic; studies in pregnant women have not been performed.

Idarubicin

Idarubicin [Idamycin] is a structural analog of daunorubicin and doxorubicin. The drug has one approved indication: induction therapy of *acute myelogenous leukemia* in adults. Like other anthracyclines, idarubicin (1) intercalates DNA to disrupt synthesis of DNA, RNA, and proteins; and (2) causes DNA strand breaks by disrupting function of topoisomerase II. Idarubicin works best during S phase and G₂ but is still considered phase nonspecific. Following IV infusion, the drug undergoes rapid and widespread distribution. Elimination is by hepatic metabolism followed by biliary excretion. The principal dose-limiting toxicity is bone marrow suppression. Like other anthracyclines, idarubicin is cardiotoxic, especially when the cumulative dose exceeds 150 mg/m². Additional toxicities include nausea, vomiting, alopecia,

and stomatitis. Idarubicin is a vesicant and can cause severe local injury upon extravasation.

Mitoxantrone

Although not a true anthracycline, mitoxantrone [Novantrone] is a close relative of these drugs and shares most of their properties. Like the anthracyclines, mitoxantrone appears to act by two mechanisms: (1) intercalation of DNA and (2) promotion of DNA strand breakage secondary to inhibition of topoisomerase II. The drug is cell-cycle phase nonspecific. Principal applications are *prostate cancer* and *acute nonlymphocytic leukemias*. In addition, the drug is used to reduce neurologic disability in people with multiple sclerosis (see Chapter 23). Mitoxantrone is administered intravenously and undergoes rapid and widespread distribution. Elimination occurs slowly, primarily by hepatic metabolism and biliary excretion. The major dose-limiting toxicities are bone marrow suppression and injury to the heart, especially when the cumulative dose exceeds 120 mg/m². Other important toxicities—nausea, vomiting, alopecia, and mucositis—are less severe than with doxorubicin. Some patients develop acute myelogenous leukemia while using the drug. Mitoxantrone imparts a harmless blue-green tint to the urine, skin, and sclera; patients should be forewarned.

Nonanthracyclines

There are three nonanthracycline antitumor antibiotics: dactinomycin, bleomycin, and mitomycin. In contrast to anthracyclines, nonanthracyclines do not injure the heart. However, these drugs do have serious toxicities of their own.

Dactinomycin (Actinomycin D)

Actions and Uses. Like doxorubicin, dactinomycin [Cosmegen] is a planar molecule that intercalates DNA, and thereby distorts DNA structure. As a result, RNA polymerase is unable to use DNA as a template, and hence synthesis of RNA (and proteins) is inhibited. Unlike RNA polymerase, DNA polymerase is relatively insensitive to the change in DNA. Consequently, DNA synthesis is not suppressed. Dactinomycin is *phase nonspecific*. Major indications for dactinomycin are *Wilms' tumor* and *rhabdomyosarcoma*. Other indications include *choriocarcinoma*, *Ewing's sarcoma*, *Kaposi's sarcoma*, and *testicular cancer*.

Pharmacokinetics. Administration is by IV infusion. Because of tissue uptake and binding to DNA, dactinomycin is rapidly cleared from the blood. The drug does not cross the blood-brain barrier. Elimination occurs slowly by biliary and renal excretion.

Toxicity. Dose-limiting toxicities are bone marrow suppression and oral and GI mucositis. Nausea and vomiting may be severe. Other toxicities include diarrhea, alopecia, folliculitis, and, in previously irradiated areas, dermatitis. Dactinomycin is a strong vesicant, and hence extravasation will cause severe local injury.

Bleomycin

The preparation of bleomycin used clinically contains a mixture of glycopeptides. The major components are bleomycin A₂ and bleomycin B₂. Bleomycin is unusual among the cytotoxic agents in that it causes very little bone marrow suppression. However, it can cause severe injury to the lungs. Because myelosuppression is minimal, bleomycin could be especially useful in combination chemotherapy, although the potential for lung injury often limits its use. Bleomycin binds to DNA, causing chain scission and fragmentation. The drug is most effective during G₂.

Therapeutic uses include *testicular carcinomas* (embryonal cell, choriocarcinoma, teratocarcinoma), *lymphomas* (Hodgkin's, reticulum cell sarcoma, lymphosarcoma), and *squamous cell carcinomas* (head, neck, larynx, cervix, penis, vulva, skin). The most common uses are testicular cancer and Hodgkin's disease, for which bleomycin is employed as a component of curative regimens.

Administration is parenteral (IM, IV, subQ, intrapleural). High concentrations are achieved in the skin and lungs. The drug does not enter the CNS. Most tissues contain large amounts of bleomycin hydrolase, an enzyme that renders the drug inactive. However, cells of the skin and lungs, which are sites of toxicity, lack this enzyme. Most of each dose is excreted unchanged in the urine.

The major dose-limiting toxicity is injury to the lungs, which occurs in about 10% of patients. Injury manifests initially as pneumonitis. In about 1% of patients, pneumonitis progresses to severe pulmonary fibrosis and death. Pulmonary function should be monitored and bleomycin discontinued at the first sign of adverse changes. Additional toxicities include stomatitis, alopecia, and skin reactions (hyperpigmentation, hyperkeratosis, pruritus erythema, ulceration, vesiculation). Nausea and vomiting are usually mild.

Unlike most other cytotoxic anticancer drugs, bleomycin exerts minimal toxicity to bone marrow. About 1% of patients with lymphomas experience a unique hypersensitivity reaction, characterized by fever, chills, confusion, hypotension, and wheezing.

Mitomycin

Mitomycin, formerly available as Mutamycin, is a prodrug that is converted to its active form within cells. Following activation, it functions as a bifunctional or trifunctional alkylating agent. Cell death is caused by cross-linking DNA with resultant blockade of DNA synthesis. Mitomycin may also induce strand scission. The drug is active during all phases of the cell cycle, but toxicity is greatest during late G₁ and early S phase.

Mitomycin is labeled for *disseminated adenocarcinoma of the stomach and pancreas*. Unlabeled uses include *carcinomas of the colon, rectum, esophagus, lung, breast, cervix, and bladder*.

Mitomycin is administered by IV infusion and is distributed widely, but not to the CNS. The drug undergoes rapid hepatic conversion to active and inactive metabolites. Metabolites are excreted in the urine.

The major dose-limiting toxicity is delayed bone marrow suppression; nadirs for neutropenia and thrombocytopenia usually occur 4 to 6 weeks after treatment. Mitomycin can also cause hemolytic uremic syndrome, a serious disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, and irreversible renal failure. Other toxicities include nausea, vomiting, stomatitis, alopecia, and pulmonary toxicity. Mitomycin is a vesicant and can cause severe local injury upon extravasation.

MITOTIC INHIBITORS

Mitotic inhibitors are drugs that act during M phase to prevent cell division. There are two major groups of these drugs—*vinca alkaloids* and *taxanes*—as well as three other drugs that belong to neither group.

Vinca Alkaloids

The vinca alkaloids are derived from *Vinca rosea* (the periwinkle plant), hence the group name. *Vincristine* and *vinblastine* are the most important members. These drugs have nearly identical structures and share the same mechanism of action. However, they have quite different toxicities: Vincristine is toxic to peripheral nerves, but does little damage to bone marrow. Conversely, vinblastine can cause significant bone marrow suppression, but is much less toxic to nerves.

Vincristine

Mechanism of Action. Vincristine [Oncovin, Vincasar PFS] blocks mitosis during metaphase, and hence is M-phase specific. It blocks mitosis by disrupting the assembly of microtubules, the filaments that move chromosomes during cell division. To block microtubule assembly, vincristine binds with *tubulin*, the major component of microtubules. In the absence of microtubules, cell division stops at metaphase. Metaphase block is a potent signal for apoptosis (programmed cell death).

Pharmacokinetics. Because of low and erratic oral absorption, vincristine must be given IV. The drug leaves the vascular system and enters tissues, where it becomes tightly but reversibly bound. Penetration to the CNS is poor. Most of each dose undergoes hepatic metabolism followed by biliary excretion. Only 12% is eliminated in the urine.

Therapeutic Uses. Vincristine is bone marrow sparing. Accordingly, the drug is ideal for combination chemotherapy. Indications include *Hodgkin's and non-Hodgkin's lymphomas*, *acute lymphocytic leukemia*, *Wilms' tumor*, *rhabdomyosarcoma*, *Kaposi's sarcoma*, *breast cancer*, and *bladder cancer*.

Toxicity. *Peripheral neuropathy* is the major dose-limiting toxicity. Vincristine injures neurons by disrupting neurotubules.

which are required for axonal transport of enzymes and organelles. Injury to neurotubules results from binding to tubulin, the same protein found in microtubules. Nearly all patients experience symptoms of sensory or motor nerve injury (eg, decreased reflexes, weakness, paresthesias, sensory loss). Symptoms of injury to autonomic nerves (eg, constipation, urinary hesitancy) are less common, occurring in 30% to 50% of patients. Because vincristine does not readily enter the CNS, injury to the brain is minimal.

In contrast to most cytotoxic anticancer drugs, *vincristine causes little bone marrow suppression*. As a result, the drug is especially desirable for combined therapy with other anticancer drugs, most of which do suppress the marrow.

Vincristine is a vesicant and can cause severe local injury if extravasation occurs. Alopecia develops in about 20% of patients. Significant nausea and vomiting are uncommon.

Vinblastine

Vinblastine [Velban] is a structural analog of vincristine. The two drugs share the same mechanism of action: production of metaphase arrest through blockade of microtubule assembly. Like vincristine, vinblastine is administered IV, does not cross the blood-brain barrier, and is eliminated by biliary and urinary excretion. Indications include *Kaposi's sarcoma*, *Hodgkin's and non-Hodgkin's lymphomas*, and *carcinoma of the breast and testes*. The major dose-limiting toxicity is bone marrow suppression. (Note that vinblastine differs markedly from vincristine in this regard.) Neurotoxicity can occur, but is less common and less severe than with vincristine. Additional adverse effects include nausea, vomiting, alopecia, stomatitis, and severe local injury if extravasation occurs.

Vinorelbine

Vinorelbine [Navelbine] is a semisynthetic vinca alkaloid similar in structure and actions to vincristine and vinblastine. The drug is approved only for *non-small cell lung cancer*. Investigational uses include *breast cancer*, *ovarian cancer*, and *Hodgkin's disease*. Benefits derive from causing metaphase arrest through inhibition of microtubule assembly. Vinorelbine is administered IV, undergoes hepatic metabolism, and is eliminated primarily in the bile. Like vinblastine, and unlike vincristine, vinorelbine can cause profound bone marrow suppression; neutropenia develops in about 50% of patients. Peripheral neuropathy occurs, but is less severe than with vincristine. Rarely, vinorelbine causes interstitial pulmonary damage and adult respiratory distress syndrome, typically within 1 week of treatment; most cases are fatal. Accordingly, be alert for new-onset dyspnea, cough, hypoxia, and related signs of lung injury. Other adverse effects include alopecia, constipation, nausea, and vomiting, all of which are generally mild to moderate. Like vincristine and vinblastine, vinorelbine can cause local tissue necrosis if extravasation occurs.

Taxanes

Paclitaxel

Actions and Uses. Paclitaxel [Abraxane, Onxol, Taxol[®]] is a widely used drug that acts during late G₂ and M phases to promote formation of stable microtubule bundles, thereby inhibiting cell division and producing apoptosis. Paclitaxel (in combination with cisplatin) is approved as first-line therapy for advanced *ovarian cancer* and *non-small cell lung cancer* in patients who are not candidates for potentially curative surgery or radiation therapy. In addition, the drug is approved as second-line therapy for *AIDS-related Kaposi's sarcoma* and as adjuvant therapy combined with doxorubicin-containing regimens for women with *breast cancer*. Investigational uses include *advanced head and neck cancer*, *adenocarcinoma of the upper GI tract*, and *leukemias*.

Pharmacokinetics. Paclitaxel is administered by infusion, for either 3 hours or 24 hours. The drug undergoes wide distribution, but not to the CNS. Very little is known about how paclitaxel is eliminated, small amounts appear in the urine and bile, but the fate of the remainder is unknown.

Formulations. Paclitaxel is available in two IV formulations. The older of the two, sold as Onxol and Taxol[®], contains a solvent system (Cremaphor and alcohol) that can trigger severe hypersensitivity reactions. The newer formulation, sold as Abraxane, consists of paclitaxel bound to nanoparticles of albumin. Addition of water forms a suspension; no solvent is employed.

Toxicity. Severe hypersensitivity reactions (hypotension, dyspnea, angioedema, urticaria) have occurred during infusion of Onxol and Taxol[®]—but not Abraxane—apparently in response to the solvent employed. The risk of severe hypersensitivity reactions with Onxol and Taxol[®] can be minimized by pretreatment with a glucocorticoid (dexamethasone), histamine₁ receptor antagonist (diphenhydramine), and histamine₂ receptor antagonist (cimetidine). With Abraxane, no pretreatment is needed.

The major dose-limiting toxicity is *bone marrow suppression* (neutropenia). Peripheral neuropathy develops with repeated infusions and may also be dose limiting. Paclitaxel can affect the heart, causing bradycardia, second- and third-degree heart block, and even fatal myocardial infarction. Muscle and joint pain have occurred. Practically all patients experience sudden but reversible alopecia, which frequently involves the body as well as the scalp. Gastrointestinal reactions—nausea, vomiting, diarrhea, and mucositis—are generally mild.

Docetaxel

Actions, Uses, and Source. Docetaxel [Taxotere] is similar in structure and actions to paclitaxel. Like paclitaxel, docetaxel stabilizes microtubules, and thereby inhibits mitosis. Docetaxel has three approved indications: (1) locally advanced or metastatic *breast cancer* that has progressed or relapsed despite prior chemotherapy, (2) locally advanced or metastatic *non-small cell lung cancer* that has advanced despite prior cisplatin-based therapy, and (3) advanced hormone-refractory metastatic *prostate cancer*, but only in combination with prednisone. In clinical trials, docetaxel produced objective responses in over 40% of patients with breast cancer. Recommended dosages are 60 or 100 mg/m² (for breast cancer) and 75 mg/m² (for lung and prostate cancers). For all patients, docetaxel is infused IV over 1 hour every 3 weeks. Docetaxel is manufactured by a semisynthetic process that begins with a compound extracted from needles of the European yew tree.

Toxicity. Significant neutropenia develops in virtually all patients. Docetaxel should be withheld if neutrophil counts fall below 1500/mm³. In clinical trials, death from sepsis occurred in 1% of patients with normal liver function and in 11% of patients with abnormal liver function. Because liver dysfunction increases the risk of death, docetaxel should be avoided if signs of significant liver disease are present (ie, plasma aspartate transferase [AST] and/or alanine transaminase [ALT] more than 1.5 times the upper limit of normal [ULN], together with alkaline phosphatase more than 2.5 times the ULN).

Severe hypersensitivity can occur. Manifestations include hypotension, bronchospasm, and generalized rash or erythema. Docetaxel should be avoided in patients who reacted strongly to a previous dose or to any drug containing polysorbate 80 (the vehicle docetaxel is supplied in). To reduce hypersensitivity reactions, patients should take an oral glucocorticoid for 5 days, starting 1 day before each infusion.

Severe fluid retention can occur, especially in patients with abnormal liver function. Possible manifestations include generalized edema, dyspnea at rest, cardiac tamponade, pleural effusion requiring urgent drainage, and pronounced abdominal distention (from ascites). As with hypersensitivity reactions, fluid retention can be reduced by treatment with oral glucocorticoids, which are normally started the day before dosing and continued for 2 days after.

Additional common toxicities are anemia, nausea, diarrhea, stomatitis, fever, and neurosensory symptoms (paresthesias, pain).

Cabazitaxel

Actions and Use. Cabazitaxel [Jevtana], in combination with prednisone, is indicated for second-line IV treatment of advanced hormone-refractory prostate cancer in men who have already received docetaxel. In one trial,

discomfort (57%), anorexia (55%), fever (45%), and weight loss (30%). Less common side effects include stomatitis, dyspepsia, headache, cough, rhinitis, insomnia, and rash.

Etoposide

Etoposide [Etopophos, Toposar], a drug derived from podophyllotoxin (a naturally occurring plant alkaloid), inhibits topoisomerase II. Etoposide does not prevent topoisomerase II from making double-strand breaks in DNA, but it does prevent the enzyme from resealing those breaks. Cell death results from accumulation of DNA with multiple breaks. Cells in S and G₂ phase are most sensitive. Etoposide is approved only for *refractory testicular cancer* and *small cell cancer of the lung*, but is used off-label against many other tumors.

Administration is PO or IV. Plasma protein binding is high. Penetration to the CNS is low. Etoposide is eliminated by hepatic metabolism and renal excretion, and hence dosage should be reduced in patients with liver or renal impairment.

The major dose-limiting toxicity is bone marrow suppression. Other toxicities include alopecia, mucositis, and, rarely, peripheral neuropathy. Early adverse effects include nausea, vomiting, diarrhea, and fever.

With one etoposide product—Toposar—hypotension can occur with rapid IV administration. The cause is the organic diluent used to solubilize etoposide, not etoposide itself. Hypotension can be avoided by diluting the drug in sufficient IV fluid. Hypotension is not a problem with Etopophos (etoposide phosphate), because this product is soluble in water, and hence the organic solubilizer is not needed.

Teniposide

Teniposide [Vumon] is an analog of etoposide and has the same mechanism of action: inhibition of topoisomerase II. The only approved indication is *refractory acute lymphoblastic leukemia of childhood*.

Administration is by slow IV infusion. Most of each dose becomes bound to plasma proteins. Penetration to the CNS is poor. Elimination is by hepatic metabolism and renal excretion.

The major dose-limiting toxicity is bone marrow suppression (neutropenia, thrombocytopenia, anemia). Severe hypersensitivity reactions (urticaria, angioedema, bronchospasm, hypotension) occur in about 5% of patients; symptoms can be suppressed with epinephrine. Secondary leukemias may develop within 8 years of initial drug exposure. Other toxicities include nausea, vomiting, diarrhea, and alopecia.

MISCELLANEOUS CYTOTOXIC DRUGS

Asparaginase

Asparaginase [Elspar, Erwinase*, Kidrolase*] is an enzyme that converts asparagine, an essential amino acid, into aspartic acid. By converting asparagine to aspartic acid, the drug deprives cells of asparagine needed to synthesize proteins. However, not all cells are affected. In fact, toxicity from asparaginase is limited almost exclusively to leukemic lymphoblasts. Why? Because these cells are unable to manufacture their own asparagine, whereas normal cells can. Hence, normal cells are able to replace the asparagine that asparaginase took away, but leukemic lymphoblasts can't. Asparaginase appears to act selectively during G₁.

The only indication for asparaginase is *acute lymphocytic leukemia*. To induce remission, asparaginase is usually combined with prednisone and vincristine, and perhaps daunorubicin or doxorubicin.

Administration is parenteral (IM and IV). Distribution is restricted to the vascular system. The drug does not cross the blood-brain barrier, and is inactivated by serum proteases.

Asparaginase can cause severe adverse effects. However, the spectrum of toxicities differs from that of other anticancer drugs. By inhibiting protein synthesis, the drug can cause coagulation deficiencies and can injure the liver, pancreas, and kidneys. Symptoms of CNS depression, ranging from confusion to coma, develop in about 30% of patients. Nausea and vomiting can be intense and may limit the dose that can be tolerated. Because asparaginase is a foreign protein, hypersensitivity reactions are common; fatal anaphylaxis can occur, and hence facilities for resuscitation should be immediately available. In contrast to most other anticancer drugs, asparaginase does not depress the bone marrow, and does not cause alopecia, oral mucositis, or intestinal ulceration.

Pegaspargase

Pegaspargase [Oncaspar] is a modified form of asparaginase that causes fewer hypersensitivity reactions. Otherwise, the drugs are much the same. They have the same mechanism of action (destruction of asparagine) and produce the same spectrum of adverse effects (hypersensitivity reactions, pancreatitis, coagulopathy, and liver and kidney impairment). Of the patients who had hypersensitivity reactions to asparaginase, about 30% also react to pegaspargase. Pegaspargase is indicated only for *acute lymphocytic leukemia*, and only in patients who experienced hypersensitivity to asparaginase. Administration is IM or IV.

Hydroxyurea

Hydroxyurea [Hydrea, Droxia] inhibits DNA replication by suppressing synthesis of DNA precursors. Specifically, the drug inhibits ribonucleoside diphosphate reductase, the enzyme that converts ribonucleotides into their corresponding deoxyribonucleotides. In the absence of deoxyribonucleotides, DNA cannot be made. Hydroxyurea is S-phase specific.

The principal indication for hydroxyurea is *chronic myelogenous leukemia*. The drug is also used for *squamous cell carcinoma* and recurrent, metastatic, or inoperable *carcinoma of the ovary*. In addition, hydroxyurea can relieve symptoms and prolong life in patients with *sickle cell anemia* (see Chapter 107). When used for cancer, hydroxyurea is marketed as *Hydrea*, and when used for sickle cell anemia, it's marketed as *Droxia*.

Hydroxyurea is rapidly absorbed after oral dosing. Unlike most anticancer agents, hydroxyurea crosses the blood-brain barrier with ease. Part of each dose is metabolized in the liver. Parent drug and metabolites are eliminated primarily in the urine.

The principal dose-limiting toxicity is bone marrow suppression. The drug also causes nausea, vomiting, and dysuria. Neurologic deficits and stomatitis may occur, but these are rare. Hydroxyurea is teratogenic in experimental animals. Hence, like most other anticancer agents, it should be avoided during pregnancy.

Mitotane

Mitotane [Lysdren] is a structural analog of two insecticides: DDD and DDT. For reasons that are not understood, the drug is selectively toxic to cells of the adrenal cortex, both normal and neoplastic. The only indication for mitotane is palliative therapy of inoperable *adrenocortical carcinoma*.

Mitotane is administered PO. About 40% is absorbed. The drug is distributed widely, but not to the CNS. Because of storage in tissues (primarily fat), active drug remains in the body for weeks after dosing has ceased. Elimination is by hepatic metabolism and renal excretion.

The principal dose-limiting toxicities are CNS depression, nausea, and vomiting. Because mitotane injures the adrenal cortex, adrenal insufficiency is likely. Accordingly, patients will require supplemental glucocorticoids, especially at times of stress. Dermatitis is common. Other adverse effects include visual disturbances; orthostatic hypotension; and renal damage, manifesting as hematuria, hemorrhagic cystitis, and albuminuria. Mitotane does not cause the toxicities associated with most other anticancer drugs (bone marrow suppression, alopecia, oral and GI ulceration).

Procarbazine

Mechanism of Action. Procarbazine [Matulane] is a prodrug that undergoes conversion to active metabolites in the liver. The metabolites alkylate DNA, and thereby suppress synthesis of DNA, RNA, and protein. The precise cause of cell death is unknown. Procarbazine is cell-cycle phase non-specific.

Pharmacokinetics. Procarbazine is readily absorbed following oral dosing, but undergoes rapid and extensive hepatic metabolism. Active metabolites are highly lipid soluble and cross the blood-brain barrier with ease. Procarbazine and its metabolites are excreted primarily in the urine.

Therapeutic Uses. The major uses for procarbazine are *Hodgkin's disease*, *non-Hodgkin's lymphoma*, and *primary brain cancer*. For Hodgkin's disease, procarbazine is combined with mechlorethamine, vincristine [Oncovin, Vincasar], and prednisone in the so-called MOPP regimen, formerly the regimen of choice in newly diagnosed patients.

Toxicity. The usual dose-limiting toxicity is bone marrow suppression. Nausea and vomiting may also be dose limiting. Other adverse effects include peripheral neuropathy, CNS depression, secondary leukemias, and sterility, especially in males.

Drug Interactions. Owing to its CNS effects, procarbazine should not be combined with CNS depressants (eg, barbiturates, phenothiazines, opioids). Ingestion of alcohol can induce a disulfiram-like response. Because procarbazine inhibits monoamine oxidase, there is a risk of severe hypertension in response to sympathomimetic drugs, tricyclic antidepressants, and tyramine-rich foods.

Dacarbazine

Actions and Uses. Dacarbazine [DTIC-Dome] is a prodrug that undergoes activation in the liver. Although the precise mechanism of cell kill is unknown, there is evidence for alkylation of DNA, inhibition of DNA and RNA synthesis, and interaction with sulfhydryl groups on proteins. Dacarbazine is considered cell-cycle phase nonspecific. Principal indications are metastatic malignant melanoma and Hodgkin's disease.

Pharmacokinetics. Gastrointestinal absorption of dacarbazine is erratic, and hence the drug is given IV. Penetration to the CNS is poor. Elimination is by hepatic metabolism and renal excretion.

Toxicity. Bone marrow suppression is the usual dose-limiting toxicity. Nausea and vomiting occur in most patients, occasionally requiring cessation of treatment. Other toxicities include a flu-like syndrome, hepatic necrosis, photosensitivity, and burning pain along the injection site.

Altretamine (Hexamethylmelamine)

Altretamine [Hexalen], formerly known as hexamethylmelamine, is indicated for palliative therapy of persistent or recurrent ovarian cancer. Altretamine is a prodrug that is converted to active metabolites in the body. As with procarbazine and dacarbazine, the active metabolites have alkylating activity. However, the precise mechanism of cell kill has not been established. Altretamine is well absorbed following oral dosing, but undergoes rapid and extensive hepatic metabolism. Metabolites are excreted in the urine. The principal dose-limiting toxicity is bone marrow suppression. However, nausea and vomiting can also limit dosage. Peripheral sensory neuropathy is common. Central neurotoxicity (tremors, ataxia, vertigo, hallucinations, seizures, depression) is less common. Because of peripheral and central neurotoxicity, patients should receive regular neurologic evaluations.

KEY POINTS

- Cytotoxic anticancer drugs act directly on cancer cells and healthy cells to produce cell death.
- Cell-cycle phase-specific drugs are effective only during a specific phase of the cell cycle (eg, S phase, M phase). Accordingly, they are only active against cells that are participating in the cell cycle. Quiescent cells in G_0 are spared.
- To be effective, a phase-specific drug must be present as neoplastic cells cycle through the phase in which the drugs acts. In practical terms, this means that phase-specific drugs must be in the blood continuously over a long time.
- Cell-cycle phase-nonspecific drugs can affect cells during any phase of the cell cycle, including G_0 .
- Although phase-nonspecific drugs can inflict biochemical lesions at any time during the cell cycle, they are usually more toxic to proliferating cells than to cells in G_0 . Why? Because (1) G_0 cells often have time to repair drug-induced damage before it can result in significant harm, and (2) toxicity may not become manifest until the cells attempt to divide.
- About 50% of the cytotoxic anticancer drugs are phase specific; the rest are phase nonspecific.
- Alkylating agents injure cells primarily by forming covalent bonds with DNA.
- Bifunctional alkylating agents form cross-links in DNA, and thereby prevent DNA replication. Bifunctional agents are more effective than monofunctional agents.
- Because alkylation reactions can take place at any time during the cell cycle, alkylating agents are considered cell-cycle phase nonspecific.
- Cyclophosphamide, the most widely used alkylating agent, is active against a broad spectrum of neoplastic diseases.
- Antimetabolites are analogs of important natural metabolites, and hence are able to disrupt critical metabolic processes, especially DNA replication.
- Most antimetabolites are S-phase specific.
- Methotrexate, a folic acid analog, prevents conversion of folic acid to its active form. Cell kill results primarily from disruption of DNA synthesis.
- High doses of methotrexate coupled with leucovorin rescue can be used to treat methotrexate-resistant tumors. This technique can be dangerous in that failure to give sufficient leucovorin at the right time can be lethal.
- Cytarabine, a pyrimidine analog, undergoes intracellular activation followed by incorporation into DNA, where it acts to inhibit DNA synthesis.
- Fluorouracil, a uracil analog, undergoes intracellular activation, after which it inhibits thymidylate synthetase, thereby depriving cells of thymidylate needed to make DNA.
- Antitumor antibiotics are used to treat cancer, not infections.
- Antitumor antibiotics fall into two major groups: anthracyclines (which damage the heart) and nonanthracyclines (which don't).
- Doxorubicin is an anthracycline-type antitumor antibiotic. To reduce the risk of heart failure, the cumulative lifetime dose should be kept below 550 mg/m^2 . The risk can be further reduced with dexrazoxane, a drug that helps protect the heart from doxorubicin.
- Doxorubicin is a planar molecule that intercalates DNA, thereby distorting DNA structure. As a result, DNA polymerase and RNA polymerase are unable to use DNA as a template, and hence synthesis of DNA, RNA, and proteins is disrupted. Doxorubicin also disrupts the function of topoisomerase II, thereby causing strand breakage. This may be the primary mechanism of cell kill.
- Vincristine and vinblastine block assembly of the microtubules that move chromosomes during cell division. Accordingly, the drugs are M-phase specific.
- Vincristine is toxic to peripheral nerves, but does not significantly suppress bone marrow function. Because it spares bone marrow, vincristine can be safely combined with drugs that suppress bone marrow.
- In contrast to vincristine, vinblastine causes significant bone marrow suppression, but is relatively harmless to peripheral nerves.
- Asparaginase converts asparagine into aspartic acid, and thereby deprives cells of asparagine needed to make proteins. Cytotoxicity is limited primarily to leukemic lymphoblasts. Why? Because these cells are unable to manufacture their own asparagine, whereas normal cells can.

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Anticancer Drugs II: Hormonal Agents, Targeted Drugs, and Other Noncytotoxic Anticancer Drugs

DRUGS FOR BREAST CANCER

- Antiestrogens
- Aromatase Inhibitors
- Trastuzumab
- Lapatinib
- Cytotoxic Drugs (Chemotherapy)
- Denosumab and Bisphosphonates for Skeletal-Related Events

DRUGS FOR PROSTATE CANCER

- Androgen Deprivation Therapy
 - Gonadotropin-Releasing Hormone Agonists
 - Gonadotropin-Releasing Hormone Antagonists
 - Androgen Receptor Blockers
 - Abiraterone, a CYP17 Inhibitor
 - Ketoconazole
- Other Drugs for Prostate Cancer
 - Sipuleucel-T
 - Cytotoxic Drugs

TARGETED ANTICANCER DRUGS

- Kinase Inhibitors
 - EGFR Tyrosine Kinase Inhibitors
 - BCR-ABL Tyrosine Kinase Inhibitors
 - Multi-Tyrosine Kinase Inhibitors
 - mTOR Kinase Inhibitors
 - Vemurafenib, a BRAF V600E Kinase Inhibitor
 - Crizotinib, an ALK Inhibitor
- Other Targeted Drugs
 - CD20-Directed Antibodies
 - Brentuximab Vedotin, an Antibody-Drug Conjugate
 - Angiogenesis Inhibitors
 - Proteasome Inhibitors
 - Histone Deacetylase Inhibitors
 - Ipilimumab

IMMUNOSTIMULANTS

OTHER NONCYTOTOXIC ANTICANCER DRUGS

- Glucocorticoids
- Retinoids
- Arsenic Trioxide
- Denileukin Diftitox

OTHER NONCYTOTOXIC ANTICANCER DRUGS

(continued)

- Thalidomide
- Lenalidomide
- Progestins



Box 103–1. Angiogenesis Inhibitors: Keeping Cancer in Check

Box 103–2. Thalidomide Redeemed—and Strictly Controlled

In this chapter, we continue our discussion of anticancer agents, focusing on two large groups of drugs: hormonal agents and targeted drugs. The hormonal agents, used primarily for breast cancer and prostate cancer, mimic or suppress the actions of endogenous hormones. The so-called targeted drugs bind with specific molecular targets on cancer cells, and thereby suppress tumor growth and promote cell death. Unlike the cytotoxic agents discussed in Chapter 102, many of which are cell-cycle phase specific, the drugs addressed here lack phase specificity. In addition, many of these drugs lack the serious toxicities associated with cytotoxic agents, including bone marrow suppression, stomatitis, alopecia, and severe nausea and vomiting. Nonetheless, most of these have severe toxicities of their own.

DRUGS FOR BREAST CANCER

Breast cancer is second only to skin cancer as the most common cancer among women in the United States. In 2011, an estimated 230,480 new cases were diagnosed and 39,520 were fatal. Between 2002 and 2003, the incidence of breast cancer dropped by 7%. Why? Because many women stopped using menopausal hormone therapy (formerly known as hormone replacement therapy) after data from the Women's Health Initiative showed that it increased risk of breast cancer and heart disease (see Chapter 61). Not only has the incidence of breast cancer declined, so has the death rate, thanks to earlier detection and improved treatment.

Principal treatment modalities are *surgery, radiation, cytotoxic drugs (chemotherapy), and hormonal drugs*. Surgery and radiation are considered primary therapy; chemotherapy and hormonal therapy are used as adjuvants. For a woman with early breast cancer, treatment typically consists of sur-

gery (using total mastectomy or partial mastectomy [lumpectomy]) followed by local radiation. After that, chemotherapy is used to kill cells left behind after surgery and radiation, and to kill cells that may have metastasized to other sites. Finally, hormonal agents are taken for several years to reduce recurrence. Increasingly, chemotherapy is used *before* surgery—so-called neoadjuvant therapy—to shrink large tumors, and thereby permit lumpectomy in women who would otherwise require mastectomy. Drugs for adjuvant therapy are summarized in Table 103–1.

Hormonal agents for breast cancer fall into two major groups: *antiestrogens* (eg, tamoxifen [Nolvadex]) and *aromatase inhibitors* (eg, anastrozole [Arimidex]). Antiestrogens block receptors for estrogen, whereas aromatase inhibitors block estrogen biosynthesis. In both cases, tumor cells are deprived of the estrogen they need for growth. However, there is a caveat: For these drugs to work, tumor cells must have estrogen receptors (ERs). Fortunately, the majority of breast cancers are ER positive. For years, tamoxifen had been the hormonal agent of choice. However, recent data have shown that, in postmenopausal patients, aromatase inhibitors are more effective, both in the metastatic and adjuvant setting. There is a wealth of data showing that adjuvant hormonal therapy can reduce tumor recurrence and prolong life.

In addition to chemotherapy and hormonal therapy, two other drugs—*trastuzumab* [Herceptin] and *lapatinib* [Tykerb]—can be used for adjuvant treatment. Trastuzumab blocks receptors known as HER2, and lapatinib inhibits two enzymes, known as HER2 tyrosine kinase and EGFR tyrosine kinase. Both drugs are indicated only for cancers that are HER2 positive. As discussed later in the chapter, one more drug—*bevacizumab* [Avastin]—had been approved for breast cancer, but the indication was rescinded in 2011. Why? Because in postmarketing studies, bevacizumab failed to show significant benefit.

Lastly, patients may take *denosumab* [Xgeva] or *zoledronate* [Zometa] to minimize hypercalcemia (caused by bone metastases) and fractures (caused by bone metastases as well as hormonal therapy).

What about breast cancer *prevention*? Currently, two drugs are approved for preventing breast cancer in women at high risk. Both drugs are *selective estrogen receptor modulators*, or SERMS. One of the drugs—*raloxifene* [Evista]—is approved only for postmenopausal women. The other drug—*tamoxifen* [Nolvadex]—is approved for premenopausal and postmenopausal women. In clinical trials, these drugs reduced the risk of breast cancer by about 50%. However, they both pose a risk of thrombosis, and tamoxifen also poses a risk of endometrial cancer. Nonetheless, in women at high risk for breast cancer, the benefits of these drugs outweigh the risks. Raloxifene is discussed in Chapter 75. Tamoxifen is discussed below. Two other drugs—*exemestane* [Aromasin] (discussed below) and *lasofoxifene* [Oporia]—can also prevent breast cancer, but are not yet approved for this use.

Antiestrogens

Antiestrogens are drugs that block estrogen receptors, and hence only work against cells that are ER positive. Benefits derive from depriving tumor cells of the growth-promoting influence of estrogen. Three antiestrogens—tamoxifen, toremifene, and fulvestrant—are approved for adjuvant treatment. Of these, tamoxifen is by far the most widely used.

Tamoxifen

Tamoxifen [Nolvadex] is considered the gold standard for endocrine treatment of breast cancer. The drug is approved for treating established disease and for primary prevention in women at high risk. As discussed below, tamoxifen is a prodrug that must be converted to active metabolites.

Overview of Actions. Tamoxifen blocks estrogen receptors in some tissues and activates them in others. Receptor *blockade* underlies benefits in breast cancer, and also underlies some adverse effects (especially hot flashes). Receptor *activation* leads to other beneficial effects (increased bone mineral density, reduction of low-density lipoprotein cholesterol, elevation of high-density lipoprotein cholesterol) as well as certain adverse effects (endometrial cancer and blood clots). Because tamoxifen can cause receptor activation as well as blockade, the drug is often classified as a SERM.

Mechanism of Action in Breast Cancer. Tamoxifen is a prodrug that undergoes hepatic conversion to active metabolites. These metabolites then block estrogen receptors on breast cancer cells, and thereby prevent receptor activation by estradiol, the principal endogenous estrogen. Estrogen acts on tumor cells to stimulate growth and proliferation. Hence, in the absence of estradiol's influence, the rate of tumor cell proliferation declines. Tumors regress in size as the rate of cell death outpaces new cell production. Obviously, if treatment is to be effective, target cells must be ER positive.

Use for Treatment of Breast Cancer. Tamoxifen has two treatment applications: (1) as adjuvant therapy to suppress growth of residual cancer cells following surgery, and (2) treatment of metastatic disease. Efficacy as adjuvant therapy has been evaluated in 55 randomized trials involving more than 37,000 women. The result? Treatment for 1, 2, and 5 years decreased tumor recurrence by 21%, 29%, and 47%, respectively. Benefits were limited almost entirely to women with ER-positive cancer. Tamoxifen can be used in both premenopausal and postmenopausal women.

Use for Prevention of Breast Cancer. Tamoxifen is approved for reducing the development of breast cancer in healthy women at high risk. Approval was based on results of the Breast Cancer Prevention Trial, which enrolled 13,388 otherwise healthy women who had risk factors for breast cancer (eg, age older than 60, family history of breast cancer, failure to give birth before age 30, a breast biopsy showing atypical hyperplasia). Half of the participants received tamoxifen (20 mg PO daily) and half received placebo. After an average follow-up time of 4 years, daily tamoxifen reduced the incidence of breast cancer by 44%. Unfortunately, tamoxifen *increased* the incidence of endometrial cancer, pulmonary embolism, and deep vein thrombosis. Hence, women considering tamoxifen for chemoprevention must carefully weigh the benefits of treatment (reduced risk of breast cancer) against the risks (increased risk of endometrial cancer and thromboembolic events). According to guidelines issued in 2002 by the U.S. Preventive Services Task Force (USPSTF), tamoxifen chemoprevention is appropriate only for women at *high* risk, and not for women at lower risk. Specific recommendations for high-risk women in different age groups are as follows:

- *Ages 40 through 49*—Tamoxifen is a good choice, except for women at risk for thrombosis.
- *Ages 50 through 59*—Tamoxifen is a good choice, except for women at risk for thrombosis and for women who still

TABLE 103-1 ■ Drugs for Adjuvant Therapy of Breast Cancer

Generic Name	Trade Name	Route	Mechanism	Indications	Major Adverse Effects
HORMONAL THERAPIES					
Antiestrogens					
Tamoxifen	Nolvadex	PO	Blockade of estrogen receptors	ER-positive breast cancer in pre- and postmenopausal women	Increased risk of endometrial cancer and thrombosis
Toremifene	Fareston	PO	Blockade of estrogen receptors	ER-positive breast cancer in postmenopausal women only	Hot flushes, fluid retention, vaginal discharge, nausea, vomiting, and menstrual irregularities
Fulvestrant	Faslodex	IM	Blockade of estrogen receptors	ER-positive breast cancer in postmenopausal women only	
Aromatase Inhibitors					
Anastrozole	Arimidex	PO	Inhibition of estrogen synthesis	ER-positive breast cancer in postmenopausal women only	Musculoskeletal pain, osteoporosis and related fractures
Letrozole	Femara	PO			
Exemestane	Aromasin	PO			
OTHER DRUGS FOR BREAST CANCER					
Anti-HER2 Antibody					
Trastuzumab	Herceptin		Blockade of HER2 receptors	HER2-positive breast cancer in pre- and postmenopausal women	Cardiotoxicity and hypersensitivity reactions
Kinase Inhibitor					
Lapatinib	Tykerb	PO	Inhibits HER2 tyrosine kinase and EGFR tyrosine kinase	HER2-positive breast cancer in pre- and postmenopausal women	Diarrhea, hepatotoxicity, cardiotoxicity, interstitial lung disease
Cytotoxic Drugs (Representative Agents)					
Doxorubicin <i>plus</i> cyclophosphamide	Adriamycin, Cytoxan, Neosar		Direct cell kill by DNA intercalation, topoisomerase II inhibition, and DNA alkylation	Breast cancer in all women, regardless of ER, HER2, or menopausal status	Together, these drugs can cause cardiotoxicity, bone marrow suppression, alopecia, oral and GI ulceration, and hemorrhagic cystitis
Paclitaxel	Taxol, Onxol, Abraxane		Direct cell kill by mitotic arrest	Breast cancer in all women, regardless of ER, HER2, or menopausal status	Bone marrow suppression, peripheral neuropathy, alopecia, cardiotoxicity, muscle and joint pain Severe hypersensitivity reactions with Taxol and Onxol, but not Abraxane
Eribulin	Halaven	IV	Direct cell kill by mitotic arrest	Breast cancer in all women, regardless of ER, HER2, or menopausal status	Bone marrow suppression, peripheral neuropathy
Drugs to Delay Skeletal Events					
Denosumab	Xgeva*	SubQ	Inhibits osteoclast function and production	Hypercalcemia of malignancy, prevention of malignancy-related skeletal events	Hypocalcemia, serious infections, skin reactions, osteonecrosis of the jaw
Zoledronate	Zometa†	IV	Inhibits osteoclast function	Hypercalcemia of malignancy, prevention of malignancy-related skeletal events	Kidney damage, osteonecrosis of the jaw

EGFR = epidermal growth factor receptor, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2.
 *Denosumab is also available as *Prolia* for treating postmenopausal osteoporosis.
 †Zoledronate is also available as *Reclast* for treating osteoporosis and Paget's disease.

have a uterus (the risk of endometrial cancer is higher for women over age 50).

Age 60 and above—Tamoxifen is not recommended (although older women have the highest risk for breast cancer, they also have the highest risk for complications from tamoxifen). Despite this recommendation, tamoxifen is effective in older women, and hence some authorities would still recommend using it, but only after the woman carefully considers the benefit versus the risks.

To help determine who is at high risk for breast cancer, the National Cancer Institute has created an Internet-based Breast Cancer Risk Assessment Tool. You can access the tool at www.cancer.gov/bcrisktool.

Pharmacokinetics. Tamoxifen is readily absorbed following oral administration. In the liver, CYP2D6 (the 2D6 isozyme of cytochrome P450) converts tamoxifen to two active metabolites: 4-hydroxy-*N*-desmethyltamoxifen (endoxifen) and 4-hydroxytamoxifen. The half-lives of tamoxifen and its metabolites range from 1 to 2 weeks. Because clearance is slow, once-daily dosing is adequate. When treatment is stopped, tamoxifen and its metabolites can be detected in serum for weeks.

Not surprisingly, benefits of tamoxifen are greatly reduced in women with an inherited deficiency in the gene that codes for CYP2D6. In one study, the cancer recurrence rate in poor metabolizers was 9.5 times higher than in good metabolizers. Who are the poor metabolizers? Between 8% and 10% of Caucasian women have gene variants that prevent them from converting tamoxifen to its active metabolites. However, at this time, the Food and Drug Administration (FDA) neither requires nor recommends testing for variants in the CYP2D6 gene, although a test kit is available.

Adverse Effects. The most common adverse effects are hot flushes (64%), fluid retention (32%), vaginal discharge (30%), nausea (26%), vomiting (25%), and menstrual irregularities (25%). In women with bone metastases, tamoxifen may cause transient hypercalcemia and a flare in bone pain. Because of its estrogen agonist actions, tamoxifen poses a small risk of *thromboembolic events*, including deep vein thrombosis, pulmonary embolism, and stroke.

Perhaps the biggest concern is *endometrial cancer*. Tamoxifen acts as an estrogen agonist at receptors in the uterus, causing proliferation of endometrial tissue. Proliferation initially results in endometrial hyperplasia, and may eventually lead to endometrial cancer. In women taking tamoxifen to treat breast cancer, the benefits clearly outweigh this risk. However, in women taking the drug to prevent breast cancer, the risk/benefit balance is less obvious. In postmenopausal women, endometrial cancer is usually caught early, due to abnormal menstrual bleeding.

Tamoxifen can harm the developing fetus, and hence is classified in FDA Pregnancy Risk Category D. Accordingly, women using the drug should avoid getting pregnant.

Interaction with CYP2D6 Inhibitors. Inhibitors of CYP2D6 can prevent activation of tamoxifen, and can thereby negate the benefits of treatment. Put another way, when tamoxifen is combined with a CYP2D6 inhibitor, the risk of breast cancer recurrence is greater than when tamoxifen is used alone. Accordingly, women using tamoxifen should avoid strong CYP2D6 inhibitors. Important among these are *fluoxetine* [Prozac], *paroxetine* [Paxil, Pexeva], and *sertraline* [Zoloft]—selective serotonin reuptake inhibitors

(SSRIs) taken by many women to suppress tamoxifen-induced hot flushes. Fortunately, alternatives with less effect on CYP2D6 are available. Among these are *escitalopram* [Lexapro, CipraleX] (an SSRI) and *venlafaxine* [Effexor] (a serotonin/norepinephrine reuptake inhibitor).

Dosage and Administration. The usual dosage for adjuvant treatment of breast cancer is 20 mg PO once a day. Larger doses do not increase benefits. In most cases, treatment should continue 5 years. The dosage for prevention of breast cancer in high-risk women is 20 mg PO daily for 5 years. There are no data to indicate that extending treatment beyond 5 years increases benefits.

Toremifene

Actions and Use. Toremifene [Fareston] is an antiestrogen indicated for metastatic breast cancer in postmenopausal women with ER-positive tumors or tumors for which ER status is unknown. The drug is a structural analog of tamoxifen, and shares most of that drug's properties. Like tamoxifen, toremifene is a SERM with antiestrogenic actions in some tissues and estrogenic actions in others. In women with breast cancer, toremifene blocks estrogen receptors on tumor cells, thereby depriving them of estrogen's growth-promoting effects. In clinical trials, toremifene was about as effective as tamoxifen: With both drugs, the response rate in metastatic disease was about 20%, and median survival time was about 30 months. In a crossover study, most patients who failed to respond to tamoxifen also failed to respond to toremifene. The recommended dosage is 60 mg PO once a day.

Pharmacokinetics. Toremifene is well absorbed following oral administration. Plasma levels peak in 3 hours. The drug undergoes extensive hepatic metabolism, primarily by CYP3A4 (the 3A4 isozyme of cytochrome P450). Metabolites are excreted in the feces. The half-life is prolonged (about 5 days) owing to enterohepatic recirculation. As with tamoxifen, drugs that induce CYP3A4 will reduce toremifene levels, and drugs that inhibit the enzyme will raise toremifene levels.

Adverse Effects. Adverse effects are like those of tamoxifen. Hot flushes are most common, occurring in 35% of those treated. Other common reactions are sweating (20%), nausea (14%), and vaginal discharge (13%). Patients may also experience dizziness (9%), vomiting (4%), and vaginal bleeding (2%). Hypercalcemia may occur in women with bone metastases. There is a small risk of thromboembolic events. Cataracts and elevation of liver enzymes have been reported.

Toremifene prolongs the QT interval, and thereby poses a risk of potentially fatal dysrhythmias. To reduce risk, toremifene should be avoided in patients with hypokalemia, hypomagnesemia, or pre-existing QT prolongation, and in those taking other QT drugs.

Like tamoxifen, toremifene activates estrogen receptors in the uterus. As a result, the drug can promote uterine hyperplasia and uterine cancer.

Fulvestrant

Actions and Use. Fulvestrant [Faslodex] is an antiestrogen indicated for metastatic ER-positive breast cancer in postmenopausal women. Unlike tamoxifen and toremifene, which block some estrogen receptors and activate others, fulvestrant is a *pure estrogen receptor antagonist*—the first one available. As with other antiestrogens, benefits derive from depriving breast cancer cells of required hormonal stimulation.

Clinical Trials. In two trials, fulvestrant was compared with anastrozole, an aromatase inhibitor (see below). The study enrolled postmenopausal women with locally advanced or metastatic breast cancer that had progressed despite hormonal therapy. The result? Both fulvestrant and anastrozole were equally effective with respect to objective tumor response rates and median time to disease progression. However, response duration was greater with fulvestrant (16.7 months vs. 13.6 months). At this time, there are no data on how fulvestrant compares directly with tamoxifen.

Pharmacokinetics. Plasma levels peak about 7 days after IM injection, and remain therapeutic for at least 1 month. Steady-state levels are reached after three to six monthly doses. The drug undergoes hepatic metabolism followed by renal excretion. The apparent half-life is 40 days.

Adverse Effects and Drug Interactions. Fulvestrant is generally well tolerated. The most common adverse effects are GI disturbances, hot flushes, headache, pharyngitis, and bone and back pain. Thromboembolism can occur but is uncommon. In contrast to tamoxifen, fulvestrant poses no risk of endometrial cancer. In clinical trials, injection-site reactions (inflammation; mild, transient pain) developed in 7% of women receiving a single 5-mL injection and in 27% of women receiving two 2.5-mL injections. Fulvestrant has no known drug interactions.

Preparations, Dosage, and Administration. Fulvestrant is supplied in solution (50 mg/mL) for administration by slow IM injection (1 to

2 minutes). The dosage is 500 mg on days 1, 15, and 29, followed by 500 mg once a month thereafter. Each dose is administered as two 5-mL injections, one into each buttock.

Aromatase Inhibitors

The aromatase inhibitors are used to treat ER-positive breast cancer in *postmenopausal* women. These drugs block the production of estrogen from androgenic precursors, and thereby deprive breast cancer cells of the estrogen they need for growth. Aromatase inhibitors do not block production of estrogen by the ovaries, and hence are of little benefit in premenopausal women. In fact, aromatase inhibitors may cause a compensatory rise in estradiol in premenopausal patients. Aromatase inhibitors are more effective than tamoxifen and have a different toxicity profile. Unlike tamoxifen, aromatase inhibitors pose no risk of endometrial cancer and only rarely cause thromboembolism. However, they *can* increase the risk of fractures and have been associated with moderate to severe myalgias.

Anastrozole

Mechanism, Use, and Dosage. Anastrozole [Arimidex] is approved for first-line oral therapy of *postmenopausal* women with early or advanced *ER-positive breast cancer*. The drug works by depriving breast cancer cells of estrogen. In postmenopausal women, the major source of estrogen is adrenal androgens, which are converted into estrogen by the enzyme *aromatase* in peripheral tissues. Anastrozole inhibits aromatase, and thereby reduces estrogen production. With regular use, the drug lowers estrogen to undetectable levels. In women with estrogen-dependent cancer, estrogen deprivation can arrest tumor growth, and may cause outright cell death. In clinical trials, anastrozole was not effective in women with ER-negative tumors or in women who did not respond initially to tamoxifen. The recommended dosage is 1 mg PO once a day. Treatment duration typically ranges from 2 to 5 years. Anastrozole may be used as initial therapy, or as a follow-up to therapy with tamoxifen.

Adverse Effects. Anastrozole is generally well tolerated. In clinical trials, about 5% of patients withdrew because of adverse effects. At a daily dose of 1 mg, the most common adverse effects are musculoskeletal pain, asthenia, headache, and menopausal symptoms, including hot flashes, vaginal dryness, and GI disturbances. Other reactions include anorexia, vomiting, diarrhea, constipation, dyspnea, peripheral edema, vaginal hemorrhage, and hypertension.

Up to 50% of women experience *musculoskeletal pain*, often described with the phrase “every bone in my body hurts.” The cause may be estrogen deprivation. Persistent or severe pain drives about 5% of users to discontinue treatment. For women who choose to continue anastrozole, pain can often be managed with a mild analgesic (eg, acetaminophen, ibuprofen). High-dose vitamin D may help too.

Estrogen depletion increases the risk of *osteoporosis and related fractures*. To reduce bone loss, women should ensure adequate intake of calcium and vitamin D. Women at high risk should take a bisphosphonate (eg, zoledronate [Zometa]) or denosumab [Prolia].

Comparison with Tamoxifen. As shown in the *Arimidex, Tamoxifen, Alone or in Combination* (ATAC) trial, which enrolled postmenopausal women with early breast cancer, anastrozole is more effective than tamoxifen and causes fewer adverse effects. After a median follow-up of 5.6 years, cancer

recurred in 13% fewer of the women who took anastrozole, and the time to cancer recurrence was longer. Regarding side effects, anastrozole is less likely to cause hot flashes, weight gain, or vaginal bleeding—although it may cause more nausea and irritability. In contrast to tamoxifen, anastrozole is devoid of all estrogenic activity, and hence does not promote endometrial cancer or thromboembolic events—although it does increase the risk of fractures. Because of their superior efficacy and tolerability, aromatase inhibitors have replaced tamoxifen as the drug of first choice for treating ER-positive breast cancer in postmenopausal women.

Letrozole

Letrozole [Femara], a selective aromatase inhibitor, is indicated for (1) first-line therapy of early and advanced *ER-positive breast cancer* in postmenopausal women, and (2) extended adjuvant therapy of early breast cancer following 5 years of adjuvant therapy with tamoxifen. Like anastrozole, letrozole blocks conversion of androgens into estrogens, and thereby deprives breast cancer cells of estrogen's growth-promoting influence. In one study of women with advanced breast cancer, letrozole (2.5 mg/day) was more effective than tamoxifen (20 mg/day); the objective response rate with letrozole was higher (30% vs. 20%) and the time to tumor progression was longer (9.4 months vs. 6 months). In women with early breast cancer who have received 5 years of tamoxifen therapy, following with letrozole reduces the risk of recurrence. Letrozole's most common adverse effects are musculoskeletal pain (21%) and nausea (13%). Reactions that occur in 6% to 9% of patients include headache, arthralgia, fatigue, constipation, dyspnea, cough, vomiting, diarrhea, and hot flashes. Extremely low doses are embryotoxic and fetotoxic in animals. Like anastrozole, and unlike tamoxifen, letrozole poses no risk of endometrial cancer. However, it can cause osteoporosis and fractures, and, rarely, thromboembolism. Osteoporosis can be managed with denosumab [Prolia] or a bisphosphonate (eg, zoledronate [Zometa]). No significant drug interactions have been reported.

Exemestane

Exemestane [Aromasin] is indicated for oral therapy of (1) *advanced ER-positive breast cancer* in postmenopausal women whose disease has progressed despite treatment with tamoxifen, and (2) *early ER-positive breast cancer* in postmenopausal women who have received 2 to 3 years of tamoxifen therapy and then are switched to adjuvant exemestane to complete a 5-year course of treatment. Like anastrozole, exemestane inhibits aromatase, and thereby reduces estrogen levels. A dosage of 25 mg once daily (administered after a meal) reduces circulating estrogen by 85% to 95%. In the absence of sufficient estrogen, estrogen-dependent tumors cannot thrive. In clinical trials, the objective response rate was about 25%.

In addition to treating breast cancer, exemestane can be effective for breast cancer prevention, as shown in the *Mammary Prevention 3* trial, reported in 2011. The trial enrolled 4560 postmenopausal women at high risk for breast cancer, and randomized them to receive exemestane or placebo. The result? After a median follow-up of 35 months, the incidence of invasive breast cancer was 65% lower in the exemestane group. If exemestane is approved for breast cancer prevention, it will become an attractive alternative to raloxifene and tamoxifen.

Exemestane is rapidly absorbed following oral dosing, and is widely distributed to tissues. In the liver, the drug undergoes extensive metabolism, mainly by CYP3A4. Excretion is via the urine and feces. Its half-life is about 24 hours.

Exemestane is generally well tolerated. The most common adverse effects are fatigue (22%), nausea (18%), hot flashes (13%), depression (13%), and weight gain (8%). Like anastrozole and letrozole, exemestane often causes musculoskeletal pain. Increased risk of osteoporosis and fractures is a concern. Women at high risk of osteoporosis can be treated with denosumab [Prolia] or a bisphosphonate (eg, zoledronate [Zometa]).

Drugs that induce CYP3A4 (eg, phenytoin, phenobarbital, rifampin, St. John's wort) can cause a significant drop in exemestane levels. Accordingly, if these drugs are combined, exemestane dosage may need to increase.

Trastuzumab

Actions and Use. Trastuzumab [Herceptin] is a monoclonal antibody originally approved for *HER2-positive metastatic breast cancer* and for *adjuvant therapy of HER2-positive breast*

cancer. In 2011, trastuzumab received a new indication: *HER2-positive metastatic gastric cancer*. Discussion here is limited to breast cancer.

Trastuzumab is only effective against tumors that overexpress *human epidermal growth factor receptor 2 (HER2)*, a transmembrane receptor that helps regulate cell growth. Trastuzumab binds with HER2 and thereby (1) inhibits cell proliferation and (2) promotes antibody-dependent cell death. Between 25% and 30% of metastatic breast cancers produce excessive HER2. High numbers of HER2 receptors are associated with unusually aggressive tumor growth. For treatment of breast cancer, trastuzumab may be used (1) alone in women who failed to respond to prior chemotherapy, (2) in combination with paclitaxel as first-line therapy, and (3) for adjuvant treatment as part of a regimen containing doxorubicin, cyclophosphamide, and paclitaxel.

Clinical Trials. In one trial involving women with metastatic disease, treatment with trastuzumab alone produced a complete response in 3% of patients, and a partial response (more than 50% tumor regression) in 14% of patients. In a trial reported in 2005, chemotherapy alone—doxorubicin plus cyclophosphamide, followed by paclitaxel—was compared with chemotherapy plus trastuzumab. The result? Adding trastuzumab to the regimen produced a significant increase in 3-year disease-free survival (87% vs. 75% with chemotherapy alone), and also produced a significant reduction in 3-year mortality. These data suggest that trastuzumab should be considered for most women who have HER2-positive disease.

Adverse Effects. The principal concern with trastuzumab is *cardiotoxicity*, manifesting as ventricular dysfunction and congestive heart failure. In clinical trials, the incidence of symptomatic heart failure was 7% with trastuzumab alone, and 28% when trastuzumab was combined with doxorubicin, a drug with prominent cardiotoxic actions. Combining trastuzumab with paclitaxel can also result in cardiac damage. Because of cardiotoxicity, trastuzumab should be used with caution in women with pre-existing heart disease. Concurrent use with doxorubicin and other anthracyclines should generally be avoided. In contrast to the cytotoxic anticancer drugs, trastuzumab does not cause bone marrow suppression or alopecia.

Many patients experience a *flu-like syndrome*, which also occurs with other monoclonal antibodies. Symptoms include chills, fever, pain, weakness, nausea, vomiting, and headache. The syndrome develops in 40% of patients receiving their first infusion, and then diminishes with subsequent infusions.

Postmarketing reports indicate that trastuzumab can cause potentially fatal *hypersensitivity reactions, infusion reactions, and pulmonary events*. Symptoms include urticaria, bronchospasm, angioedema, hypotension, dyspnea, wheezing, pleural effusions, pulmonary edema, and hypoxia requiring oxygen. Most severe reactions developed in association with the first dose, either during the infusion or by 12 hours after. If symptoms develop during the infusion, the infusion should be stopped. Death has occurred primarily in patients with pre-existing pulmonary disorders. Accordingly, patients with compromised pulmonary function should be managed with extreme caution.

Dosage and Administration. Treatment consists of a loading dose (12 mg/kg infused over at least 30 minutes) followed by weekly maintenance doses (2 mg/kg infused over 30 minutes). An alternative regimen uses a larger loading dose (8 mg/kg), and larger but less frequent maintenance doses (8 mg/kg every 3 weeks).

Lapatinib

Actions and Use. Lapatinib [Tykerb] is an oral inhibitor of two enzymes—HER2 tyrosine kinase and epidermal growth factor receptor (EGFR) tyrosine kinase—that are involved in cell signal transduction. Enzyme inhibition results in apoptosis and suppression of tumor cell growth. Lapatinib is approved for treating advanced HER2-positive breast cancer, but only in combination with either (1) *capecitabine* (in patients who have received prior therapy with multiple drugs, including an anthracycline, a taxane, and trastuzumab) or (2) *letrozole* (in postmenopausal women for whom estrogen deprivation therapy is indicated). EGFR tyrosine kinase is discussed further below under *EGFR Tyrosine Kinase Inhibitors*.

Adverse Effects. The most common adverse effects of *lapatinib plus capecitabine* are GI disturbances (diarrhea, nausea, vomiting), fatigue, rash, and palmar-plantar erythrodysesthesia (swelling and numbness of the hands and feet). The most common adverse effects of *lapatinib plus letrozole* are diarrhea, rash, nausea, and fatigue. Diarrhea occurs in 65% of patients, and is the most common reason for stopping treatment. Like other HER2 inhibitors, lapatinib may pose a risk of cardiotoxicity. Accordingly, the drug should be used with caution in patients with existing cardiac impairment. Rarely, letrozole has been associated with severe liver injury. Liver function tests should be performed at baseline and periodically throughout treatment. When used alone and together with other drugs, letrozole has been associated with interstitial lung disease and pneumonitis. In laboratory animals, giving letrozole during pregnancy resulted in death of the pups a few days after birth. Women using the drug should avoid getting pregnant.

Drug Interactions. Lapatinib is metabolized by CYP3A4, and hence CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort) can lower lapatinib levels, and CYP3A4 inhibitors (eg, ketoconazole, itraconazole, erythromycin, indinavir, nelfinavir) can raise lapatinib levels. If possible, CYP3A4 inducers and inhibitors should be avoided.

Preparations, Dosage, and Administration. Lapatinib [Tykerb] is supplied in 250-mg tablets for oral dosing without food (either 1 hour before a meal or 1 hour after). Two dosing regimens are used:

- *Lapatinib with capecitabine*—The recommended dosage is 1250 mg (5 tablets) taken *once every day*, along with capecitabine (2000 mg/m²), taken once a day on *days 1 through 14* of a repeating 21-day cycle.
- *Lapatinib with letrozole*—The recommended dosage is 1500 mg (6 tablets) taken *once every day*, along with letrozole (2.5 mg) taken *once every day*.

Cytotoxic Drugs (Chemotherapy)

Cytotoxic drugs may be used before breast surgery or after. When used before surgery, chemotherapy can shrink large tumors, thereby permitting lumpectomy in women who would otherwise require a mastectomy. When used after surgery, chemotherapy can kill cancer cells that remain in the breast, as well as cells that may have metastasized to distant sites. A common regimen for breast cancer consists of doxorubicin (an anthracycline-type anticancer antibiotic) plus cyclophosphamide (an alkylating agent) followed by paclitaxel (a mitotic inhibitor). Representative cytotoxic drugs are presented in Table 103-1.

Denosumab and Bisphosphonates for Skeletal-Related Events

Women with breast cancer are at risk for skeletal-related events (SREs), especially hypercalcemia and fractures. There are two causes: the cancer itself and the drugs used for treatment. In breast cancer, most metastases occur in bone. These metastases promote hypercalcemia by increasing the activity of osteoclasts, the cells that promote bone resorption. Not only does resorption promote hypercalcemia, it weakens bone, and thereby increases the risk of fractures. Fracture risk is further increased by use of antiestrogens and aromatase inhibitors. Why? As we discussed in Chapter 61, estrogens

promote bone health by inhibiting bone resorption and promoting bone deposition. Hence, by removing the influence of estrogen, the antiestrogens and aromatase inhibitors accelerate bone resorption and reduce bone deposition. Both actions weaken bone, and thereby increase the risk of fractures. To reduce the risk of SREs, we can treat patients with denosumab or a bisphosphonate (usually zoledronate).

Zoledronate and Other Bisphosphonates

In women with breast cancer, bisphosphonates can help preserve bone integrity, and can thereby decrease the risk of hypercalcemia and fractures. Benefits derive from inhibiting the activity of osteoclasts. At this time, two bisphosphonates—*zoledronate* [Zometa] and *pamidronate* [Aredia]—are approved for hypercalcemia of malignancy, and one of them—pamidronate—is also approved for managing osteolytic bone metastases. However, although zoledronate is not approved for osteolytic bone metastases, it is just as effective as pamidronate. Furthermore, compared with pamidronate, zoledronate has three advantages: onset is faster, duration is longer, and infusion time is shorter (15 minutes vs. 2 to 4 hours). Accordingly, zoledronate is generally preferred to pamidronate. Principal adverse effects of the bisphosphonates are kidney damage and osteonecrosis of the jaw.

In addition to reducing fractures and hypercalcemia, bisphosphonates may actually prevent metastases and prolong life. These benefits were discovered somewhat by accident. In women with breast cancer, bisphosphonates were originally employed to suppress bone resorption caused by metastases. While using bisphosphonates for this purpose, researchers noted something surprising: Bisphosphonates appeared to reduce the incidence of new bony metastases. Results of a follow-up study confirmed the original observation: In women with breast cancer, treatment with a bisphosphonate reduced metastases to bone and prolonged survival. These results were obtained using *clodronate*, an oral bisphosphonate available in Europe and Canada. However, other bisphosphonates should also be effective.

How do bisphosphonates suppress metastases? When cancer cells spread to bone, they stimulate the activity of osteoclasts, the cells responsible for bone resorption. In turn, osteoclasts release growth factors that stimulate the cancer cells, thereby setting up a self-reinforcing cycle. Bisphosphonates interrupt the cycle by inhibiting osteoclast function and blocking tumor adhesion to bone.

The basic pharmacology of the bisphosphonates is discussed in Chapter 75.

Denosumab

Denosumab, marketed as *Xgeva*, is indicated for preventing (delaying) SREs in patients with breast cancer and other solid tumors that have metastasized to bone. Benefits derive from inhibiting the formation and function of osteoclasts. Efficacy was demonstrated in three double-blind trials that compared denosumab with zoledronate. One trial enrolled patients with breast cancer, one enrolled patients with prostate cancer, and one enrolled patients with other cancers, including multiple myeloma, kidney cancer, small cell lung cancer, and non-small cell lung cancer. Patients received either denosumab (120 mg subQ every 4 weeks) or zoledronate (4 mg IV every 4 weeks). The results? In patients with breast cancer or prostate cancer, denosumab was superior to zoledronate at delay-

ing SREs. In patients with other cancers, denosumab was equal to zoledronate at delaying SREs. Principal adverse effects of denosumab are hypocalcemia, serious infections, skin reactions, and osteonecrosis of the jaw. The pharmacology of denosumab is presented in Chapter 75.

DRUGS FOR PROSTATE CANCER

Cancer of the prostate is the most common cancer among men in the United States. In 2011, an estimated 240,890 new cases were diagnosed, and 33,720 were fatal. For men with *localized* prostate cancer, the preferred treatments are surgery and radiation, with or without adjunctive use of drugs. For men with *metastatic* prostate cancer, drug therapy and castration are the only options. Among the drugs employed, agents for *androgen deprivation therapy* (ADT) comprise the largest and most widely used group. The only other choices are cytotoxic drugs and a new immunotherapy known as sipuleucel-T [Provenge]. As with breast cancer, most metastases (65% to 75%) go to bone. To minimize hypercalcemia and fractures caused by bone metastases, men may take *zoledronate* [Zometa] or *denosumab* [Xgeva] (see discussion of breast cancer above). The drugs used to treat prostate cancer are summarized in Table 103-2.

ANDROGEN DEPRIVATION THERAPY

The term *androgen deprivation therapy* refers to the use of castration and/or drugs to deprive prostate cancers of the androgens they need for growth. By implementing ADT, we can slow disease progression and increase comfort. Initially, ADT was reserved for patients with metastatic disease. However, ADT is now used as an adjuvant in earlier stage disease. Unfortunately, the benefits of ADT are time limited: After 18 to 24 months of treatment, disease progression often resumes. Side effects of ADT include hot flashes, reduced libido, erectile dysfunction, gynecomastia, decreased muscle mass, and decreased bone mass with associated increased risk of fractures.

Where do androgens come from? And how can we reduce their influence? About 90% of circulating androgens are produced by the testes. The remaining 10% are produced by the adrenals and by the prostate cancer itself. Accordingly, we can reduce the influence of androgens in three ways. Specifically, we can block testosterone receptors with drugs; we can lower testosterone production with drugs; and we can lower testosterone production by castration. Drug therapy is more effective than castration. Why? Because castration only eliminates testicular androgens, leaving androgen synthesis by the adrenals and cancer cells intact. In contrast, by using drugs to block testosterone receptors and testosterone synthesis, we can reduce the influence of testosterone from all sources (testes, adrenals, prostate cancer).

Gonadotropin-Releasing Hormone Agonists

The gonadotropin-releasing hormone (GnRH) agonists suppress production of androgens by the testes—but not by the adrenals and prostate cancer cells. Currently, four GnRH agonists are available: leuprolide, triptorelin, goserelin, and his-

TABLE 103-2 ■ Drugs for Prostate Cancer

Generic Name	Trade Name	Route	Major Adverse Effects
DRUGS FOR ANDROGEN DEPRIVATION THERAPY			
GnRH Agonists*			
Leuprolide	Lupron, Lupron Depot	IM	Hot flushes, erectile dysfunction, decreased libido, decreased muscle mass, gynecomastia, osteoporosis
	Eligard	SubQ	
	Viadur	SubQ implant	
Triptorelin	Trelstar	IM	
Goserelin	Zoladex	SubQ	
Histrelin	Supprelin LA, Vantas	SubQ implant	
GnRH Antagonist			
Degarelix	Firmagon	SubQ	Same as the GnRH agonists <i>plus</i> hepatotoxicity
Androgen Receptor Blockers			
Flutamide	Eulexin	PO	Same as the GnRH agonists <i>plus</i> hepatotoxicity
Bicalutamide	Casodex	PO	Same as the GnRH agonists <i>plus</i> hepatotoxicity
Nilutamide	Nilandron, Anandron [‡]	PO	Same as the GnRH agonists <i>plus</i> hepatotoxicity and interstitial pneumonitis
CYP17 Inhibitor			
Abiraterone	Zytiga	PO	Same as the GnRH agonists <i>plus</i> hepatotoxicity, edema, hypertension, hypokalemia, glucocorticoid insufficiency
OTHER DRUGS FOR PROSTATE CANCER			
Immunotherapy			
Sipuleucel-T	Provenge	IV	Infusion reactions, fatigue, fever
Cytotoxic Drugs			
Cabazitaxel	Jevtana	IV	Neutropenia, hypersensitivity reactions, diarrhea
Docetaxel	Taxotere	IV	Neutropenia, anemia, hypersensitivity reactions, fluid retention
Estramustine	Emcyt	PO	Gynecomastia, thrombosis
Drugs to Delay Skeletal Events			
Denosumab	Xgeva [†]	SubQ	Hypocalcemia, serious infections, skin reactions, osteonecrosis of the jaw
Zoledronate	Zometa [‡]	IV	Kidney damage, atrial fibrillation, osteonecrosis of the jaw

*Gonadotropin-releasing hormone agonists, also known as luteinizing hormone-releasing hormone (LHRH) agonists.

[†]Denosumab is also available as *Prolia* for treating postmenopausal osteoporosis.

[‡]Zoledronate is also available as *Reclast* for treating osteoporosis and Paget's disease.

trilin. All four are indicated for cancer of the prostate. In addition, leuprolide is used for endometriosis (see Chapter 63).

Leuprolide

Therapeutic Use. Leuprolide [Eligard, Lupron, Lupron Depot, Viadur] is a synthetic analog of GnRH, also known as *luteinizing hormone-releasing hormone* (LHRH). Leuprolide is indicated for *advanced carcinoma of the prostate*. Palliation is the primary benefit. For patients with prostate cancer, leuprolide represents an alternative to orchiectomy (surgical castration). Leuprolide may be administered daily (subQ); monthly (IM); every 3, 4, or 6 months (IM); or once a year (subQ implant).

Mechanism of Action. Cells of the prostate, both normal and neoplastic, are androgen dependent. Leuprolide provides palliation by suppressing androgen production in the *testes*. During the initial phase of treatment, leuprolide *mimics* GnRH. That is, the drug acts on the pituitary to *stimulate* release of interstitial cell-stimulating hormone (ICSH), which acts on the

testes to *increase* production of testosterone. As a result, there may be a transient "flare" in prostate cancer symptoms. However, with continuous exposure to leuprolide, GnRH receptors in the pituitary become desensitized. As a result, release of ICSH declines, causing testosterone production to decline too. After several weeks of treatment, testosterone levels are equivalent to those seen after surgical castration. Because leuprolide therapy mimics the effects of orchiectomy, treatment is often referred to as *chemical castration*.

It is important to note that leuprolide does *not* decrease production of androgens made by the adrenals or by the prostate cancer itself. As noted, these nontesticular sources account for about 10% of the androgens in circulation. Hence, even though production of testicular androgens is essentially eliminated, adrenal and prostatic androgens can still provide some support for prostate cancer cells.

Co-treatment with an Androgen Receptor Blocker. In patients receiving leuprolide, an androgen receptor blocker can help in two ways. Specifically, (1) it can prevent cancer

cells from undergoing increased stimulation during the initial phase of GnRH therapy, when androgen production is increased; and (2) it can block the effects of adrenal and prostatic androgens, whose production is not reduced by GnRH agonists. The current trend is to use an androgen receptor blocker during the first weeks of leuprolide therapy (to prevent leuprolide-induced tumor flare), after which the drug is discontinued unless there is tumor progression despite continued leuprolide treatment.

Adverse Effects. Leuprolide is generally well tolerated. Hot flushes are the most common adverse effect, but these usually decline as treatment continues. Reduced testosterone may also lead to erectile dysfunction, loss of libido, gynecomastia, reduced muscle mass, new-onset diabetes, myocardial infarction, and stroke. During the initial weeks of treatment, elevation of testosterone levels may aggravate bone pain and urinary obstruction caused by prostate cancer. As a result, patients with vertebral metastases or pre-existing obstruction of the urinary tract may find treatment intolerable. As noted, concurrent treatment with an androgen receptor blocker can minimize these problems.

By suppressing testosterone production, leuprolide may increase the risk of osteoporosis and related fractures. Bone loss can be minimized by consuming adequate calcium and vitamin D, and by performing regular weight-bearing exercise. In addition, a bisphosphonate (eg, zoledronic acid [Zometa]) or denosumab [Xgeva] can be used to preserve bone and reduce fracture risk (see below).

Preparations, Dosage, and Administration. Leuprolide is supplied in three basic formulations for parenteral dosing:

- *Leuprolide short-acting injection* [Lupron] is supplied as a 5-mg/mL solution for IM administration. The recommended dosage is 1 mg once a day.
- *Leuprolide depot injection* is available in single-dose kits under two trade names: *Lupron Depot* (for IM injection) and *Eligard* (for subQ injection). With either product, the dosage is 7.5 mg once a month, 22.5 mg every 3 months, 30 mg every 4 months, or 45 mg every 6 months.
- *Leuprolide implant*, sold as *Viadur*, is formulated as a 65-mg pellet for subQ implantation in the inner aspect of the upper arm once every 12 months.

Triptorelin, Goserelin, Histrelin

Triptorelin, goserelin, and histrelin are GnRH analogs indicated for palliative treatment of *advanced prostate cancer*. All three have the same mechanism and adverse effects of leuprolide, our prototype GnRH agonist. Preparations, dosage, and administration are as follows:

- *Triptorelin* [Trelstar] is administered by IM injection. The recommended dosage is 3.75 mg once a month, 11.25 mg once every 3 months, or 22.5 mg once every 6 months.
- *Goserelin* [Zoladex] is formulated as pellets (3.6 mg and 10.8 mg) for subQ implantation in the upper abdominal wall. The 3.6-mg pellets are implanted every 4 weeks, and the 10.8-mg pellets are implanted every 12 weeks.
- *Histrelin* [Supprelin LA, Vantas] is formulated as a 50-mg pellet for subQ implantation in the inner aspect of the upper arm once every 12 months.

Gonadotropin-Releasing Hormone Antagonists

Like the GnRH agonists, the GnRH *antagonists* suppress production of androgens by the testes. However, in contrast to the GnRH agonists, the GnRH antagonists do not produce an initial tumor flare. Currently, only one GnRH antagonist—degarelix—is available. An older drug—*abarelix* [Plenaxis]—has been withdrawn.

Degarelix

Degarelix [Firmagon], approved in 2009, is a synthetic decapeptide GnRH antagonist indicated for palliative therapy of *advanced prostate cancer* in men who are not candidates for a GnRH agonist, and who do not want surgical castration. Benefits derive from suppressing testosterone production by the testes. The underlying mechanism is blockade of GnRH receptors in the anterior pituitary, which decreases release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn deprives the testes of the stimulus they need for testosterone production. In clinical trials, patients received an initial 240-mg dose followed by monthly maintenance 80-mg doses. The result? Testosterone levels fell rapidly to those produced by castration, and then remained low for at least 12 months. Because degarelix works through direct blockade of GnRH receptors, the drug does not cause the initial surge in testosterone production seen with GnRH agonists, and hence there is no early tumor flare.

Degarelix is administered subQ, and absorption is slow. Plasma levels peak in 2 days. Elimination is primarily by peptide bond hydrolysis, a process that occurs in the liver but does not involve cytochrome P450 enzymes. The drug's half-life is long: 53 days.

As with other drugs for ADT, major side effects are hot flushes, reduced libido, erectile dysfunction, gynecomastia, decreased muscle mass, and decreased bone mass with associated increased risk of fractures. In addition, degarelix often causes injection-site reactions (pain, erythema, swelling), weight gain, and elevation of liver transaminases. After a year of treatment, about 10% of patients develop antibodies against degarelix. However, the antibodies do not reduce the effectiveness of treatment. In contrast to abarelix (which has been withdrawn), degarelix does not cause severe, immediate-onset allergic reactions.

Degarelix is supplied as a powder (80 and 120 mg) to be reconstituted for subQ injection. The regimen consists of an initial 240-mg dose (two 120-mg injections), followed by monthly 80-mg injections for maintenance.

Androgen Receptor Blockers

Androgen receptor blockers, or simply *antiandrogens*, are indicated only for advanced androgen-sensitive prostate cancer—and only in combination with surgical castration or chemical castration using a GnRH agonist. Currently, three androgen receptor blockers are available: flutamide, bicalutamide, and nilutamide.

Flutamide

Flutamide, formerly available as Eulexin, is indicated for *prostate cancer* only. Benefits derive from blocking androgen receptors in tumor cells, thereby depriving them of needed androgenic support. In patients taking a GnRH agonist, flutamide can serve two purposes: (1) it can prevent tumor flare when GnRH therapy is started, and (2) it can block the effects of adrenal and prostatic androgens. As a rule, the combination of an androgen antagonist plus a GnRH agonist—so-called complete androgen blockade—is reserved for suppressing the initial flare and for suppressing the tumor after it has stopped responding to a GnRH agonist alone. The combination is not used continuously because it does not increase survival, but does increase toxicity.

Flutamide is administered orally and undergoes rapid and complete absorption. Most of each dose is converted to an active metabolite on the first pass through the liver. Parent drug and metabolites are excreted in the urine.

As with other drugs for ADT, prominent side effects are hot flushes, reduced libido, erectile dysfunction, gynecomastia, decreased muscle mass, and decreased bone mass with associated increased risk of fractures. Nausea, vomiting, and diarrhea are also common. Rarely, potentially fatal liver toxicity has occurred. To reduce the risk of serious harm, liver function should be assessed at baseline, monthly during the first 4 months of treatment, and periodically thereafter.

Flutamide may cause fetal harm, and hence is classified in FDA Pregnancy Risk Category D. Accordingly, the drug should not be used during pregnancy. Of course, since flutamide is approved only for prostate cancer, use during pregnancy should not happen anyway.

Flutamide is supplied in 125-mg capsules. The usual dosage is 250 mg three times a day.

Bicalutamide

Like flutamide, bicalutamide [Casodex] is an androgen receptor blocker used for *advanced androgen-sensitive prostate cancer* in men undergoing therapy with a GnRH agonist (eg, leuprolide). The rationale for the combination is explained in the discussion of flutamide. When bicalutamide is used alone, the most common side effects are breast pain (38%) and gynecomastia (39%). When the drug is combined with leuprolide, the most common side effect is hot flushes (49%). Like all other drugs used for ADT, bicalutamide can also cause reduced libido, erectile dysfunction, decreased muscle mass, and decreased bone mass with associated increased risk of fractures. Also, like flutamide, bicalutamide poses a small risk of liver injury, and hence liver function should be monitored. Bicalutamide poses a significant risk of fetal harm, and hence is classified in FDA Pregnancy Risk Category X. Bicalutamide is just as effective as flutamide, and dosing is more convenient (50 mg once a day vs. 250 mg 3 times a day). As a result, bicalutamide is preferred.

Nilutamide

Like flutamide and bicalutamide, nilutamide [Nilandron, Anandron⁺] blocks receptors for androgens. The drug is approved for *metastatic prostate cancer* in men who have undergone surgical castration. Benefits derive from blocking the actions of adrenal androgens, which are not reduced by castration. In clinical trials, nilutamide reduced bone pain, prolonged progression-free survival, and increased median survival time. The recommended dosage is 300 mg once daily PO for 30 days followed by 150 mg once daily thereafter. Treatment should begin within 24 hours of castration.

Although nilutamide is structurally similar to flutamide, the drug is not as well tolerated. The most common adverse effects are hot flushes (67%), delayed adaptation to darkness (57%), nausea (24%), constipation (20%), insomnia (16%), and gynecomastia (11%). In addition, nilutamide can cause reduced libido, erectile dysfunction, decreased muscle mass, and decreased bone mass with associated increased risk of fractures. Other reactions occur less frequently, but are more dangerous. About 2% of patients experience dyspnea secondary to interstitial pneumonitis. If this develops, nilutamide should be withdrawn. About 1% of patients develop hepatitis. To ensure early diagnosis, liver function should be monitored.

Abiraterone, a CYP17 Inhibitor

Actions and Use. Abiraterone [Zytiga], approved in 2011, is indicated for combined use with prednisone to treat *metastatic castration-resistant prostate cancer* in men previously treated with docetaxel. Benefits derive from inhibiting production of androgens by the adrenal gland and by the prostate cancer itself. (If castration has not been done, abiraterone can also inhibit androgen production by the testes.) In all cases, the underlying mechanism is inhibition of cytochrome

P450 17 (CYP17), an enzyme needed by the adrenals, testes, and prostate tumors for androgen synthesis. When tested in men with metastatic castration-resistant prostate cancer, the combination of abiraterone plus prednisone increased overall survival by nearly 4 months, and progression-free survival by 2 months.

Adverse Effects. The most common adverse effects are hypokalemia (28.3%), edema (26.7%), joint swelling/discomfort (29.5%), muscle discomfort (26.2%), hot flushes (19%), diarrhea (17.6%), urinary tract infection (11.5%), cough (10.6%), and hypertension (8.5%). Like all other drugs for ADT, abiraterone can also decrease libido, muscle mass, and bone mass, and can cause erectile dysfunction and gynecomastia.

Inhibition of CYP17 in the adrenals can lead to overproduction of mineralocorticoids and underproduction of glucocorticoids. High levels of mineralocorticoids can cause retention of sodium and loss of potassium, leading to fluid retention, edema, hypertension, and hypokalemia. Low levels of glucocorticoids can increase the risk of death from traumatic events. Co-treatment with prednisone (a glucocorticoid) helps compensate for reduced production of glucocorticoids by the adrenals and, by suppressing release of adrenocorticotrophic hormone from the pituitary, prednisone can reduce excessive production of mineralocorticoids.

Hepatotoxicity, manifesting as a marked elevation of liver transaminases—alanine aminotransferase (ALT) and aspartate aminotransferase (AST)—develops in about 30% of patients. To monitor liver status, ALT and AST should be measured at baseline, every 2 weeks for the first 3 months of treatment, and once a month thereafter. If these tests indicate significant liver injury, abiraterone should be discontinued or the dosage reduced.

Abiraterone can harm the developing fetus, and hence is classified in FDA Pregnancy Risk Category X. Accordingly, the drug should be avoided by women who are pregnant. Of course, since abiraterone is approved only for prostate cancer, use during pregnancy should not be an issue.

Drug Interactions. Abiraterone is a substrate for CYP3A4, and hence its levels can be raised by CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, ritonavir), and lowered by CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin). Abiraterone inhibits hepatic CYP2D6, and hence can raise levels of CYP2D6 substrates (eg, dextromethorphan, thioridazine).

Preparations, Dosage, and Administration. Abiraterone is supplied in 250-mg capsules, which should be swallowed with water on an empty stomach (1 hour before a meal or 2 hours after). Dosing should not be done with food, owing to greatly *increased* absorption, which could cause toxicity. The usual regimen is 1000 mg abiraterone once daily combined with 5 mg prednisone twice daily. Dosage of abiraterone should be reduced in patients with liver impairment.

Ketoconazole

Ketoconazole [Nizoral], used primarily for fungal infections (see Chapter 92), can be used off-label for prostate cancer. As with abiraterone, benefits derive from inhibiting testicular, adrenal, and prostatic production of androgens. Ketoconazole is employed as secondary therapy in men who have rising prostate-specific antigen levels despite treatment with a GnRH agonist plus an antiandrogen. Dosages are higher than those used for antifungal therapy (400 mg 3 times a day compared with 200 mg once a day), and hence side effects are common. Among these are nausea, vomiting, fatigue, skin changes, liver damage, and gynecomastia. Because high-dose ketoconazole can suppress adrenal production of glucocorticoids, the drug is usually combined with hydrocortisone (to avoid adrenal insufficiency).

OTHER DRUGS FOR PROSTATE CANCER

Sipuleucel-T

Sipuleucel-T [Provenge], approved in 2010, is the name for a patient-specific form of immunotherapy designed to stimulate an immune attack against prostate cancer cells. Each dose is custom made from the patient's own immune cells, and hence cannot be used by any other patient. Unfortunately, sipuleucel-T is very expensive—and only moderately effective. Nonetheless, sipuleucel-T is of great interest in that it represents an entirely new approach to cancer treatment.

Therapeutic Use. Sipuleucel-T is indicated for treatment of asymptomatic or minimally symptomatic metastatic castration-resistant (hormone-refractory) prostate cancer. Treatment consists of three infusions given 2 weeks apart. In clinical trials, sipuleucel-T prolonged life by about 4 months, compared with 2.4 months using standard chemotherapy (eg, docetaxel [Taxotere]). Of note, although sipuleucel-T improves survival, it does not cause measurable tumor regression, nor does it delay the time to tumor progression—suggesting that the mechanism underlying prolonged survival may be something other than immune-mediated injury to cancer cells.

Production. Sipuleucel-T is produced in two steps: collection of circulating immune cells (macrophages) from the patient, followed by modification of those cells in the laboratory. This process—cell collection plus modification—takes about 2 days, and must be done for *each dose*.

Macrophage collection is done by *leukapheresis*, a process in which venous blood is circulated from the patient, through a machine, and then back into the patient. The machine separates out macrophages (along with some platelets and other blood cells), and then returns the remaining cells and serum to the patient. The whole procedure takes 3 to 4 hours.

In the laboratory, the macrophages—also known as *antigen-presenting cells*, or *APCs*—are modified by incubation with a recombinant human protein consisting of prostatic acid phosphatase (PAP) linked with granulocyte-macrophage colony-stimulating factor (GM-CSF). PAP is a protein that is highly expressed by more than 95% of prostate cancer cells. As discussed in Chapter 56, GM-CSF is a blood growth factor that stimulates the production and function of macrophages and some other blood cells. During incubation, the APCs engulf the PAP-GM-CSF, break it into small peptides, and then express those peptides on the APC surface. The modified APCs can now activate cytolytic T cells (killer T cells), causing them to attack prostate cancer cells by recognizing the PAP molecules on their surface.

Adverse Effects. Sipuleucel-T can cause multiple adverse effects. The most common are chills (53%), fatigue (41%), fever (31%), back pain (30%), nausea (22%), joint ache (20%), and headache (18%). Other common reactions include paresthesias, vomiting, anemia, constipation, dizziness, weakness, and extremity pain.

Acute infusion reactions develop in over 70% of patients. Symptoms include fever, chills, nausea, vomiting, fatigue, hypertension, tachycardia, and respiratory reactions (dyspnea, hypoxia, and bronchospasm). Severe reactions may require hospitalization. Infusion reactions can be reduced by premedication with acetaminophen plus an antihistamine, such as diphenhydramine [Benadryl].

Dosage, Administration, and Cost. Patients receive three doses 2 weeks apart. Three days before treatment, the

patient undergoes leukapheresis to collect the APCs for that dose. Each dose is supplied in a sealed, patient-specific infusion bag that contains a minimum of 50 million activated APCs, suspended in 250 mL of lactated Ringer's injection. Administration is by IV infusion—without a cell filter—over a period of 60 minutes. Pretreatment with acetaminophen plus an antihistamine can reduce infusion reactions. In the event of a severe reaction, the infusion may be slowed or discontinued. Sipuleucel-T is expensive: The three-dose series costs about \$93,000.

Cytotoxic Drugs

Docetaxel and Cabazitaxel

Docetaxel [Taxotere] and cabazitaxel [Jevtana] are cytotoxic anticancer drugs indicated for *hormone-refractory prostate cancer* (ie, prostate cancer that no longer responds to ADT). Either drug (in combination with prednisone) can prolong overall survival as well as progression-free survival. At this time, docetaxel is considered a first-line drug for hormone-refractory prostate cancer. Cabazitaxel is reserved for patients who have already been treated with docetaxel. The major adverse effects of docetaxel are neutropenia, hypersensitivity reactions, and fluid retention. The major adverse effects of cabazitaxel are neutropenia, hypersensitivity reactions, anemia, and diarrhea. With both drugs, benefits derive from causing mitotic arrest. The pharmacology of docetaxel and cabazitaxel is discussed in Chapter 102.

Estramustine

Estramustine [Emcyt] is a hybrid molecule composed of estradiol (an estrogen) coupled to nitrogen mustard (an alkylating agent; see Chapter 102). The only indication for the drug is palliative therapy of *advanced prostate cancer*. Estramustine is administered orally, and becomes concentrated in prostate cells, apparently through the actions of a unique “estramustine-binding protein.” Injury to prostate cells appears to result from three mechanisms. First, estramustine acts as a weak alkylating agent. Second, hydrolysis of estramustine releases free estradiol, which suppresses ICSH release by the pituitary, thereby depriving prostate cells of hormonal support. Third, and most importantly, the drug binds to microtubules of mitotic spindles, and thereby disrupts mitosis. As a result, estramustine has M-phase specificity.

Adverse effects are caused primarily by free estradiol. Gynecomastia is common. The most serious effect is thrombosis, with resultant myocardial infarction and stroke. Other adverse effects include fluid retention, nausea, vomiting, diarrhea, and hypercalcemia.

Estramustine is supplied in 140-mg capsules for oral dosing on an empty stomach (1 hour before meals or 2 hours after). The usual dosage is 14 mg/kg/day administered in three or four divided doses.

TARGETED ANTICANCER DRUGS

Targeted anticancer drugs are designed to bind with specific molecules (targets) with the goal of suppressing tumor growth. The hope is that these drugs will be more selective than hormones and cytotoxic anticancer drugs, and hence will be able to destroy cancer cells while leaving normal cells untouched. A few targeted drugs, such as imatinib [Gleevec], have been remarkably successful, producing complete responses with relatively mild adverse effects. Unfortunately, with many other targeted drugs, responses have been less impressive, while adverse effects have been more severe. Nonetheless, the concept of targeted therapy has great appeal, and intensive research is underway to make it more of a reality.

How do targeted drugs work? Many of these drugs are *antibodies* that bind with specific antigens on tumor cells; others are *small molecules* that inhibit intracellular enzymes. Some antibodies mark cancer cells for immune attack, some block cell-surface receptors, some deliver toxic drugs or radioactivity, and some inhibit angiogenesis, and thereby deprive tumor cells of their blood supply. Most of the small

molecules inhibit specific tyrosine kinases, and thereby disrupt intracellular signaling pathways. Properties of the targeted drugs are summarized in Table 103-3.

KINASE INHIBITORS

What are kinases? And how does inhibiting them suppress cancer growth? A kinase is an enzyme that catalyzes the transfer of a phosphate group from a nucleoside triphosphate donor (eg, ATP) to an acceptor molecule, often a protein involved in regulation of cell behavior. This process, known as phosphorylation, alters the structure of the acceptor protein, and thereby increases or decreases its activity. Put another way, the result of phosphorylation is like flipping a switch, turning it on or turning it off. Of interest to us are the protein "switches" that help promote cancer growth. For example, certain regulatory proteins, when phosphorylated, activate signaling pathways that increase cell proliferation and cell survival. Accordingly, if we prevent phosphorylation with a kinase inhibitor, we can shut down the signaling pathway, and thereby inhibit proliferation and promote apoptosis (cell death).

Most of the drugs below inhibit *tyrosine kinases* of one type or another. What's a tyrosine kinase? It's simply a kinase that transfers a phosphate group specifically to tyrosine, one of the amino acid components of the protein undergoing phosphorylation. Other kinases phosphorylate different amino acids, often serine or threonine.

EGFR Tyrosine Kinase Inhibitors

The *epidermal growth factor receptor* (EGFR) is a transmembrane regulatory molecule that works through activation of intracellular tyrosine kinase. The receptor portion of EGFR, which is found on the outer surface of the cell membrane, is coupled with tyrosine kinase on the inner surface of the cell membrane. Binding of an agonist to EGFR activates tyrosine kinase, which in turn activates signaling pathways that regulate cell proliferation and survival. EGFRs are expressed constitutively in many normal epithelial tissues (eg, skin, hair follicles) and are overexpressed in several cancers, including cancers of the lung, breast, prostate, bladder, ovary, colon, and rectum. Overexpression is associated with unregulated cell growth and poor prognosis. Drugs that inhibit EGFR suppress cell proliferation and promote apoptosis (programmed cell death). At this time, we have five EGFR tyrosine kinase inhibitors. Two of these drugs—cetuximab and panitumumab—are monoclonal antibodies that bind with the receptor portion of EGFR tyrosine kinase, and thereby prevent its activation by agonists. The other three drugs—erlotinib, gefitinib, and lapatinib—are small molecules that work inside the cell to inhibit tyrosine kinase directly. It should be noted that EGFRs belong to the same receptor family as HER2 (human epidermal growth factor receptor 2), the target that trastuzumab [Herceptin] works through.

Cetuximab

Cetuximab [Erbix] is a monoclonal antibody that blocks EGFRs. The drug is approved for refractory colorectal cancer and for carcinoma of the head and neck. Infusion reactions, acneiform rash, low magnesium, and GI symptoms are common.

Mechanism of Action. Cetuximab acts as a competitive antagonist at EGFRs. As noted, these receptors, which help

regulate cell growth, are overexpressed in certain cancers, including those of the colon and rectum. EGFR blockade inhibits cell growth and promotes apoptosis. In animal studies, cetuximab decreased growth and survival of cancer cells that overexpress EGFR, but had no effect on cancer cells that lack EGFR.

Therapeutic Uses. Colorectal Cancer. Cetuximab is approved for metastatic, EGFR-positive colorectal cancer. The drug may be added to an irinotecan-based regimen (if the cancer has progressed despite irinotecan treatment), or it may be used alone (in patients who cannot tolerate irinotecan). In clinical trials, cetuximab delayed tumor growth and promoted tumor regression. Treatment improves quality of life, but there is no proof that it prolongs survival.

Head and Neck Cancer. Cetuximab, in combination with radiation, is approved for initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck. In addition, the drug can be used for recurrent or metastatic cancers that have progressed despite treatment with a platinum-based regimen.

Adverse Effects. Cetuximab causes adverse effects in most patients. The effects of greatest concern are severe infusion reactions, severe rash, and interstitial lung disease.

Cetuximab causes severe *infusion reactions* in 2% to 5% of patients. Manifestations include rapid-onset airway obstruction, hypotension, shock, loss of consciousness, myocardial infarction, and cardiopulmonary arrest. Severe reactions can happen with any infusion, but most (90%) occur with the first infusion. If a severe reaction develops, cetuximab should be discontinued immediately and never used again. Agents for medical management—epinephrine, glucocorticoids, IV antihistamines, bronchodilators, and oxygen—should always be on hand. To reduce the risk of a severe reaction, premedication with an IV antihistamine (eg, 50 mg diphenhydramine) is recommended.

Acne-like rash, mainly on the face and upper torso, develops in 88% of patients, and is severe in 12%. Severe rash has led to *Staphylococcus aureus* sepsis and abscesses that require incision and drainage. Sunlight can exacerbate dermatologic reactions, and hence patients should limit sun exposure, use a sunblock, and wear protective clothing.

Very rarely, cetuximab has been associated with *interstitial lung disease*, characterized by inflammation, scarring, and hardening of the lungs. One case of fatal interstitial pneumonitis with pulmonary edema has been reported. Whether cetuximab is truly the cause of these lung disorders has not been established.

The combination of cetuximab and irinotecan often causes *GI toxicity*, manifesting as diarrhea (72%), nausea (55%), abdominal pain (45%), vomiting (41%), anorexia (36%), and constipation (30%).

In clinical trials, *hypomagnesemia* developed in 55% of patients, and was severe in 6% to 17%. Magnesium supplements are often required.

Cetuximab can cross the placenta, but whether it causes fetal harm has not been studied. Until more is known, prudence dictates avoiding cetuximab during pregnancy. Cetuximab is classified in FDA Pregnancy Risk Category C.

Dosage, Administration, and Cost. Cetuximab [Erbix] is given by slow IV infusion. Treatment consists of a loading dose (400 mg/m² infused over 2 hours) followed by maintenance doses (250 mg/m² infused over 1 hour), given either weekly (for head and neck cancer) or every other week (for colorectal cancer). For an average adult, the monthly cost is about \$11,000 (for colorectal cancer) or \$22,000 (for head and neck cancers).

TABLE 103-3 • Targeted Anticancer Drugs

Drug	Molecular Target	Drug Structure	Indications	Major Toxicities
KINASE INHIBITORS				
EGFR Tyrosine Kinase Inhibitors				
Cetuximab [Erbix]	Inhibits EGFR	Antibody	EGFR-positive colorectal cancer and head and neck cancer	Rash, infusion reactions, interstitial lung disease
Panitumumab [Vectibix]	Inhibits EGFR	Antibody	EGFR-positive colorectal cancer	Rare infusion reactions, rash, rare interstitial pneumonitis
Gefitinib* (generic only)	Inhibits EGFR tyrosine kinase	Small molecule	Non-small cell lung cancer	Rash, diarrhea, interstitial lung disease
Erlotinib [Tarceva]	Inhibits EGFR tyrosine kinase	Small molecule	Non-small cell lung cancer	Blistering, GI perforation, interstitial lung disease, corneal ulceration/perforation
Lapatinib [Tykerb]	Inhibits EGFR tyrosine kinase and HER2 tyrosine kinase	Small molecule	HER2-positive breast cancer	Diarrhea, hepatotoxicity, cardiotoxicity, interstitial lung disease
BCR-ABL Tyrosine Kinase Inhibitors				
Imatinib [Gleevec]	Inhibits BCR-ABL tyrosine kinase	Small molecule	Chronic myeloid leukemia, GI stromal tumors	Nausea, diarrhea, myalgia, edema, liver injury
Dasatinib [Sprycel]	Inhibits BCR-ABL tyrosine kinase	Small molecule	Chronic myeloid leukemia	Myelosuppression, QT prolongation, fluid retention, pulmonary arterial hypertension
Nilotinib [Tasigna]	Inhibits BCR-ABL tyrosine kinase	Small molecule	Chronic myeloid leukemia	Myelosuppression, QT prolongation
Multi-Tyrosine Kinase Inhibitors				
Pazopanib [Votrient]	Inhibits multiple tyrosine kinases	Small molecule	Renal cell carcinoma	Bone marrow suppression, hepatotoxicity
Sorafenib [Nexavar]	Inhibits multiple cell-surface and intracellular tyrosine kinases	Small molecule	Renal cell carcinoma, hepatocellular carcinoma	Rash, diarrhea, hand-and-foot syndrome, bleeding, QT prolongation, hypertension
Sunitinib [Sutent]	Inhibits multiple tyrosine kinases	Small molecule	Renal cell carcinoma, GI stromal tumors, pancreatic neuroendocrine tumors	Hepatotoxicity, heart failure, QT prolongation, hypertension, hemorrhage
Vandetanib [Caprelsa]	Inhibits multiple tyrosine kinases	Small molecule	Medullary thyroid cancer	QT prolongation, rash, diarrhea/colitis
mTOR Kinase Inhibitors				
Everolimus [Afinitor]	Inhibits mTOR kinase	Small molecule	Renal cell carcinoma	Oral ulceration, bone marrow suppression, metabolic abnormalities
Temsirolimus [Torisel]	Inhibits mTOR kinase	Small molecule	Renal cell carcinoma	Mucositis, bone marrow suppression, metabolic abnormalities
Anaplastic Lymphoma Kinase (ALK) Inhibitor				
Crizotinib [Xalkori]	Inhibits ALK	Small molecule	ALK-positive non-small cell lung cancer	Pneumonitis, hepatotoxicity, QT prolongation
BRAF V600E Kinase Inhibitor				
Vemurafenib [Zelboraf]	Inhibits BRAF 600E kinase	Small molecule	BRAF V600E-positive melanoma	Cutaneous squamous cell carcinoma, arthralgia, QT prolongation, severe skin reactions, photosensitivity

CTLA-4 = cytotoxic T lymphocyte-associated antigen-4, EGFR = epidermal growth factor receptor, which is coupled with tyrosine kinase, HDAC = histone deacetylase, HER2 = human epidermal growth factor receptor 2, mTOR = mammalian target of rapamycin, PML = progressive multifocal leukoencephalopathy, VEGF = vascular endothelial growth factor.

*Gefitinib is no longer available in the United States.

TABLE 103-3 Targeted Anticancer Drugs—cont'd

Drug	Molecular Target	Drug Structure	Indications	Major Toxicities
OTHER TARGETED DRUGS				
CD20-Directed Antibodies				
Ofatumumab [Arzerra]	Binds CD20 antigen, causing apoptosis and immune attack	Antibody	B-cell chronic lymphocytic leukemia	Severe infusion reactions, cytopenias, PML
Rituximab [Rituxan]	Binds CD20 antigen, causing apoptosis and immune attack	Antibody	B-cell chronic lymphocytic leukemia, B-cell non-Hodgkin's lymphoma	Severe infusion reactions, severe mucocutaneous reactions, tumor lysis syndrome, PML
Ibritumomab tiuxetan/ ⁹⁰ yttrium [Zevalin]	Binds CD20 antigen, causing radiation injury	Antibody/ ⁹⁰ yttrium hybrid	B-cell non-Hodgkin's lymphoma	Bone marrow suppression and infusion reactions
Tositumomab/ ¹³¹ I-tositumomab [Bexxar]	Binds CD20 antigen, causing immune attack and radiation injury	Antibody/ ¹³¹ I hybrid	B-cell non-Hodgkin's lymphoma	Bone marrow suppression, infusion reactions, hypersensitivity reactions
Antibody-Drug Conjugate				
Brentuximab vedotin [Adcetris]	Binds CD30 antigen, to deliver a toxin that causes mitotic arrest	Antibody/drug hybrid	Hodgkin's lymphoma, anaplastic large cell lymphoma	Peripheral neuropathy, neutropenia
Angiogenesis Inhibitor				
Bevacizumab [Avastin]	Binds VEGF and thereby inhibits angiogenesis	Antibody	Colorectal cancer, non-small cell lung cancer, glioblastoma, renal cell carcinoma [†]	Hypertension, GI perforation, impaired wound healing, hemorrhage, thromboembolism, nephrotic syndrome
Proteasome Inhibitor				
Bortezomib [Velcade]	Inhibits proteasome activity	Small molecule	Multiple myeloma	Bone marrow suppression, GI disturbances, peripheral neuropathy, weakness
Histone Deacetylase Inhibitors				
Romidepsin [Istodax]	Inhibits HDAC	Small molecule	Cutaneous T-cell lymphoma	Bone marrow suppression, infection, QT prolongation
Vorinostat [Zolinza]	Inhibits HDAC	Small molecule	Cutaneous T-cell lymphoma	Pulmonary embolism, bone marrow suppression, fatigue, nausea, diarrhea
Additional Targeted Anticancer Drugs				
Alemtuzumab [Campath]	Binds CD52 antigen	Antibody	B-cell chronic lymphocytic leukemia	Bone marrow suppression, infusion reactions, infection
Trastuzumab [Herceptin]	Binds HER2	Antibody	HER2-positive breast cancer	Cardiotoxicity, infusion reactions
Ipilimumab [Yervoy]	Binds CTLA-4 to unleash an immune attack	Antibody	Melanoma	Severe immune-mediated enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies
Gemtuzumab ozogamicin [‡] [Mylotarg]	Binds CD33 antigen to deliver cytotoxic drug	Antibody/cytotoxic drug hybrid	CD33-positive myeloid leukemia	Bone marrow suppression, hepatic veno-occlusive disease, hypersensitivity reactions

[†]Postmarketing studies have failed to show a significant improvement in overall survival or quality of life in patients with breast cancer, and hence approval for breast cancer has been withdrawn.

[‡]In 2000, gemtuzumab ozogamicin received fast-track approval for treatment of CD33-positive acute myeloid leukemia. However, in 2010, the drug was voluntarily withdrawn after postmarketing studies revealed new, severe adverse effects and failed to confirm any clinical benefit.

Panitumumab

Panitumumab [Vectibix], approved in 2006, is a monoclonal antibody similar to cetuximab with respect to mechanism, indications, and adverse effects. The principal difference between the drugs is that panitumumab is a fully human antibody, whereas cetuximab is not. Like cetuximab, panitumumab blocks EGFRs, causing inhibition of tyrosine kinase and, ultimately, apoptosis. At this time, the drug has only one indication: treatment of EGFR-expressing metastatic *colorectal cancer* in patients who have already received chemotherapy. The most common adverse effect is acne-like rash. Other adverse effects include fatigue, nausea, diarrhea, and hypomagnesemia. Because panitumumab is a fully human antibody, severe infusion reactions are less frequent than with cetuximab (1% vs. 3%). The usual dosage is 6 mg/kg IV every 2 weeks.

Gefitinib

Therapeutic Use. Gefitinib, formerly available as *Iressa*, is approved for oral therapy of advanced *non-small cell lung cancer* (NSCLC) that has been refractory to first-line treatment (platinum- or docetaxel-based therapy). In clinical trials, between 8.2% and 19% of patients achieved an objective response. Unfortunately, postmarketing studies failed to show any survival benefit. As a result, gefitinib is no longer available in the United States, but remains available in Canada. NSCLC is the most common form of lung cancer, and cells of this cancer often overexpress EGFRs.

Mechanism of Action. Like cetuximab, gefitinib disrupts cellular processes regulated by EGFRs. However, unlike cetuximab, which acts on the cell surface to block EGFRs, gefitinib acts within the cell to inhibit tyrosine kinase that is linked with EGFR. Under normal conditions, activation of EGFR leads to activation of tyrosine kinase, which in turn activates signaling pathways that regulate cell proliferation and survival. By inhibiting EGFR-linked tyrosine kinase, gefitinib has the same effect as EGFR blockade: suppression of cell proliferation and promotion of apoptosis.

Responding Populations. A mutation in the EGFR tyrosine kinase gene predicts who will respond to gefitinib. This mutation is more likely in women, Asians, and patients with the adenocarcinoma subtype of NSCLC. People in these populations are more likely to respond.

Pharmacokinetics. Gefitinib is slowly absorbed from the GI tract. Plasma levels peak 3 to 7 hours after dosing. The drug undergoes extensive hepatic metabolism, primarily by CYP3A4, followed by excretion in the feces. The elimination half-life is 48 hours.

Adverse Effects. Gefitinib is generally well tolerated. As with cetuximab, the most frequent reactions are diarrhea (48%) and acne-like rash (43%). Other fairly common reactions are dry skin (13%), nausea (13%), and vomiting (12%). Ocular effects—amblyopia, conjunctivitis, eye pain, and corneal erosion or ulceration—occur infrequently. Asymptomatic elevation of liver transaminases has been reported.

Interstitial lung disease (ILD) is the most serious adverse effect. This condition begins with acute-onset dyspnea, sometimes with cough or fever. Rapid deterioration may ensue. The overall incidence is about 1%, with one-third of cases being fatal. If respiratory symptoms develop, gefitinib should be interrupted and the patient evaluated. If ILD is diagnosed, gefitinib should not be used again. The risk of ILD is highest among patients with prior radiation or chemotherapy.

Drug and Herb Interactions. Drugs that inhibit CYP3A4 (eg, itraconazole, ketoconazole) can decrease gefitinib metabolism, and may thereby increase its plasma level. Conversely, agents that induce CYP3A4 (eg, rifampin, phenytoin, carbamazepine, St John's wort) can accelerate gefitinib metabolism, and may thereby reduce its level. Likewise, drugs that lower gastric pH (eg, histamine₂ antagonists, proton pump inhibitors, antacids) can decrease gefitinib absorption, and may thereby lower its level.

Use in Pregnancy and Lactation. Gefitinib can harm the developing fetus, and hence should not be used by pregnant women. In laboratory animals, the drug decreased the number of live births, increased neonatal mortality, and reduced fetal weight. We don't know if gefitinib is safe during breastfeeding.

Dosage and Administration. The usual dosage is 250 mg PO once a day, taken with or without food. Dosing should be interrupted if the patient develops severe rash, severe diarrhea, or ocular complications, and should be discontinued if ILD is diagnosed. For patients taking a potent inducer of CYP3A4, dosage may be increased to 500 mg/day.

Erlotinib

Actions and Use. Erlotinib [Tarceva] has three indications: (1) advanced *non-small cell lung cancer* (NSCLC) after previous chemotherapy has failed; (2) maintenance therapy of advanced NSCLC when the disease has remained stable after four cycles of platinum-based first-line therapy, and

(3) first-line treatment of inoperable *pancreatic cancer* in combination with gemcitabine.

Like gefitinib, erlotinib inhibits tyrosine kinase coupled with EGFR, and thereby suppresses cell proliferation and promotes apoptosis. However, in contrast to gefitinib, erlotinib has been shown to prolong survival: In one trial of patients with NSCLC, median survival was 6.7 weeks with erlotinib, compared with 4.7 weeks with placebo. Survival was longest among patients who had never smoked and those with high levels of EGFR.

Responding Populations. As with gefitinib, a mutation in the EGFR tyrosine kinase gene predicts who will respond to erlotinib. As noted, this mutation is more likely in women, Asians, and patients with the adenocarcinoma subtype of NSCLC, and hence people in these populations are more likely to respond.

Pharmacokinetics. Oral bioavailability is 60% in the absence of food, and nearly 100% in the presence of food. Plasma levels peak about 4 hours after dosing. In the blood, erlotinib is 93% bound to proteins. The drug undergoes extensive metabolism by hepatic CYP3A4, followed by excretion in the bile.

Adverse Effects. Although erlotinib is generally well tolerated, adverse effects occur often. The most common are rash (75%), diarrhea (54%), nausea (33%), and vomiting (23%). Diarrhea can usually be managed with loperamide. Rarely, patients develop interstitial lung disease (ILD), a potentially fatal condition that begins with dry cough and sudden onset of dyspnea (or sudden worsening of existing dyspnea). Hepatotoxicity, manifesting as asymptomatic elevation of liver transaminases, occurs in some patients. Rarely, erlotinib causes GI perforation or severe skin reactions, both of which can be fatal. The drug can also cause ocular disorders, including corneal perforation, corneal ulceration, and abnormal eyelash growth. In animal studies, erlotinib caused fetal death and abortion, and hence should not be used during pregnancy.

Drug Interactions. Strong inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, ritonavir) can decrease metabolism of erlotinib, causing its level to rise. Conversely, inducers of CYP3A4 (eg, rifampin, carbamazepine) can accelerate metabolism of erlotinib, causing its level to fall, sometimes dramatically. Erlotinib may increase the risk of bleeding in patients taking warfarin; close monitoring of prothrombin time or the international normalized ratio (INR) is recommended.

Preparations, Dosage, and Administration. Erlotinib [Tarceva] is supplied in tablets (25, 100, and 150 mg). For NSCLC, the recommended dosage is 150 mg once daily, taken at least 1 hour before eating or 2 hours after. For pancreatic cancer, the recommended dosage is 100 mg once daily. Dosage reduction should be considered for all patients who develop serious skin reactions or liver impairment, and in those taking inhibitors of CYP3A4. If symptoms of ILD develop, dosing should be interrupted until ILD has been ruled out.

Lapatinib

Lapatinib [Tykerb] is a small-molecule inhibitor of EGFR tyrosine kinase and HER2 tyrosine kinase. Lapatinib and its use in breast cancer are discussed above.

BCR-ABL Tyrosine Kinase Inhibitors

The BCR-ABL tyrosine kinase inhibitors are the preferred agents for treating *chronic myeloid leukemia* (CML). Three of these drugs are available: imatinib, dasatinib, and nilotinib. Imatinib was introduced in 2001, and quickly became the "gold standard" for CML therapy. Unfortunately, relapse can occur, owing to evolution of subclones that have imatinib-resistant BCR-ABL mutations. The two newer drugs—dasatinib and nilotinib—are active against all but one of these resistant subclones, and hence can be effective even in patients who no longer respond to imatinib.

Imatinib

Indications. In 2001, imatinib [Gleevec] was approved for oral therapy of CML, but only after treatment with interferon alfa had failed. By 2003, because of clear superiority, imatinib had displaced interferon alfa as the initial treatment of choice. Imatinib may be continued as long as there is no

evidence of disease progression, and as long as side effects remain tolerable.

Imatinib is also approved for *myelodysplastic/myeloproliferative diseases, aggressive systemic mastocytosis, acute lymphoblastic leukemia, dermatofibrosarcoma protuberans, hypereosinophilic syndrome, chronic eosinophilic leukemia*, and unresectable and/or metastatic malignant *gastrointestinal stromal tumor (GIST)*, a rare form of stomach/intestinal cancer. These applications are not discussed further.

CML and Its Treatment. CML is a cancer in which myeloid cells undergo massive clonal expansion. The disease begins with a chronic phase, progresses through an accelerated phase, and ends with the blast crisis phase. The underlying cause is a genetic abnormality known as the *Philadelphia chromosome*, which is produced by translocation of genetic material between chromosomes 9 and 22. Because of this genetic change, CML cells make an abnormal, continuously active enzyme, called *BCR-ABL tyrosine kinase*. This enzyme phosphorylates, and thereby activates, as-yet unidentified regulatory proteins, which in turn inhibit apoptosis and stimulate cell proliferation. Major treatment options are imatinib, dasatinib, nilotinib, interferon-based regimens, and stem cell transplantation (the only potentially curative treatment).

Mechanism of Action and Clinical Effects. Imatinib is a highly specific competitive inhibitor of *BCR-ABL tyrosine kinase*. By inhibiting this enzyme, imatinib prevents the phosphorylation and resultant activation of regulatory proteins, and thereby suppresses proliferation of CML cells and promotes apoptosis. Imatinib is selective for cells that express *BCR-ABL tyrosine kinase*; normal cells are not affected. When tested during the chronic phase of CML, imatinib was superior to the combination of interferon alfa plus cytarabine. After 18 months, disease progression was stopped in 92% of imatinib users, compared with 74% of those getting interferon. Furthermore, imatinib was better tolerated. Long-term follow-up is needed to determine how long responses to imatinib will last, and whether imatinib prolongs survival.

Over time, resistance to imatinib may develop. Why? Because the genes that code for *BCR-ABL* can mutate, thereby causing production of imatinib-resistant forms of the enzyme.

Pharmacokinetics. Imatinib is well absorbed following oral administration. Bioavailability is 98%. In the blood, the drug is highly protein bound. Imatinib undergoes extensive metabolism, primarily by hepatic CYP3A4, followed by excretion in the feces. The elimination half-lives of imatinib and its major active metabolite are 18 hours and 40 hours, respectively.

Adverse Effects. Imatinib causes adverse effects in most patients. The incidence and severity of adverse effects is lowest during the chronic phase of CML, higher during the accelerated phase, and highest during blast crisis. However, even though adverse effects occurred often during trials, discontinuation because of them was uncommon: only 1% during the chronic phase, 2% during the accelerated phase, and 5% during blast crisis. Common reactions include nausea (55% to 68%), vomiting (28% to 54%), diarrhea (33% to 49%), rash (32% to 39%), headache (24% to 28%), fatigue (24% to 33%), fever (14% to 38%), and musculoskeletal complaints, including muscle cramps (25% to 46%), muscle pain (27% to 37%), and arthralgia (21% to 24%). Fluid retention occurs in 52% to 68% of patients, and may lead to pleural effusion, pericardial effusion, pulmonary edema, or ascites. Neutropenia and thrombocytopenia develop often, posing a risk of infection and bleeding. Ac-

cordingly, complete blood counts should be obtained weekly during the first month of treatment, biweekly during the second month, and periodically thereafter. Hepatotoxicity, indicated by severe elevations of transaminases or bilirubin, develops in 1.1% to 3.5% of patients. Other reported effects include severe congestive heart failure, serious skin reactions (eg, erythema multiforme, Stevens-Johnson syndrome), and hypothyroidism in thyroidectomy patients receiving thyroid hormone replacement therapy.

Effects in Pregnancy and Breast-Feeding. In animal studies, doses equivalent to those used clinically have caused major fetal malformations. Accordingly, imatinib is classified in FDA Pregnancy Risk Category D, and hence should be avoided during pregnancy. Women of child-bearing age should use adequate contraception.

Imatinib achieves high concentrations in breast milk, and hence poses a risk to the breast-fed infant. The manufacturer recommends against breast-feeding while taking the drug.

Drug Interactions. Imatinib is a substrate for and competitive inhibitor of CYP3A4, CYP2C9, and CYP2D6. By inhibiting these CYP isozymes, imatinib can raise levels of warfarin and other drugs that are metabolized by them. Drugs that inhibit CYP3A4 (eg, ketoconazole, erythromycin) can raise levels of imatinib. Conversely, drugs that induce CYP3A4 (eg, carbamazepine, rifampin, St. John's wort) can reduce levels of imatinib.

Preparations, Dosage, and Administration. Imatinib [Gleevec] is supplied in 100- and 400-mg tablets, for administration with a meal and a large glass of water. The dosage for adults with CML is 400 mg once daily during the chronic phase, and 600 mg once daily during the accelerated phase or blast crisis. The dosage for children with CML (during the chronic phase) is 340 mg/m² once daily. The dosage for adults with GIST is 400 mg once daily.

Dasatinib

Dasatinib [Sprycel], approved in 2006, is indicated for all three phases of CML: chronic, accelerated, and blast crisis. Initially, the drug was approved only for patients who were unresponsive to or intolerant of imatinib. However, in 2010, the FDA approved dasatinib as first-line therapy.

Dasatinib inhibits *BCR-ABL tyrosine kinase* more effectively than imatinib. Why? First, dasatinib binds to both the active and inactive conformations of *BCR-ABL tyrosine kinase*, whereas imatinib only binds to the inactive conformation. Second, dasatinib binds the enzyme with greater affinity than imatinib. Third, dasatinib binds a wider variety of protein kinases. As a result of these differences, dasatinib is active against nearly all imatinib-resistant mutant clones. In fact, the only exception is the T315I mutation, which is resistant to all available drugs.

Adverse effects of dasatinib are much like those of imatinib, with one important exception: Dasatinib produces more myelosuppression, and thereby poses a risk of severe neutropenia, thrombocytopenia, and anemia. Fluid retention is seen in about 35% of patients. Severe cases can cause pulmonary edema. Rarely, dasatinib has been associated with pulmonary arterial hypertension, although a causal relationship has not been established. Dasatinib has the potential to prolong the QT interval, but the clinical significance is unclear.

Levels of dasatinib can be affected by other drugs. Dasatinib is a substrate for CYP3A4, and hence drugs that induce CYP3A4 can lower dasatinib levels, and drugs that inhibit CYP3A4 can raise dasatinib levels. Solubility of dasatinib is pH dependent, and hence drugs that raise gastric pH (antacids, proton pump inhibitors, H₂-receptor blockers) can reduce dasatinib absorption.

Dasatinib is available in film-coated tablets (20, 50, 70, 80, 100, and 140 mg) for oral dosing. The dosage is 100 mg once daily during the chronic phase, and 140 mg once daily during the accelerated phase or blast crisis.

Nilotinib

Nilotinib [Tasigna], approved in 2007, is indicated for (1) accelerated-phase CML in patients resistant to or intolerant of imatinib and (2) chronic-phase CML in treatment-naïve patients, as well as patients previously treated with imatinib. Like imatinib, nilotinib binds to the inactive form of *BCR-ABL*.

However, the binding affinity is much greater. Like dasatinib, nilotinib is active against all imatinib-resistant clones, except those with the T315I mutation.

In general, patients tolerate nilotinib better than imatinib. The most common adverse effects are thrombocytopenia, neutropenia, rash, pruritus, nausea, fatigue, headache, and constipation. Of much greater concern, nilotinib prolongs the QT interval, posing a risk of severe dysrhythmias and sudden cardiac death. Accordingly, the drug should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Also, it should not be combined with other QT drugs, or with strong inhibitors of CYP3A4 (eg, ketoconazole, clarithromycin, ritonavir).

Like dasatinib, nilotinib is a substrate for CYP3A4, and hence drugs that induce CYP3A4 can lower nilotinib levels, and drugs that inhibit CYP3A4 can raise nilotinib levels.

Nilotinib is supplied in 150- and 200-mg capsules. Dosing must be done *without* food. Why? Because food greatly increases absorption, and hence increases toxicity. The dosage for CML is 300 or 400 mg twice daily.

Multi-Tyrosine Kinase Inhibitors

In contrast to the EGFR tyrosine kinase inhibitors and the BCR-ABL tyrosine kinase inhibitors, which inhibit just one type of tyrosine kinase, the drugs in this section inhibit several types of tyrosine kinase. However, despite their diverse actions, the multi-tyrosine kinase inhibitors have limited indications: Three of the available agents—sorafenib, sunitinib, and pazopanib—are approved for advanced renal cell carcinoma. In addition, sorafenib is approved for hepatocellular carcinoma, and sunitinib is approved for GI stromal tumor and pancreatic neuroendocrine tumors. A fourth drug—vandetanib—is approved for medullary thyroid cancer.

Sorafenib

Sorafenib [Nexavar], approved in 2005, is an oral multi-tyrosine kinase inhibitor approved for *advanced renal cell carcinoma* and *unresectable hepatocellular carcinoma*. The drug inhibits multiple cell-surface and intracellular kinases that are associated with angiogenesis, apoptosis, and cell proliferation.

The most common adverse effects are diarrhea (43%), rash (40%), fatigue (37%), and hand-and-foot syndrome (30%). Between 15% and 20% of patients develop hypertension. Nausea and vomiting are usually mild. Sorafenib prolongs the QT interval, and thereby poses a risk of serious dysrhythmias. In addition, the drug doubles the risk of bleeding (by inhibiting vascular endothelial growth factor [VEGF] tyrosine kinase). Myocardial ischemia and GI perforation occur rarely. Sorafenib (in low doses) is teratogenic and embryolethal in animals, and hence should be avoided during pregnancy (FDA Pregnancy Risk Category D).

Sorafenib is supplied in 200-mg tablets. The recommended dosage is 400 mg twice daily. To optimize absorption, dosing should be done *without* food (at least 1 hour before eating or 2 hours after).

Sunitinib

Sunitinib [Sutent], approved in 2006, is an oral multi-tyrosine kinase inhibitor with three indications: *advanced renal cell carcinoma*, *pancreatic neuroendocrine tumor (PNET)*, and *GI stromal tumor (GIST)* in patients unresponsive to or intolerant of imatinib. The drug inhibits multiple tyrosine kinases, and thereby disrupts angiogenesis, cellular growth, and tumor metastasis.

Adverse effects are very common. Twenty percent or more of patients experience fatigue, weakness, anorexia, altered taste, fever, dyspnea, cough, GI disturbances (nausea, vomiting, diarrhea, dyspepsia, abdominal pain, mucositis), pain (headache, back pain, arthralgia, extremity pain), and skin reactions (rash, dryness, hand-and-foot syndrome, discolored skin and hair). Of much greater concern, sunitinib can cause heart damage, liver damage, and hemorrhage. About 15% of patients develop irreversible heart failure, and hence cardiac function should be monitored closely. Like sorafenib, sunitinib prolongs the QT interval, and hence can cause severe dysrhythmias. Sunitinib can cause potentially fatal liver injury. Accordingly, liver function tests should be conducted at baseline and periodically throughout the treatment period. By suppressing platelet production, sunitinib can cause hemorrhage. To reduce risk, serial blood counts should be conducted. About 25% of patients develop mild to moderate hypertension, which responds to standard antihypertensive drugs. Other serious effects include impairment of wound healing, adrenal function, and thyroid function. In animal studies, sunitinib has been teratogenic and fetotoxic, and hence is classified in FDA Pregnancy Risk Category D.

Sunitinib is a substrate for CYP3A4, and hence medications that inhibit CYP3A4 (eg, ketoconazole, erythromycin) can raise levels of sunitinib and

increase toxicity. Conversely, drugs that induce CYP3A4 (eg, carbamazepine, rifampin, St. John's wort) can reduce levels and thereby decrease efficacy.

Sunitinib is supplied in capsules (12.5, 25, and 50 mg) for dosing with or without food. For patients with renal cell carcinoma or GIST, the recommended dosage is 50 mg once daily, taken on a repeating cycle consisting of 4 weeks of treatment followed by 2 weeks off. For patients with PNET, the recommended dosage is 375 mg once daily, with no scheduled off time.

Pazopanib

Pazopanib [Votrient], approved in 2009, is an oral multi-tyrosine kinase inhibitor indicated only for *advanced renal cell carcinoma*. In one clinical trial, average progression-free survival was 9.2 months among patients taking pazopanib, compared with 4.2 months among those taking placebo. Like sunitinib and sorafenib, pazopanib disrupts tumor growth and angiogenesis by inhibiting multiple forms of tyrosine kinase.

Adverse effects are common, and sometimes severe. Effects seen often include hepatotoxicity (53%), diarrhea (52%), hypertension (47%), hyperglycemia (41%), change in hair color (38%), leukopenia (37%), and thrombocytopenia (32%), sometimes associated with hemorrhage. Rarely, pazopanib has caused fatal GI perforation (0.3%), fatal thrombotic events (0.3%), and potentially fatal torsades de pointes (less than 1%) secondary to prolonging the QT interval. In pregnant animals, pazopanib has been teratogenic, embryolethal, and abortifacient. Accordingly, the drug is classified in FDA Pregnancy Risk Category D.

Like sunitinib, pazopanib is metabolized by CYP3A4, and hence medications that inhibit CYP3A4 can raise levels of pazopanib (and thereby increase toxicity), and medications that induce CYP3A4 can reduce levels of pazopanib (and thereby decrease efficacy).

Pazopanib is supplied in 200- and 400-mg tablets. The usual dosage is 800 mg once daily, taken *without* food (at least 1 hour before eating or 2 hours after). In patients taking a strong inhibitor of CYP3A4, dosage should be reduced to 400 mg once daily. Patients taking a strong inducer of CYP3A4 should avoid pazopanib. In patients with moderate liver impairment, dosage should be reduced to 200 mg once daily. Patients with severe liver impairment should avoid pazopanib.

Vandetanib

Vandetanib [Caprelsa], approved in 2011, is indicated for *advanced medullary thyroid cancer*, a rare disease that accounts for just 3% to 5% of all thyroid cancers. In the United States, this translates to about 1300 to 2200 cases a year. Benefits of vandetanib appear to result from inhibiting multiple tyrosine kinases, including EGFR tyrosine kinase. In a trial known as ZETA, median progression-free survival was at least 22.6 months with vandetanib, versus 16.4 months with placebo.

The most common adverse effects are diarrhea/colitis (57%), rash (53%), acne (35%), nausea (33%), hypertension (33%), headache (26%), fatigue (24%), decreased appetite (21%), and abdominal pain (21%). More importantly, vandetanib poses a significant risk of QT prolongation, which can lead to potentially fatal dysrhythmias. Furthermore, since vandetanib has a long half-life (19 days), this risk can persist long after dosing is stopped. To monitor QT effects, an electrocardiogram should be obtained at baseline, between weeks 2 and 4, between weeks 8 and 12, and every 3 months thereafter. Other drugs that prolong the QT interval should be avoided. In laboratory animals, low-dose vandetanib is fetotoxic and teratogenic. Accordingly, the drug is classified in FDA Pregnancy Risk Category X, and hence should be avoided by women who are pregnant.

Vandetanib is supplied in 100- and 300-mg tablets. The usual dosage is 300 mg once daily, taken with or without food. Dosage should be reduced in the event of severe toxicity or QT prolongation. In patients with moderate to severe renal impairment, the starting dosage is 200 mg once daily.

mTOR Kinase Inhibitors

Temsirolimus

Temsirolimus [Torisel], approved in 2007, is indicated for IV therapy of *advanced renal cell carcinoma*. Following conversion to its active form—sirolimus—the drug inhibits mTOR (mammalian target of rapamycin), a protein kinase that helps regulate cell growth, proliferation, and survival. Inhibition of mTOR leads to G₁ arrest and apoptosis. Adverse effects, which are common, include weakness (51%), rash (47%), mucositis (41%), nausea (37%), edema (35%), anorexia (32%), dyspnea (28%), pain (28%), and fever (24%). Common laboratory abnormalities include anemia (94%), neutropenia (53%), hyperglycemia (38%), and increases in cholesterol (87%), triglycerides (83%), and alkaline phosphatase (68%). Sirolimus (the active metabolite of temsirolimus) is metabolized by CYP3A4, and hence levels of

sirolimus can be altered by drugs that induce or inhibit CYP3A4. Temsirolimus is available in single-dose, 25-mg vials. The recommended dosage is 25 mg infused over 30 to 60 minutes once weekly, continuing until disease progression recurs or toxicity becomes intolerable.

Everolimus

Everolimus [Afinitor], approved in 2009, has three anticancer indications: (1) *advanced renal cell carcinoma* after failure with sorafenib or sunitinib, (2) *subependymal giant cell astrocytoma (SEGA)* in patients who are not candidates for curative surgical resection, and (3) *pancreatic neuroendocrine tumors (PNETs)* that are unresectable, locally advanced, or metastatic. As with temsirolimus, benefits derive from inhibiting mTOR kinase. In addition to its use in cancer, everolimus, sold as Zortress, is used to prevent organ rejection in transplant recipients (see Chapter 69).

Everolimus causes multiple adverse effects, including weakness (33%), fatigue (31%), diarrhea (30%), nausea (26%), cough (30%), dyspnea (24%), rash (29%), and peripheral edema (25%). Hematologic effects include reduced hemoglobin levels (92%), reduced lymphocyte counts (51%), and reduced platelet counts (23%). Neutropenia (37%) predisposes to infections. Metabolic abnormalities include elevations of cholesterol (77%), triglycerides (73%), and glucose (37%). About 44% of patients develop oral mucositis, stomatitis, or mouth and tongue ulcers. Everolimus is toxic to the developing fetus, and hence is categorized in FDA Pregnancy Risk Category D.

Everolimus for cancer therapy is supplied in tablets (2.5, 5, and 10 mg) sold as Afinitor. For patients with renal cell carcinoma or PNET, the usual dosage is 10 mg once daily, taken with or without food. Treatment should continue until disease progression recurs or side effects become intolerable. For patients with SEGA, the initial dosage is 2.5 to 7.5 mg once daily.

Vemurafenib, a BRAF V600E Kinase Inhibitor

Actions and Use. Vemurafenib [Zelboraf], approved in 2011, is a kinase inhibitor indicated for patients with unresectable or metastatic *melanoma* that expresses *BRAF V600E kinase*, a variant form of BRAF kinase that is found in 30% to 60% of melanoma cells. In healthy cells, BRAF kinase (a cell-membrane protein) stimulates cell proliferation, but only when activated by specific growth factors. BRAF V600E differs from normal BRAF kinase in that BRAF V600E is highly active in the *absence* of stimulation by growth factors. As a result, cells with the BRAF V600E mutation undergo excessive proliferation and metastasis. Vemurafenib is a small molecule that inhibits BRAF V600E kinase activity, and thereby suppresses tumor growth. Before vemurafenib is used, the BRAF V600E mutation must be confirmed using an FDA-approved assay, such as the *cobas 4800 BRAF V600 Mutation Test*.

Clinical Trial. In a trial known as BRIM-3 (BRAF Inhibitor in Melanoma-3), vemurafenib was compared to dacarbazine, considered standard treatment for melanoma. All subjects had melanoma with the BRAF V600E mutation. The results? Compared with dacarbazine, vemurafenib improved progression-free and overall survival. Median progression-free survival was 5.3 months with vemurafenib versus 1.6 months with dacarbazine. Overall 6-month survival was 84% with vemurafenib versus 64% with dacarbazine. Because patients responded so well to vemurafenib, the committee monitoring the trial recommended that patients receiving dacarbazine be switched to the new drug.

Adverse Effects. Vemurafenib can cause serious adverse effects. Cutaneous squamous cell carcinoma, seen in 24% of patients, is of greatest concern. Other serious effects include hepatotoxicity, severe hypersensitivity reactions (eg, anaphylaxis), severe skin reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis), serious ophthalmic reactions (eg, uveitis, iritis, retinal vein occlusion), and QT prolongation,

which poses a risk of severe dysrhythmias. Less serious effects include arthralgia (53%), hair loss (45%), fatigue (38%), rash (37%), photosensitivity reactions (33%), itching (23%), nausea (35%), and diarrhea (28%). Because of its mechanism, vemurafenib is likely to cause fetal harm, and hence is classified in FDA Pregnancy Risk Category D. Accordingly, women using the drug should avoid getting pregnant.

Drug Interactions. Vemurafenib is subject to multiple drug interactions, which could be hard to predict. Vemurafenib is a substrate for CYP3A4 and P-glycoprotein (a transporter that pumps drugs out of cells), and hence levels of vemurafenib can be altered by drugs that induce or inhibit these pathways. Also, vemurafenib itself is an inhibitor of P-glycoproteins as well as several CYP isozymes, and hence vemurafenib can increase levels of drugs that employ these pathways. Lastly, vemurafenib can induce CYP3A4, and hence can reduce levels of CYP3A4 substrates.

Preparations, Dosage, and Administration. Vemurafenib [Zelboraf] is supplied in 240-mg film-coated tablets for dosing with or without food. The recommended dosage is 960 mg twice daily. Tablets should be swallowed whole with a glass of water.

Crizotinib, an ALK Inhibitor

Crizotinib [Xalkori], approved in 2011, is indicated for advanced *non-small cell lung cancer (NSCLC)* that is *anaplastic lymphoma kinase (ALK) positive*. Benefits derive from inhibiting ALK. What's ALK? It's a tyrosine kinase found in normal and cancerous cells. However, the form of ALK found in normal cells differs from the form found in cancer cells. Because of this difference, ALK activity in normal cells is *low*, whereas ALK activity in certain cancer cells is *high*—so high, in fact, that it drives proliferation and prolongs survival. Hence, by inhibiting ALK, crizotinib can suppress tumor growth. Because crizotinib is approved only for NSCLC that is ALK positive, the cancer must be tested for ALK prior to treatment. Among patients with NSCLC, about 2% to 10% have the ALK-positive type. In clinical trials, crizotinib was highly effective: virtually every patient with ALK-positive NSCLC experienced some benefit, although the degree of benefit varied.

Crizotinib is generally well tolerated. The most common adverse effects are nausea (53% to 57%), diarrhea (43% to 49%), vomiting (40% to 45%), constipation (27% to 38%), edema (28% to 38%), fatigue (20% to 31%), dizziness (16% to 24%), and neuropathies (13% to 23%). Elevation of liver enzymes is seen in 4% to 7% of patients. Crizotinib prolongs the QT interval, and hence poses a risk of serious dysrhythmias. The most serious adverse effect—potentially fatal pneumonitis—develops in 1.6% of patients. If pneumonitis is diagnosed, crizotinib should be stopped and never used again. In laboratory animals, crizotinib was fetotoxic at doses close to those used clinically. Accordingly, women using the drug should avoid pregnancy.

Crizotinib is a substrate for and inhibitor of CYP3A4. Accordingly, crizotinib levels can be increased by CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, ritonavir), and can be decreased by CYP3A4 inducers (eg, carbamazepine, phenytoin, St. John's wort). By inhibiting CYP3A4, crizotinib can raise levels of CYP3A4 substrates, including cyclosporine, fentanyl, and alfentanil.

Crizotinib is supplied in 200- and 250-mg capsules. The usual dosage is 250 mg twice daily.

OTHER TARGETED DRUGS

CD20-Directed Antibodies

Antibodies directed against CD20 are used to treat B-cell non-Hodgkin's lymphoma and B-cell chronic lymphocytic leukemia. What's CD20? It's a molecule found on the cell membrane surface of B lymphocytes (B cells), important components of the immune system (see Chapter 67). Most other cells lack CD20. When antibodies bind with CD20, they trigger an immune attack against the B cell itself. Since most other cells do not have CD20, injury is limited to normal and malignant B lymphocytes.

At this time, four products containing anti-CD20 antibodies are available. Two of these products—ibritumomab [Zevalin] and tositumomab [Bexxar]—consist of a monoclonal an-

tibody that has been linked with a radioactive isotope. With these drugs, cell kill results largely from radiation damage, rather than from immune attack. The other two drugs—rituximab [Rituxan] and ofatumumab [Arzerra]—have no radioactivity, and hence cell kill results from immune attack promoted by the antibody.

Rituximab

Actions, Use, and Dosage. Rituximab [Rituxan] is a monoclonal antibody indicated for IV therapy of *B-cell non-Hodgkin's lymphoma* and *B-cell chronic lymphocytic leukemia*. The antibody is directed against the CD20 antigen, found on the surface of most normal and malignant B cells. Binding of rituximab recruits components of the immune system, which then cause cell lysis. In a study of patients with non-Hodgkin's lymphoma, rituximab produced a complete response in 6% of patients, and another 42% experienced a partial response (50% or greater reduction in tumor burden). The recommended dosage is 375 mg/m² given by slow infusion once a week for 4 weeks. A 4-week course costs about \$45,000.

In addition to its use in cancer, rituximab is used for rheumatoid arthritis (see Chapter 73), and for two inflammatory disorders of blood vessels: microscopic polyangiitis and Wegener's granulomatosis.

Adverse Effects. Infusion Reactions. Rituximab can cause severe infusion-related hypersensitivity reactions. Prominent symptoms are hypotension, bronchospasm, and angioedema. Deaths have occurred. Management includes slowing or discontinuing the infusion and injecting epinephrine.

Tumor Lysis Syndrome (TLS). Rapid and massive death of tumor cells can lead to TLS, characterized by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia. Rarely, the syndrome proves fatal. TLS begins within 12 to 24 hours of the first rituximab infusion. The risk of TLS is increased by a high tumor burden. Management includes dialysis and correction of fluid and electrolyte abnormalities.

Mucocutaneous Reactions. Rituximab has been associated with severe mucocutaneous reactions, including Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. Deaths have occurred. Reaction onset is typically 1 to 3 weeks after rituximab exposure. Patients who experience these reactions should seek immediate medical attention, and should not receive rituximab again.

Hepatitis B Reactivation. There have been reports of hepatitis B virus (HBV) reactivation, leading to fulminant hepatitis, hepatic failure, and death. Patients at high risk of HBV should be screened before getting rituximab. Asymptomatic carriers should be closely monitored for clinical and laboratory signs of active HBV infection while taking rituximab, and for several months after stopping.

Progressive Multifocal Leukoencephalopathy (PML). Rituximab has been associated with rare cases of PML, a severe infection of the CNS caused by reactivation of the JC virus, an opportunistic pathogen resistant to all available drugs.

Other Adverse Effects. Like other monoclonal antibodies, rituximab can cause a flu-like syndrome, especially during the initial infusion. Symptoms include fever, chills, nausea, vomiting, and myalgia. Rituximab causes transient neutropenia, but this does not appear to increase the risk of infection.

Ofatumumab

Actions and Use. Ofatumumab [Arzerra] is a monoclonal antibody directed against the CD20 antigen on B lymphocytes. In 2009, the drug was approved as second-line therapy for *B-cell chronic lymphocytic leukemia* in patients refractory to fludarabine [Fludara] and alemtuzumab [Campath]. Like rituximab, ofatumumab binds with CD20 antigens on B cells, and thereby promotes immune-mediated cell lysis. In patients refractory to fludarabine and alemtuzumab, the overall response rate to ofatumumab is 42%, with a median response duration of 6.5 months.

Adverse Effects. Ofatumumab can cause severe adverse effects. Like rituximab, the drug can cause infusion reactions, PML, and reactivation of hepatitis B. In addition, ofatumumab can cause severe neutropenia and thrombocytopenia, thereby increasing the risk of infections and bleeding. Intestinal obstruction may also occur. Common, but less serious effects include fever, cough, dyspnea, diarrhea, fatigue, rash, and nausea.

Dosage and Administration. Treatment consists of an initial dose (300 mg IV), followed by 11 more doses (2000 mg IV each) over the following 24 weeks. A single, 2000-mg dose costs \$21,000 for the drug alone, or roughly \$235,000 for the full series. To minimize infusion reactions, patients should be pretreated with acetaminophen (PO), an antihistamine (PO or IV), and a glucocorticoid (IV).

Ibritumomab Tiuxetan Linked with Yttrium-90

Description, Actions, and Use. Ibritumomab tiuxetan (IT), marketed as *Zevalin*, is a compound molecule composed of ibritumomab (a monoclonal antibody) that has been covalently bound with tiuxetan. Like rituximab, IT binds selectively with the CD20 antigen present on most normal and malignant B cells. However, unlike rituximab, which is used by itself to treat cancer, IT is first linked with yttrium-90 (Y90), a beta particle-emitting radioisotope. When the IT-Y90 complex binds with cellular CD20 antigens, cell kill results from radiation-induced injury, rather than from injury caused by ibritumomab itself. Because beta particles have a relatively short path length (about 5 mm), injury is restricted to CD20-containing cells and to neighboring cells within a 5-mm radius. The radioactive drug poses no danger to persons in proximity. IT-Y90 was the first anticancer treatment to employ an antibody complexed with a radioactive compound. IT-Y90 was originally approved for *low-grade, B-cell non-Hodgkin's lymphoma*, and then later approved for *follicular non-Hodgkin's lymphoma*. Therapy with IT-Y90 is expensive: A single course costs about \$30,000.

Before patients receive IT-Y90, they are given two small doses of rituximab, 7 to 9 days apart. The contribution of rituximab is twofold. First, it binds with circulating B cells, and thereby greatly reduces their numbers. Second, it occupies nonspecific binding sites that could otherwise attract IT-Y90, and hence would reduce the amount of IT-Y90 available to bind with target cells. For the purpose of diagnostic imaging, the first dose of rituximab is accompanied by a small dose of IT that has been linked to radioactive indium-111.

Adverse Effects. Adverse effects of treatment are due to IT-Y90 itself and to the rituximab given before it. As noted above, rituximab can cause severe infusion reactions. With IT-Y90, hematologic toxicity is the major concern: severe, prolonged cytopenias develop in more than 50% of patients. Counts of neutrophils and platelets reach their nadir 7 to 9 weeks after treatment, and take 3 to 7 weeks to recover. In clinical trials, about 30% of patients developed infection or febrile neutropenia; of these, 7% required hospitalization. Deaths have occurred. Because of its hematologic toxicity, IT-Y90 is contraindicated for patients with (1) lymphoma bone marrow involvement of 25% or more or (2) limited bone marrow reserve (eg, platelet count below 100,000/mm³ or neutrophil count below 1500/mm³; history of prior myeloablative therapy).

Bexxar (Tositumomab with ¹³¹I-Tositumomab)

Description, Actions, and Use. *Bexxar* is the trade name for a regimen that consists of (1) *tositumomab*, a monoclonal antibody, and (2) *¹³¹I-tositumomab*, tositumomab covalently linked with radioactive iodine-131. This regimen, which was the second to employ a radiolabeled antibody, is very similar in mechanism and uses to the Zevalin regimen (ibritumomab tiuxetan/yttrium-90), the first to employ a radiolabeled antibody. Like the Zevalin regimen, the Bexxar regimen is both very toxic and very expensive. The cost of a single course (for the drug alone) is over \$30,000.

How does Bexxar kill cancer cells? Through a combination of immune activation and radiation damage. Like ibritumomab and rituximab, tositumomab binds selectively with the CD20 antigen found on the surface of most normal and malignant B cells. This binding stimulates an immune attack on the cell, with three possible results: complement-dependent cytotoxicity, antibody-dependent cytotoxicity, and induction of apoptosis (programmed cell death). Cell death also results when ¹³¹I-tositumomab binds with the CD20 antigen, thereby exposing target cells to a high dose of ionizing radiation.

Treatment is performed in two steps, called the *dosimetric step* and the *therapeutic step*. The dosimetric step is conducted to determine, for each patient, the specific dose of radiation to be given in the therapeutic step.

Bexxar is approved for CD20-positive *follicular B-cell non-Hodgkin's lymphoma* (NHL), a form of low-grade B-cell NHL. However, the drug should be used only if the cancer (1) is refractory to rituximab and (2) has relapsed following chemotherapy. In clinical trials, Bexxar produced an objective response in 63% of patients, and complete remission in 29%. The median duration of the response was 16 to 25 months.

Adverse Effects. Like Zevalin, Bexxar can cause *severe, prolonged cytopenias*. Neutropenia (63%) and thrombocytopenia (53%) are most common, often leading to infections (45%) and hemorrhage (12%). Management may require infusion of blood products (platelets and red blood cells) as well as treatment with a hematologic growth factor (epoetin alfa, granulocyte colony-stimulating factor). To monitor hematologic status, complete blood counts should be obtained at baseline and then weekly for 10 to 12 weeks. Like Zevalin, Bexxar is contraindicated for patients with lymphoma bone marrow involvement of 25% or more and for those with limited bone marrow reserve.

Hypersensitivity reactions, including anaphylaxis, occur in 6% of patients. Medication for treating severe reactions (epinephrine, antihistamines, glucocorticoids) should be immediately available.

Many patients experience *infusional toxicity*, either during the infusion or within 48 hours after. Symptoms include fever, rigors, chills, sweating, hypotension, dyspnea, nausea, and bronchospasm. Pretreatment with acetaminophen or diphenhydramine may help.

The radioactive iodine in ¹³¹I-tositumomab can damage the thyroid gland, causing *hypothyroidism*. To protect the thyroid, patients should take oral potassium iodide (tablets or solution), starting at least 24 hours before the dosimetric dose and continuing for 2 weeks after the therapeutic dose.

Gastrointestinal toxicity is seen in 38% of patients. Symptoms include nausea, vomiting, abdominal pain, and diarrhea.

Secondary malignancies—myelodysplastic syndrome and/or acute leukemia—occur in 2% to 3% of patients, usually within 3 years of treatment.

Use in Pregnancy and Lactation. Radioactive iodine can harm the developing thyroid gland. Irreversible hypothyroidism may result. Accordingly, Bexxar is classified in *FDA Pregnancy Risk Category X*, and hence must not be used during pregnancy. Radioiodine and (probably) tositumomab are excreted in breast milk, posing a risk to the breast-fed infant. Mothers should be warned not to breast-feed while receiving Bexxar.

Elimination of Iodine-131. Elimination of iodine-131 occurs by radioactive decay and excretion in the urine. About 67% is cleared by 5 days after the infusion. Of the amount not eliminated through radioactive decay, 98% is eliminated in the urine.

Radiation Precautions. For several days after treatment, persons in close proximity to the patient receiving Bexxar could be harmed by radiation from iodine-131. Therefore, prior to discharge, the patient should be given oral and written instruction on how to minimize exposure of family, friends, and the general public. Specific measures include staying at least 9 feet from others, sleeping alone, maintaining sole bathroom use (owing to urinary radiation excretion), avoiding contact with children and pregnant women, refraining from travel by plane or mass transit, and avoiding prolonged car travel with other people.

Brentuximab Vedotin, an Antibody-Drug Conjugate

Brentuximab vedotin [Adcetris], approved in 2011, is an antibody-drug conjugate (ADC), composed of brentuximab coupled with monomethyl auristatin E (MMAE). Brentuximab is a monoclonal antibody that selectively binds with CD30, an antigen expressed on the surface of certain cancer cells. MMAE is a toxic compound that binds with intracellular tubulin. Cell kill results as follows: After binding with CD30 on the cell surface, the entire ADC is rapidly internalized, and then cleaved to release free MMAE, which then binds with tubulin to cause mitotic arrest.

Brentuximab vedotin has two indications: *Hodgkin's lymphoma* after failure of autologous stem cell transplantation or after failure of at least two multidrug chemotherapy regimens, and (2) *systemic anaplastic large cell lymphoma* after failure of at least one multidrug chemotherapy regimen. In clinical

trials, the drug was highly effective. Among patients with Hodgkin's lymphoma, the overall response rate was 73%, including 32% with complete remission. And among patients with anaplastic large cell lymphoma, the overall response rate was 86%, including 57% with complete remission. Of note, these response rates are higher than those produced with any available chemotherapy regimen.

Adverse effects are generally "manageable." The most common are peripheral sensory neuropathy (52%), neutropenia (54%), anemia (33%), fatigue (49%), nausea (42%), diarrhea (36%), and fever (29%). Of these, neuropathy and neutropenia are the greatest concerns. In clinical trials, neuropathy led to discontinuation of treatment in 10% of patients, and a reduction of dosage in 9% more. For most patients, neuropathy resolves after stopping the drug. In laboratory animals, low-dose brentuximab vedotin was teratogenic and fetotoxic. Accordingly, the drug should be avoided in women who are pregnant (FDA Pregnancy Risk Category D).

Brentuximab vedotin is supplied as a 50-mg powder to be reconstituted with 10.5 mL of sterile water, to yield a single-use solution containing 5 mg/mL. The recommended dosage is 1.8 mg/kg infused IV over 30 minutes every 3 weeks, for a maximum of 16 doses. In the event of a severe infusion reaction (which is rare), stop the infusion and never give the drug again. If neuropathy or neutropenia develops, dosage should be reduced or the dosing interval increased.

Angiogenesis Inhibitors

Angiogenesis inhibitors suppress formation of new blood vessels, and thereby deprive solid tumors of the expanding blood supply they need for continued growth. It is important to note, however, that although tumor growth is suppressed, angiogenesis inhibitors, by themselves, cannot kill tumor cells that already exist. At this time, only one angiogenesis inhibitor—bevacizumab—is approved for treating cancer. The history and unique potential of the angiogenesis inhibitors are discussed in Box 103-1.

Bevacizumab

In 2004, bevacizumab [Avastin] became the first angiogenesis inhibitor approved for clinical use. In patients with metastatic colorectal cancer or nonsquamous non-small cell lung cancer, the drug can delay tumor progression and prolong life. Unfortunately, bevacizumab can also cause life-threatening side effects, including GI perforation, hemorrhage, and thromboembolism. Nonetheless, bevacizumab is now the best-selling anticancer drug in history, with annual sales of about \$6 billion. For individuals, treatment costs about \$96,000 a year.

Mechanism of Action. Bevacizumab is a monoclonal antibody that binds with vascular endothelial growth factor (VEGF), an endogenous compound that stimulates blood vessel growth. Binding with bevacizumab prevents VEGF from binding with its receptors on vascular endothelial cells, and thereby prevents VEGF from promoting new vessel formation. As a result, further tumor growth is suppressed.

Therapeutic Use. Bevacizumab has four approved uses:

- *Metastatic cancer of the colon or rectum*, in combination with a regimen based on IV 5-fluorouracil (5-FU)
- *Nonsquamous non-small cell lung cancer (NSCLC)*, in combination with carboplatin and paclitaxel

ANGIOGENESIS INHIBITORS: KEEPING CANCER IN CHECK

Like all other tissues, tumors need blood vessels to bring them nutrients and oxygen. To ensure adequate blood flow, tumor cells induce angiogenesis—growth of new blood vessels. Without new vessels, tumors could not grow. In fact, their maximum size would be limited to 2 mm³ (about the size of a pinhead). Because tumors require their own blood supply, drugs that block angiogenesis have the potential to profoundly limit tumor expansion. Furthermore, because angiogenesis inhibitors attack the blood supply, rather than the tumor itself, they should be active against a broad range of cancer types.

The field of angiogenesis inhibition owes much to Dr. Judah Folkman and his colleagues at Harvard Medical School. In 1971, Dr. Folkman discovered tumor-induced angiogenesis, and postulated that inhibitors of the process could cause tumor starvation. For many years, Folkman's lab was unable to find an angiogenesis inhibitor safe enough to use. Then, in 1997, the group reported dramatic results with two new compounds: angiostatin and endostatin. These agents were compared with cytotoxic drugs in mice with three kinds of primary tumors. Initially, both treatments caused tumor regression. However, with repeated rounds of therapy, the tumors developed resistance to the cytotoxic agents. In contrast, after six rounds of antiangiogenesis treatment, the tumors regressed to microscopic size—and then remained dormant a long time. Furthermore, the angiogenesis inhibitors were devoid of adverse effects, in sharp contrast to the cytotoxic drugs.

Angiogenesis in Normal Tissues and Tumors

In normal tissues, angiogenesis occurs during fetal development, growth, wound repair, and the uterine cycle. New blood vessels are derived from endothelial cells—the flat cells that form the inner lining of blood vessels. Angiogenesis has four basic steps:

- Activation of endothelial cells in an existing blood vessel
- Production, by the endothelial cells, of matrix metalloproteinases (MMPs), which break down the extracellular matrix of the surrounding tissue
- Proliferation and migration of endothelial cells
- Assembly of the endothelial cells into new blood vessels

This process is tightly regulated by two groups of opposing factors: activators of endothelial cell growth and inhibitors of endothelial cell growth. At least 35 endogenous factors are known to activate endothelial cell growth and migration. Important among these are

- Vascular endothelial growth factor (VEGF)
- Basic fibroblast growth factor (bFGF)
- Epidermal growth factor
- Platelet-derived growth factor
- Placental growth factor
- Interleukin-8
- Tumor necrosis factor-alpha (TNF-alpha)
- Angiogenin
- Angiotropin

Naturally occurring inhibitors of endothelial growth include angiostatin, endostatin, interferons, platelet factor 4, thrombospondin, and three tissue inhibitors of metalloproteinase (TIMP-1, TIMP-2, and TIMP-3).

Tumors can stimulate angiogenesis by releasing growth factors. Two such factors—VEGF and bFGF—are produced by many tumors, and appear important for promoting and sustaining tumor growth. In tumors, a good blood supply is associated with aggressive growth and increased ability to metastasize. Interestingly, MMPs, which break down the matrix that holds cells together, are required for both angiogenesis and metastatic spread.

Comparison with Cytotoxic Anticancer Drugs

The angiogenesis inhibitors differ from cytotoxic drugs in four important ways. First, angiogenesis inhibitors are safer. Second, angiogenesis inhibitors can be used without interruption. Third, tumor resistance to angiogenesis inhibitors does not develop. Fourth, angiogenesis inhibitors can prolong life without causing tumor regression.

Angiogenesis inhibitors are generally *safer* than cytotoxic anticancer drugs. Unlike cytotoxic drugs, which attack *all* proliferating cells, angiogenesis inhibitors have limited effects. Accordingly, these agents do not cause myelosuppression, GI ulceration, or hair loss—toxicities that are common with the cytotoxic drugs. However, because of their effects on blood vessels, angiogenesis inhibitors *are* likely to interfere with wound healing and fetal development, and they may be harmful to growing children. In addition, they increase the risk of thromboembolism and hypertension. As we gain more experience with these drugs, additional toxicities may be revealed.

Angiogenesis inhibitors can be *used continuously*. Why? Because these drugs do not cause dose-related myelosuppression and mucositis. Cytotoxic drugs must be used intermittently, so as to permit recovery of bone marrow and mucosal tissue.

In long-term preclinical studies, *no tumor resistance* to angiogenesis inhibitors has been observed. By contrast, resistance is common with cytotoxic drugs. Why the difference? Cytotoxic drugs are directed against cancer cells, which are heterogeneous and genetically unstable. As a result, drug-resistant variants can readily evolve and emerge. In contrast, angiogenesis inhibitors are directed at endothelial cells, which are genetically stable, and hence are unlikely to evolve into potentially resistant forms.

With angiogenesis inhibitors, the treatment goal is *tumor stabilization*, rather than tumor regression. Although these drugs can block formation of new blood vessels, they do not cause existing vessels to dissolve. Hence, they can block tumor growth, but may not cause an existing tumor to shrink. When cytotoxic drugs are tested, the clinical endpoint is tumor regression. In contrast, when angiogenesis inhibitors are tested, the endpoint is prolongation of life; the tumor may or may not get smaller.

A New Treatment Paradigm

Angiogenesis inhibitors may enable a completely new approach to cancer therapy: long-term maintenance, instead of outright cure. By suppressing growth of new blood vessels, angiogenesis inhibitors can stabilize existing tumors and prevent growth of new ones. With continuous therapy, we may be able to keep the cancer in check indefinitely, even though it is unlikely to go away. Hence, although treatment may not eliminate the cancer, chronic therapy may still permit a long life. In essence, cancer would become a chronic but treatable disease, much like hypertension or diabetes—diseases that we can manage with drugs, even though we can't cure them. Perhaps the angiogenesis inhibitors will permit cancer patients to live long and otherwise healthy lives, just as drugs have done for patients with these other once-fatal diseases.

- Metastatic *renal cell carcinoma*, in combination with interferon alfa
- *Glioblastoma*, as a single agent following prior therapy

What about breast cancer? Until recently, bevacizumab was widely used for breast cancer. However, approval for treatment of breast cancer has been withdrawn. Why? Because five postmarketing studies failed to show a significant improvement in overall survival or quality of life, and also failed to confirm the benefit seen in the single trial upon which approval was originally based. Given these data, members of the FDA's Oncologic Drugs Advisory Committee agreed that bevacizumab:

- Has not been shown effective for the breast cancer indication for which it was approved
- Has not been shown safe for the breast cancer indication for which it was approved
- Has not been shown to offer a clinical benefit that justifies the risks associated with its use for breast cancer
- Should not remain approved while Genetech (the manufacturer) conducts additional trials to verify possible benefits

As a result, on November 8, 2011, the FDA rescinded the breast cancer indication. The indication was rescinded in Canada shortly thereafter.

In addition to its use in cancer, bevacizumab is used off-label to treat the neovascular form of *age-related macular degeneration* (see Chapter 104).

Pharmacokinetics. The pharmacokinetics of bevacizumab are poorly understood. We do know that the drug has an average half-life of 20 days, and that clearance occurs faster in males and in patients with a high tumor burden. However, there is no evidence that faster clearance reduces the clinical response. How clearance occurs is unknown.

Adverse Effects. The most serious adverse effects are GI perforation, hemorrhage, thromboembolism, nephrotic syndrome, disruption of wound healing, and hypertensive crisis. Less serious effects include diarrhea, rhinitis, proteinuria, taste alteration, dry skin, headache, and back pain.

During clinical trials, 2% of patients developed *GI perforation*, with or without abscess formation. Some cases were fa-

Clinical Status

More than 60 angiogenesis inhibitors are in clinical trials, and one agent—bevacizumab [Avastin]—has been approved for general use (see chapter body). These drugs work by four basic mechanisms: (1) inhibition of MMPs, (2) direct inhibition of endothelial cell proliferation and migration, (3) antagonism of angiogenic growth factors, and (4) inhibition of integrin, a protein found on the endothelial cell surface. In addition, they may improve delivery of chemotherapy to tumors. Specific agents under investigation include *marimastat* (which inhibits MMP), *endostatin* (which directly inhibits endothelial cells), and *vitaxin* (which blocks integrin). Target diseases include melanoma, Kaposi's sarcoma, malignant glioma, and cancers of the breast, lung, ovary, prostate, colon, and pancreas.

Primary symptoms are abdominal pain in association with constipation and vomiting. If GI perforation occurs, bevacizumab should be stopped and never used again.

Bevacizumab greatly increases the risk of *severe or fatal hemorrhage*. Patients have experienced GI bleeding, intracranial bleeding, vaginal bleeding, and nosebleeds. In addition, patients with NSCLC have experienced life-threatening *pulmonary hemorrhage*. The risk of a life-threatening or fatal lung bleed is very high (31%) in patients with squamous cell histology, and much lower (4%) in those with non-squamous cell histology. Onset of pulmonary bleeding is sudden and presents as major or massive hemoptysis (expectoration of blood). Bevacizumab should be avoided in patients with recent hemoptysis or serious hemorrhage.

When added to a regimen based on 5-FU, bevacizumab doubles the risk of *arterial thromboembolic events*, including ischemic stroke, myocardial infarction, and transient ischemic attacks. Deaths have occurred. Patients who experience a thromboembolic event should stop bevacizumab and never use it again.

Bevacizumab *impairs wound healing* and can induce wound dehiscence (splitting open). Because of these effects, if bevacizumab is initiated too soon after surgery, or if it is not discontinued soon enough before surgery, impaired wound healing can result. To minimize healing complications, guidelines suggest waiting at least 28 days after surgery before using the drug, and stopping the drug at least 28 days before elective surgery.

Bevacizumab can cause *severe hypertension* that may persist for months after the drug is withdrawn. Some patients have experienced hypertensive encephalopathy and subarachnoid hemorrhage. Blood pressure should be monitored in all patients. If severe hypertension develops, bevacizumab should be permanently discontinued.

In clinical trials, *nephrotic syndrome* (severe kidney damage) developed in 0.5% of patients. One patient required dialysis, and one died. Patients should be monitored for development or worsening of proteinuria, a sign of kidney injury. If moderate to severe proteinuria occurs, bevacizumab should be withdrawn.

Effect in Pregnancy. Angiogenesis is critical to fetal development, and hence angiogenesis inhibition is likely to

cause fetal harm. Although human data are lacking, animal studies indicate that bevacizumab decreases fetal weight, increases fetal resorption, and can promote gross malformations. Currently, bevacizumab is classified in *FDA Pregnancy Risk Category C*, and should be used only if the benefits to the mother are judged to outweigh the risks to the fetus.

Dosage, Administration, and Cost. Bevacizumab is supplied in solution (100 mg/4 mL, 400 mg/16 mL) for IV infusion. Infusion time is 90 minutes for the first dose, then 60 minutes for the second dose (if the first dose was well tolerated), and 30 minutes thereafter (if the second dose was well tolerated). Dosages are as follows:

- *Colorectal cancer*—5 mg/kg or 10 mg/kg every 2 weeks in combination with IV 5-fluorouracil-based therapy
- *Nonsquamous non-small cell lung cancer*—15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel
- *Glioblastoma*—10 mg/kg every 2 weeks
- *Renal cell carcinoma*—10 mg/kg every 2 weeks in combination with interferon alfa

Treatment should be interrupted 28 days before elective surgery, and not resumed for at least 28 days after major surgery. Treatment should be permanently discontinued in the event of GI perforation, serious bleeding, thromboembolism, nephrotic syndrome, or hypertensive crisis.

Proteasome Inhibitors

What are proteasomes, and how does inhibiting them harm cells? Proteasomes are intracellular multienzyme complexes that degrade proteins. Their physiologic role is to rid cells of proteins that are not needed, including proteins that regulate transcription, cell adhesion, apoptosis, and progression through the cell cycle. Proteasome inhibitors can cause these proteins to accumulate, and can thereby disrupt various aspects of cell physiology. In cancer cells, these drugs appear to promote accumulation of proteins that promote apoptosis (programmed cell death). Why this effect is limited largely to cancer cells is not clear, but may be related to inhibition of NF-kappa B, a transcription factor critical to the growth of several types of cancer, including multiple myeloma.

Bortezomib

Actions. Bortezomib [Velcade], approved in 2004, is the first proteasome inhibitor available for general use. The drug inhibits a specific proteasome, known as the 26S proteasome, and thereby alters the concentration of proteins that regulate cell growth and division. The result is reduced cell viability, increased apoptosis, and increased sensitivity to the lethal effects of radiation and cytotoxic anticancer drugs. Does bortezomib hurt normal cells too? Yes. However, *in vitro* studies suggest that normal cells are less vulnerable than cancer cells.

Therapeutic Use. Bortezomib is approved for (1) *multiple myeloma*, both as first-line therapy and for patients who have not responded adequately to other therapies (eg, thalidomide, autologous stem cell transplantation); and (2) *mantle cell lymphoma* in patients with at least 1 prior year of therapy. In a clinical trial involving multiple myeloma patients who had received an average of six prior therapies, treatment with bortezomib, by itself, produced a measurable response in 35% of patients, and complete cancer regression in 4%. The median response duration was 1 year. Given that these patients were, in essence, refractory to virtually all other treatments, these results are especially impressive. Bortezomib is now being studied in a variety of solid tumors, including non-Hodgkin's lymphoma, colorectal cancer, and lung cancer.

Adverse Effects. Adverse effects are common and often serious. The most frequent reactions are weakness (65%), nausea (64%), and diarrhea (51%). Also common are hematologic effects—thrombocytopenia (43%), anemia (32%), and neutropenia (24%)—as well as constipation (43%), anorexia (43%), peripheral neuropathy (37%), fever (36%), and postural hypotension (12%). Bortezomib is fetotoxic in rabbits, and has been classified in *FDA Pregnancy Risk Category D*. Accordingly, pregnancy should be avoided.

Drug Interactions. No formal studies on drug interactions have been conducted. However, we do know that bortezomib is metabolized in the liver by CYP isozymes. Accordingly, inhibitors or inducers of these isozymes might be expected to alter bortezomib levels.

Dosage and Administration. Multiple Myeloma. Bortezomib is administered by IV bolus in nine 6-week cycles. One cycle consists of a single dose (1.3 mg/m²) on days 1, 4, 8, 11, 22, 25, 29, and 32, followed by

a 10-day rest period. In the event of painful peripheral neuropathy or any other severe toxicity, interruption of treatment and/or dosage reduction may be needed.

Mantle Cell Lymphoma. Bortezomib is administered by IV bolus in repeated 3-week cycles. One cycle consists of a single dose (1.3 mg/m²) on days 1, 4, 8, and 11, followed by a 10-day rest period.

Histone Deacetylase Inhibitors

The histone deacetylase (HDAC) inhibitors are a relatively new class of targeted anticancer drugs. The first two members, vorinostat and romidepsin, were approved in 2006 and 2009, respectively. Both drugs are indicated only for *cutaneous T-cell lymphoma* (CTCL), a rare form of cancer with only 1500 new cases a year in the United States. As their name implies, these drugs inhibit HDAC, and thereby increase the acetylation of histones, regulatory proteins in the cell nucleus that help control DNA transcription. When histones are in their acetylated state, they turn on gene transcription. In tumor cells, increased transcription leads to cell-cycle arrest and apoptosis.

Vorinostat

Vorinostat [Zolinza], the first HDAC inhibitor available, is indicated for oral therapy of CTCL that has progressed or returned after treatment with two systemic therapies. Unfortunately, benefits of vorinostat are modest. In clinical trials, the most common adverse effects were fatigue (52%), diarrhea (52%), nausea (41%), altered taste (28%), anorexia (24%), weight loss (21%), thrombocytopenia (26%), and anemia (14%). Pulmonary embolism (4.7%) is the most common serious effect. Drug interactions have not been studied, but appear to be minimal. Vorinostat is supplied in 100-mg capsules. The usual dosage is 400 mg once daily.

Romidepsin

Romidepsin [Istodax] is indicated for intravenous therapy of CTCL that has progressed or returned despite treatment with at least one systemic agent. As with vorinostat, benefits are modest. In clinical trials, 35% of patients showed a partial response, and only 6% showed a complete response. Response duration was 13.8 months. Although benefits of romidepsin and vorinostat appear about equal, the two drugs have not been compared directly.

Romidepsin can cause multiple adverse effects. The most common are nausea, vomiting, fatigue, anorexia, taste disturbance, and hematologic deficits: anemia, leukopenia, and thrombocytopenia. Because of leukopenia, patients are at increased risk of serious infections. Primary cardiac effects are electrocardiographic T-wave changes and QT prolongation. Romidepsin can harm the developing fetus, and hence should not be used during pregnancy. In contrast to vorinostat, romidepsin has *not* been associated with pulmonary embolism.

Romidepsin undergoes extensive metabolism by CYP3A4, and hence strong inhibitors (eg, clarithromycin) and inducers (eg, carbamazepine) should be avoided. Romidepsin binds with receptors for estrogen, and can thereby reduce the effects of estrogen-containing contraceptives.

Romidepsin is supplied as a powder to be reconstituted for IV infusion. The recommended dosage is 14 mg/m², infused over a 4-hour interval, on days 1, 8, and 15 of a repeating 28-day cycle.

Ipilimumab

Ipilimumab [Yervoy], approved in 2011, is indicated for unresectable or metastatic *melanoma*. Benefits derive from unleashing an immune attack on cancer cells. Here's how it works. Ipilimumab is a monoclonal antibody directed against CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4), a regulatory molecule that puts a brake on T-cell function. When ipilimumab binds with CTLA-4, it releases the brake, thereby allowing T cells to attack and kill cancer cells.

In clinical trials, ipilimumab produced a significant increase in survival. In one trial, overall survival was 10.1 months in patients who received ipilimumab, compared to 6.4 months in patients who received gp100 (an experimental vaccine designed to stimulate a T-cell attack against cancer). In another trial, overall survival was significantly greater in patients who received ipilimumab plus dacarbazine (a standard treatment for melanoma), compared with patients who received dacarbazine alone.

By promoting T-cell activation and proliferation, ipilimumab can cause severe fatal immune-mediated effects. Among these are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathies (both motor and sensory), and endocrinopathies (eg, hypopituitarism, hypothyroidism, adrenal insufficiency). Patients should be closely monitored for signs and symptoms. If a severe immune-mediated reaction is diagnosed, ipilimumab should be discontinued.

umab should be immediately and permanently discontinued, and patients should be treated with high-dose systemic glucocorticoids.

Ipilimumab is supplied as a concentrated solution (50 mg/10 mL, 200 mg/40 mL) that must be diluted to 1 to 2 mg/mL before use. A single dose is 3 mg/kg infused IV over 90 minutes. A full course of treatment consists of four doses given 3 weeks apart.

IMMUNOSTIMULANTS

As their name implies, the immunostimulants enhance the body's immune attack on cancer cells. In the discussion below, we focus on three agents: interferon alfa-2b, aldesleukin, and BCG vaccine. Indications and routes are summarized in Table 103-4.

Interferon Alfa-2b

Interferons are naturally occurring proteins with complex antiviral, anticancer, and immunomodulatory actions. Release of endogenous interferons is triggered by viral infections and other stimuli. Interferons are active against a variety of solid tumors and hematologic malignancies. They are also used for multiple sclerosis (see Chapter 23) and hepatitis (see Chapter 93).

Discussion here is limited to two interferons: *interferon alfa-2b* [Intron A] and *peginterferon alfa-2b* [Sylatron]. (Peginterferon alfa-2b is simply a long-acting form of interferon alfa-2b produced by a process known as pegylation, in which a polymer of polyethylene glycol [PEG] is attached to native interferon alfa-2b.) Although the active component of interferon alfa-2b and peginterferon alfa-2b is the same, these preparations have different indications. Specifically, interferon alfa-2b is approved for *melanoma, hairy cell leukemia, chronic myelogenous leukemia, follicular lymphoma, and AIDS-related Kaposi's sarcoma*, whereas peginterferon alfa-2b is approved only for *melanoma*.

Anticancer effects of interferon alfa-2b are thought to result from two basic processes: (1) enhancement of host immune responses and (2) direct antiproliferative effects on cancer cells. Both processes are mediated by binding of interferon alfa-2b to cell-surface receptors, with resultant increased expression of certain genes and reduced expression of others. Interferon alfa-2b can cause G_0 cells to remain dormant, thereby preventing proliferation. In addition, it can cause proliferating cells to differentiate into nonproliferative mature forms.

Interferon alfa can cause multiple adverse effects. The most common is a flu-like syndrome characterized by fever, fatigue, myalgia, headache, and chills. Symptoms tend to diminish with continued therapy. Some symptoms (fever, headache, myalgia) can be reduced with acetaminophen. Other common effects include anorexia, weight loss, diarrhea, abdominal pain, dizziness, and cough. Prolonged or high-dose therapy can cause fatigue, cardiotoxicity, thyroid dysfunction, and bone marrow suppression, manifesting as neutropenia and thrombocytopenia. Neuropsychiatric effects—especially depression—are a serious concern, owing to a risk of death by suicide.

The pharmacology of interferon alfa-2b and peginterferon alfa-2b is discussed at greater length in Chapter 93.

Aldesleukin (Interleukin-2)

Aldesleukin [Proleukin], also known as interleukin-2 (IL-2), is an immunostimulant indicated for advanced renal carcinoma and melanoma. Because severe adverse effects occur often, the drug must be administered in a hospi-

tal that has an intensive care facility; a specialist in cardiopulmonary or intensive care medicine must be available.

Description and Actions. Aldesleukin is a large glycoprotein nearly identical in structure and actions to human IL-2. The drug is produced by recombinant DNA technology. Like IL-2, aldesleukin stimulates immune function. Specific responses include enhanced production and cytotoxicity of lymphocytes; increased production of interleukin-1, interferon gamma, and tumor necrosis factor; and induction of lymphokine-activated killer cell activity. These powerful immunostimulant actions are believed to underlie antitumor effects.

Therapeutic Use. Aldesleukin has two approved uses: *metastatic renal cell carcinoma* and *metastatic melanoma*. Among patients with renal cell cancer, 4% respond completely and 11% respond partially. The median response duration is 2 years.

Pharmacokinetics. Aldesleukin is administered by IV infusion and distributes throughout the extracellular space. About 70% of each dose undergoes preferential uptake by the liver, kidneys, and lungs. Renal enzymes convert the drug into inactive metabolites, which are excreted in the urine. The drug's half-life is short—just 85 minutes.

Adverse Effects. Practically all patients experience significant toxicity. The fatality rate is high (4%). Effects seen most frequently are fever and chills (89%), nausea and vomiting (87%), hypotension (85%), anemia (77%), diarrhea (76%), altered mental status (76%), sinus tachycardia (70%), impaired renal function (61%), impaired liver function (56%), pulmonary congestion (54%), dyspnea (52%), and pruritus (48%). Depression may also occur.

Capillary leak syndrome (CLS) is of particular concern. This potentially fatal reaction is characterized by hypotension and reduced organ perfusion (secondary to loss of vascular tone and extravasation of plasma proteins and fluid). Symptoms begin to develop immediately after treatment. CLS may be associated with angina pectoris, cardiac dysrhythmias, myocardial infarction, pronounced respiratory insufficiency, renal insufficiency, GI bleeding, and altered mental status. Because of the risk of CLS, aldesleukin must not be given to patients with cardiac, pulmonary, renal, hepatic, or CNS impairment. Careful monitoring is essential.

BCG Vaccine

Description and Therapeutic Use. BCG vaccine [TheraCys, TICE BCG] is a freeze-dried preparation of live, attenuated *Mycobacterium bovis* (bacillus of Calmette and Guérin). The vaccine is approved for primary and relapsed *carcinoma in situ of the bladder*, both in the presence and absence of associated papillary tumors. To treat bladder cancers, BCG vaccine is administered intravesically (ie, directly into the bladder through a urethral catheter). In addition to its use in cancer therapy, BCG vaccine is used to protect against tuberculosis (see Chapter 90).

Mechanism of Action. BCG vaccine is a nonspecific immunostimulant. Instillation in the bladder produces a local inflammatory response that, by an unknown mechanism, promotes regression of tumors in the urothelial lining.

Adverse Effects. The most common adverse effects, which result from bladder irritation, are dysuria, urinary frequency, urinary urgency, and hematuria. Urinary status should be monitored closely. The most common systemic reactions are malaise, fatigue, fever, and chills.

Because BCG vaccine consists of live *M. bovis*, therapy carries a risk of systemic infection, including fatal septic shock. Accordingly, the vaccine is contraindicated for (1) immunocompromised patients (eg, those taking immunosuppressant drugs, those with symptomatic or asymptomatic HIV infec-

TABLE 103-4 ■ Immunostimulants

Generic Name	Trade Name	Route	Indications
Interferon alfa-2b	Intron A	SubQ IM, IV	Melanoma, hairy cell leukemia, chronic myelogenous leukemia, follicular lymphoma, AIDS-related Kaposi's sarcoma
Peginterferon alfa-2b	Sylatron*	SubQ	Melanoma
Aldesleukin (interleukin-2)	Proleukin	IV	Metastatic renal cell cancer, metastatic melanoma
BCG vaccine	TheraCys, TICE BCG	Intravesical	<i>In situ</i> bladder cancer

BCG, bacillus of Calmette and Guérin.

*Peginterferon alfa-2b is also marketed as *PegIntron* for treatment of hepatitis.

tion); (2) patients with fever of unknown origin (because it may signify infection); and (3) patients with urinary tract infections (because there is an increased risk of systemic absorption of BCG vaccine).

Because BCG vaccine is infectious, it must be handled using aseptic technique. All materials employed during administration should be disposed of in plastic bags labeled "Infectious Waste." Urine voided within 6 hours of BCG instillation should be disinfected with an equal volume of 5% hypochlorite before flushing.

OTHER NONCYTOTOXIC ANTICANCER DRUGS

Glucocorticoids

The basic pharmacology of the glucocorticoids is discussed in Chapter 72. Discussion here is limited to their use in cancer. To benefit patients with cancer, dosages must be high, and hence, with long-term use, adverse effects are a concern.

Glucocorticoids (eg, *prednisone*, *dexamethasone*) are used in combination with other agents to treat cancers arising from lymphoid tissue. Specific indications are *acute and chronic lymphocytic leukemias*, *Hodgkin's disease*, *non-Hodgkin's lymphomas*, and *multiple myeloma*. Glucocorticoids are beneficial in these cancers because they are directly toxic to lymphoid tissues: High-dose therapy causes suppression of mitosis, dissolution of lymphocytes, regression of lymphatic tissue, and cell death. When glucocorticoids are used acutely, toxicity is limited and manageable. However, with prolonged treatment, multiple serious toxicities can occur, including osteoporosis, adrenal insufficiency, increased susceptibility to infection, GI ulcers, fluid and electrolyte disturbances, myopathy, growth retardation in children, cutaneous atrophy, and diabetes. Unlike the short-term toxicities, these long-term toxicities are hard to manage.

In addition to their use against lymphoid-derived cancers, glucocorticoids are used to manage complications of cancer and cancer therapy. Specific benefits include suppression of chemotherapy-induced nausea and vomiting, reduction of cerebral edema (caused by brain metastasis and irradiation to the brain), reduction of pain (caused by nerve compression or edema), and suppression of hypercalcemia in patients with steroid-responsive tumors. In addition, glucocorticoids can improve appetite and promote weight gain.

Retinoids

Retinoids are derivatives of retinol (vitamin A) that bind to and activate retinoid receptors. In their active state, retinoid receptors regulate the proliferation and differentiation of cells, both normal and neoplastic. In patients with cancer, retinoids inhibit cancer cell growth.

Alitretinoin

Alitretinoin [Panretin], an analog of retinol, is indicated for topical therapy of *cutaneous lesions* in patients with *AIDS-related Kaposi's sarcoma*. When alitretinoin is added to Kaposi's sarcoma cells in culture, it inhibits their growth.

Alitretinoin is supplied as a 0.1% gel for topical use. The drug should be applied only to cutaneous Kaposi's sarcoma lesions, not to normal skin. Following application, the area should be allowed to dry for 3 to 5 minutes before putting clothing over it. Occlusive dressings should be avoided. Treatment is initiated with twice-daily application. Later on, the drug may be applied 3 or 4 times a day, if tolerance permits. Most patients respond in 4 to 8 weeks. However, some respond in only 2 weeks, but others may not respond until 16 weeks.

Adverse effects are limited to the site of application. Local reactions—erythema, scaling, irritation, rash, and dermatitis—occur in 25% to 77% of patients. The incidence of severe reactions is 10%. Other retinoids are known to cause photosensitivity reactions. Although photosensitivity has not been reported with alitretinoin, exposing the treated area to sunlight or sunlamps

should nonetheless be minimized. Retinoids are highly teratogenic. Accordingly, women using alitretinoin should avoid getting pregnant (even though systemic absorption of alitretinoin appears to be minimal).

Alitretinoin is expensive: a 60-gm tube costs over \$2000. However, this is actually cheaper than other treatments for Kaposi's sarcoma.

Bexarotene

Mechanism and Use. Bexarotene [Targretin] is indicated for oral therapy of *cutaneous T-cell lymphoma* in patients who have been refractory to prior systemic therapy. Like alitretinoin, bexarotene is an analog of vitamin A (retinol) and can activate retinoid receptors. The result is altered regulation of cellular proliferation and differentiation. *In vitro*, bexarotene can inhibit growth of some tumor cell lines. In clinical trials, a dosage of 300 mg/m²/day produced a complete response in 4% of patients, and a partial response (more than 50% improvement) in 48% of patients.

Pharmacokinetics. Plasma levels peak 2 hours after oral administration. Taking the drug with a high-fat meal increases absorption. Bexarotene undergoes metabolism by CYP3A4 followed by excretion in the bile.

Adverse Effects and Interactions. Bexarotene causes lipid abnormalities and other serious side effects. In clinical trials, toxicity caused 30% of patients to discontinue treatment.

Major lipid abnormalities are common. Plasma triglycerides rise to a level 2.5 times above the upper limit of the normal range in 70% of patients. Sixty percent of patients have significant elevations in total cholesterol and low-density lipoprotein cholesterol. Levels of high-density lipoprotein cholesterol (good cholesterol) are reduced.

Bexarotene frequently causes headache, asthenia, leukopenia, anemia, infection, rash, and photosensitivity. The incidence of clinically significant hypothyroidism is 30%. Fatal pancreatitis and fatal cholestasis have been reported.

Bexarotene and other retinoids are powerful teratogens. Accordingly, bexarotene is absolutely contraindicated for use during pregnancy. Women taking the drug must ensure that pregnancy does not occur.

In theory, drugs that inhibit CYP3A4 can increase bexarotene levels, and drugs that induce CYP3A4 can reduce its levels. Combining vitamin A with bexarotene could result in increased toxicity.

Tretinoin

Tretinoin [Vesanoid], also known as all-*trans* retinoic acid (ATRA), is approved for induction of remission in patients with *acute promyelocytic leukemia* (APL). Rates of complete remission are high. Unfortunately, although tretinoin can be very effective, it can also cause severe toxicity, and hence the benefits of treatment must be carefully weighed against the risks. The mechanism underlying beneficial effects is not well established.

The most common adverse effects are rash, dry skin, and CNS toxicity, manifesting as headache, depression, confusion, and anxiety. The most serious effect, seen in 25% of patients, is *retinoic acid-APL syndrome*, characterized by fever, pleural and pericardial effusions, and hypoxia. In its most severe form, the syndrome can lead to respiratory failure and death. Milder reactions generally respond to high-dose IV glucocorticoids, without interruption of tretinoin. In severe cases, tretinoin should be withdrawn.

Tretinoin is a substrate for hepatic CYP enzymes, and hence CYP inducers (eg, rifampin, phenytoin, St. John's wort) and inhibitors (eg, erythromycin,azole antifungals, diltiazem) should be avoided.

The recommended dosage is 45 mg/m²/day administered PO as two evenly divided doses. Dosing with food improves absorption.

The use of tretinoin for dermatologic disorders is discussed in Chapter 105.

Arsenic Trioxide

Arsenic trioxide [Trisenox] is approved for *acute promyelocytic leukemia* (APL), a rare subtype of acute myelogenous leukemia in which myeloid cells are blocked from undergoing normal differentiation and apoptosis. In patients who have relapsed following standard therapy of APL, arsenic trioxide has produced a high rate of complete remission. The drug appears to work by reversing the blockade on myeloid differentiation and apoptosis, and by inhibiting angiogenesis.

Toxicity occurs in most patients. Common side effects include nausea, vomiting, diarrhea, fatigue, edema, hyperglycemia, dyspnea, cough, rash, headache, and dizziness. Leukoerythrosis (elevation of white blood cell counts) occurs in 50% of patients. Of greater concern, about 23% experience a potentially fatal condition known as *APL differentiation syndrome*, characterized by fever, weight gain, pulmonary infiltrates, dyspnea, musculoskeletal pain, and pleural and pericardial effusions. Symptoms can be reduced by immediate therapy with high-dose glucocorticoids. Prolongation of the QT interval is common and can lead to life-threatening dysrhythmias. An electro-

THALIDOMIDE REDEEMED—AND STRICTLY CONTROLLED

On July 16, 1998, the Food and Drug Administration (FDA) finally approved thalidomide for American use—after denying approval nearly 40 years earlier. Because thalidomide is a powerful teratogen, the FDA requires that prescribers, pharmacists, and patients follow strict safety rules. At this time, the drug has only two approved uses (1) multiple myeloma, an incurable cancer of the bone marrow; and (2) erythema nodosum leprosum (ENL), a painful complication of leprosy. However, thalidomide has shown promise in many other diseases, including inflammatory disorders and several additional types of cancer.

The thalidomide story goes back to the late 1950s, when the drug caused the most notorious tragedy in pharmaceutical history. Thalidomide was developed in Germany for use as a sedative, and was sold over the counter in Europe. Many pregnant women took the drug for morning sickness and insomnia. It was not until 1961 that a terrible truth became known: Thalidomide was causing horrific birth defects. Thousands of children were born with stunted, flipper-like limbs (phocomelia). Others suffered deafness, blindness, facial paralysis, brain damage, kidney malformation, and congenital heart disease. Between 1957 and 1961, thalidomide deformed more than 12,000 babies, and killed untold others *in utero*.

Thanks to Dr. Frances Oldham Kelsey of the FDA, most infants in the United States were spared. It was Dr. Kelsey's job to review the application to market thalidomide here. She had just joined the FDA and this was her first assignment. However, Dr. Kelsey was no ordinary new hire, having both a medical degree and a PhD in pharmacology. Given her background and the sketchy data on toxicity, Dr. Kelsey was concerned about the drug's safety. So she turned down the application and demanded more studies. Despite pressure from the manufacturer and from her superiors at the FDA, she continued to hold her ground. The drug's teratogenic potential became known before approval was ever granted. In recognition of her courage and dedication, President John F. Kennedy honored Dr. Kelsey with the Distinguished Federal Civilian Service Award, the highest civilian award in the United States.

Thalidomide appears to have great potential as a therapeutic agent. Responses in cancer have been especially encouraging. In patients with multiple myeloma, thalidomide produced complete remission in 10% of recipients; another 20% or so experienced significant improvement. Furthermore, thalidomide caused fewer adverse effects than traditional anticancer drugs. Early evidence indicates that thalidomide may also help patients with cancer of the prostate, brain, colon, skin, and other organs. Additional conditions for which thalidomide has shown promise include rheumatoid arthritis, systemic lupus erythematosus (SLE), Crohn's disease (an inflammatory bowel disorder), macular degeneration, chronic host-versus-graft disease, and oral aphthous ulcers associated with AIDS.

Several pharmacologic actions may explain therapeutic effects. Of special note are anti-inflammatory and immunomodulating actions, mediated in part by decreased synthesis of tumor necrosis factor-alpha. In addition, thalidomide suppresses angiogenesis (growth of new blood vessels). This action may underlie benefits in cancer and ENL.

Thalidomide can cause multiple adverse effects. Teratogenesis is most important. A single 100-mg dose can cause birth de-

fects. The incidence is nearly 100% when the drug is taken between days 21 and 36 of gestation. Drowsiness occurs in 36% of patients, and can be intensified by other sedative drugs. Peripheral neuropathy—manifesting as limb weakness, incoordination, and tingling in the fingers and toes—develops frequently, and may be irreversible. Other common effects include constipation, orthostatic hypotension, dizziness, dry mouth, and rash.

Thalidomide is available in capsules (50, 100, and 200 mg) under the trade name *Thalomid*. Dosing is done in the evening, preferably at bedtime—and at least 1 hour after eating. The dosages employed for ENL, multiple myeloma, and some disorders under investigation are as follows:

- *ENL*—100 to 300 mg/day for at least 2 weeks
- *Multiple myeloma*—200 to 800 mg/day for at least 6 weeks
- *SLE*—50 mg/day
- *Crohn's disease*—50 to 300 mg/day
- *Aphthous ulcers*—50 to 300 mg/day

Because thalidomide is a powerful teratogen, all persons who prescribe, dispense, or use the drug must comply with a strict set of FDA-mandated safeguards, known as the *System for Thalidomide Education and Prescribing Safety*, or *S.T.E.P.S.* The objective of S.T.E.P.S. is to ensure full awareness of teratogenic risk, and to implement measures for risk reduction. The program includes the following important provisions:

- Providers who prescribe thalidomide and pharmacists who dispense it must be registered with the S.T.E.P.S. program.
- Female patients must receive oral and written warning of the risk of birth defects, and must acknowledge their understanding in writing.
- A pregnancy test must be conducted no more than 24 hours before starting therapy. The provider cannot prescribe thalidomide without a written report of a negative test. In addition, pregnancy testing must be done weekly during the first month of treatment, and every 4 weeks thereafter (for women with regular menstrual cycles) or every 2 weeks thereafter (for women with irregular cycles). Thalidomide must be discontinued immediately if pregnancy is detected.
- Female patients must agree in writing to use *two* methods of contraception, a *highly reliable* method (hormonal contraception, tubal ligation, intrauterine device, vasectomy of male partner) and a *reliable* method (cervical cap, diaphragm, latex condom)—beginning 1 month before initiating thalidomide and continuing 1 month after stopping. Contraception is unnecessary for women who (1) have undergone a hysterectomy, (2) are at least 2 years postmenopausal, or (3) choose to abstain from heterosexual intercourse.
- Male patients must receive verbal and written warning of the teratogenic hazards of thalidomide, and must agree to use a latex condom during heterosexual intercourse, even if they've had a successful vasectomy. (We don't know if thalidomide achieves appreciable levels in semen or sperm. Until more is known, precautions for males are prudent.)
- Each box of *Thalomid* capsules contains a photograph of a thalidomide victim—a baby girl with flipper-like arms and legs. Every time patients reach for a pill, they receive this startling reminder of what thalidomide can do.

cardiogram should be obtained prior to treatment and at least weekly thereafter. If possible, drugs known to cause QT prolongation should be withdrawn. Among these are class I and class III antidysrhythmics, clarithromycin, daunorubicin, mesoridazine, and thioridazine. Arsenic trioxide has the potential to cause fetal harm, and hence is classified in FDA Pregnancy Risk Category D. In contrast to cytotoxic anticancer drugs, arsenic trioxide does not cause alopecia or mucositis.

Denileukin Diftitox

Therapeutic Use. Denileukin diftitox [Ontak] is an IV drug approved for *cutaneous T-cell lymphoma* (CTCL). In clinical trials, 10% to 16% of patients experienced complete tumor regression, and another 20% to 22% experienced partial regression. Unfortunately, adverse events are very common, and sometimes severe. Denileukin can cause life-threatening hypersensitivity reactions, and hence must be administered in a facility equipped for cardiopulmonary resuscitation.

Description and Mechanism of Action. Denileukin is a hybrid molecule consisting of interleukin-2 (IL-2) coupled to diphtheria toxin. The IL-2 portion of the molecule enables it to bind with CTCL cells that have IL-2 receptors. Once the drug is bound, the diphtheria toxin moiety inhibits protein synthesis, causing cell death within hours. Denileukin is produced by recombinant DNA technology.

Adverse Effects. In clinical trials, 21% of patients required hospitalization for adverse events. The incidence of severe or life-threatening reactions was 5%.

Acute hypersensitivity reactions occur in 69% of patients. Prominent symptoms are hypotension (50%), back pain (30%), dyspnea (28%), vasodilation (28%), rash (25%), chest pain (24%), and tachycardia (12%). Management consists of stopping the infusion and, if necessary, administering IV epinephrine, antihistamines, and glucocorticoids.

Denileukin can cause potentially fatal *capillary leak syndrome*, characterized by hypoalbuminemia, edema, and hypotension. Onset usually occurs during the first or second week of treatment. In clinical trials, 6% of patients required hospitalization for the disorder. Because of vascular leak, hypoalbuminemia occurs in 83% of patients. Serum albumin should be monitored and, if it falls below 3 gm/dL, the next round of treatment should be postponed.

A *flu-like syndrome* occurs in 91% of patients. Symptoms include fever or chills (81%), asthenia (66%), nausea and vomiting (64%), myalgia (18%), and arthralgia (8%). Diarrhea occurs in 29% of patients, and leads to dehydration in 9%.

Denileukin can cause *eye damage*, manifesting as a decrease in color vision and vision acuity. For a few patients, these effects are irreversible. However, most report persistent impairment.

Thalidomide

Thalidomide [Thalomid] is a drug with complex pharmacologic actions, including the ability to cause severe birth defects. In the United States, thalidomide has two approved indications: (1) erythema nodosum leprosum, a complication of leprosy; and (2) multiple myeloma, a cancer of the bone mar-

row. Promising results have also been seen with other cancers, including plasma cell leukemia and various solid tumors, including renal cell carcinoma, AIDS-related Kaposi's sarcoma, and cancers of the brain, breast, ovary, prostate, and colon. Anticancer effects are thought to derive from (1) effects on the immune system and (2) inhibition of angiogenesis. Compared with cytotoxic anticancer drugs, thalidomide is relatively well tolerated, but can cause clinically important neuropathy, sedation, and constipation. Neuropathy can be a chronic dose-limiting toxicity. Because thalidomide is a powerful teratogen, patients must comply with a strict set of FDA-mandated safeguards, known as the System for Thalidomide Education and Prescribing Safety, or S.T.E.P.S. The history and pharmacology of thalidomide, as well as the S.T.E.P.S. program, are discussed at length in Box 103-2.

Lenalidomide

Lenalidomide [Revlimid], an analog of thalidomide, is indicated for (1) *multiple myeloma* (MM) and (2) raising red blood cell (RBC) counts in patients with transfusion-dependent anemia due to *myelodysplastic syndrome* (MDS)—but only if their MDS is associated with a specific cytogenetic abnormality known as a 5q deletion, which is seen in up to 30% of MDS patients. In these patients, lenalidomide increases RBC production and greatly reduces the need for RBC transfusions. The mechanism underlying benefits in MM and MDS is unclear.

Lenalidomide has serious toxicities, including thrombocytopenia and neutropenia. In patients with MM, the drug has caused deep vein thrombosis and pulmonary embolism. Like thalidomide, lenalidomide is teratogenic in primates, and hence must not be used during pregnancy. To reduce risk, the drug is available only through a restricted distribution program, known as *RevAssist*, similar to the S.T.E.P.S. program used for thalidomide.

Lenalidomide is supplied in capsules (5, 10, 15, and 25 mg) for oral dosing with water. For patients with MDS, the starting dosage is 10 mg daily. For patients with MM, the starting dosage is 25 mg/day on days 1 through 21 of a repeating 28-day cycle. For all patients, dosage must be reduced when neutropenia or thrombocytopenia develops.

Progestins

Two progestins can be employed to treat cancer: *medroxyprogesterone acetate* [Depo-Provera] and *megestrol acetate* [Megace]. Medroxyprogesterone is indicated for *advanced endometrial and renal cancer*. Megestrol is indicated for *advanced endometrial and breast cancer*. In women with metastatic endometrial cancer, progestins promote palliation and tumor regression. About 30% of patients have an objective response. Among those who respond, survival time is increased to about 2 years. This compares with survival times of 6 months among nonresponders. Benefits appear to derive from depriving these cancers of estrogen. How? By inducing enzymes that metabolize estradiol, the primary endogenous estrogen. The principal adverse effects of progestins are fluid retention and nonfluid weight gain. Hypercalcemia may occur if bone metastases are present. Progestins may be teratogens, and hence should be avoided during the first 4 months of pregnancy. The basic pharmacology of the progestins is discussed in Chapter 61.

KEY POINTS

- Nearly all of the anticancer drugs discussed in this chapter—hormonal agents, targeted drugs, and immunostimulants—are cell-cycle phase nonspecific, in contrast to many cytotoxic anticancer drugs, which are phase specific.
- Nearly all of the drugs discussed in this chapter lack the characteristic toxicities of the cytotoxic anticancer drugs, including bone marrow suppression, stomatitis, alopecia, and severe nausea and vomiting. Nonetheless, most can cause severe toxicities of their own.
- Breast cancer is treated with surgery, radiation, cytotoxic drugs, and hormonal agents, of which there are two major groups: antiestrogens and aromatase inhibitors.
- Antiestrogens block estrogen receptors, whereas aromatase inhibitors block estrogen synthesis. For either group to work, the cancer must be ER positive.
- Tamoxifen is an antiestrogen approved for prevention and treatment of breast cancer. Benefits derive from blocking estrogen receptors on tumor cells. The drug is not active against cancers that are ER negative.
- Tamoxifen is a prodrug that undergoes activation by hepatic CYP2D6.
- Women using tamoxifen should not take fluoxetine, paroxetine, or sertraline to suppress hot flashes. Why? Because these SSRIs are strong inhibitors of CYP2D6 that can prevent tamoxifen activation, thereby increasing the

risk of breast cancer recurrence. Safe alternatives include escitalopram and venlafaxine, which are not strong CYP2D6 inhibitors.

- By activating certain estrogen receptors, tamoxifen increases the risk of endometrial cancer and thromboembolism.
- Anastrozole, an aromatase inhibitor, is used to treat ER-positive breast cancer in postmenopausal women only. Benefits derive from preventing biosynthesis of estrogen from adrenal androgens.
- Anastrozole is more effective than tamoxifen and poses no risk of endometrial cancer.
- Adverse effects of anastrozole include musculoskeletal pain, osteoporosis, fractures, and (rarely) thromboembolism.
- Trastuzumab, a monoclonal antibody used for breast cancer, binds HER2 receptors, causing inhibition of cell proliferation and immune-mediated cell death.
- When breast cancer metastasizes to bone (the most common metastasis site), it can cause hypercalcemia and fractures. Risk of fractures and hypocalcemia can be reduced with denosumab or zoledronate (a bisphosphonate).
- Advanced prostate cancer is treated with androgen deprivation therapy (ADT), which can be achieved with castration and/or drugs. Early (localized) prostate cancer is treated with surgery or radiation, sometimes followed by ADT.
- Androgen deprivation can be achieved with four types of drugs: gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, androgen receptor blockers, and CYP17 inhibitors.
- Side effects of ADT include erectile dysfunction, loss of libido, gynecomastia, reduced muscle mass, new-onset diabetes, myocardial infarction, and stroke.
- Leuprolide, a GnRH agonist, has a biphasic mechanism of action. During the initial phase, the drug stimulates release of interstitial cell-stimulating hormone (ICSH) from the pituitary, and thereby increases production of testosterone by the testes. As a result, there may be a transient "flare" in prostate cancer symptoms. With continuous use, the drug suppresses ICSH release, and thereby causes testosterone production to fall. Note: leuprolide does *not* decrease androgen production by the adrenals or by the prostate cancer itself.
- Flutamide is an androgen receptor blocker used in combination with a GnRH agonist to treat prostate cancer. Benefits derive from (1) preventing cancer cells from undergoing increased stimulation during the initial phase of GnRH therapy, and (2) blocking the effects of adrenal and prostatic androgens on prostate cells.
- Abiraterone is a first-in-class CYP17 inhibitor used to suppress androgen production in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel.
- Sipuleucel-T is the name for patient-specific immunotherapy designed to stimulate an immune attack against prostate cancer cells. Each dose is custom made from the patient's own immune cells, collected by leukapheresis.
- Targeted anticancer drugs are designed to bind with specific molecules (targets) that drive tumor growth. If the

target molecules are found only (or mainly) on cancer cells, targeted drugs should be able to arrest tumor growth while causing little or no injury to normal cells. The current reality, however, is that most targeted drugs cause serious adverse effects.

- Many targeted drugs are monoclonal antibodies directed at antigens found primarily on cancer cells. Most other targeted drugs are small molecules that inhibit specific kinases that regulate cell proliferation.
- EGFR (epidermal growth factor receptor) linked with tyrosine kinase, a regulatory molecule found in certain normal cells and many cancer cells, plays an important role in regulating cell proliferation.
- Cetuximab is a monoclonal antibody that blocks the receptor portion of EGFR tyrosine kinase, and thereby suppresses cell growth and promotes apoptosis.
- Cetuximab can cause severe infusion reactions and severe acne-like rash.
- Cells of chronic myeloid leukemia (CML) produce an abnormal, continuously active enzyme—BCR-ABL tyrosine kinase—that activates regulatory proteins, which in turn inhibit apoptosis and stimulate excessive cell proliferation.
- Imatinib is a highly specific competitive inhibitor of BCR-ABL tyrosine kinase. In patients with CML, the drug suppresses cell proliferation and promotes apoptosis.
- Imatinib can be considered the model of a successful targeted anticancer drug, being both highly effective and well tolerated.
- Vemurafenib is a BRAF V600E kinase inhibitor indicated for patients with unresectable or metastatic melanoma with the BRAF V600E mutation.
- The CD20 antigen is a molecule present in the cell membrane of normal and malignant B lymphocytes (B cells).
- Rituximab is a monoclonal antibody that binds with CD20, and thereby initiates apoptosis and causes a lethal immune attack on B cells. The drug is indicated only for B-cell non-Hodgkin's lymphoma.
- Rituximab can cause severe infusion-related hypersensitivity reactions.
- Brentuximab vedotin is an antibody-drug conjugate (ADC), composed of brentuximab (a CD30-directed antibody) coupled with MMAE (a toxin that binds tubulin to cause mitotic arrest). The antibody serves only to deliver MMAE to cells that express CD30. MMAE does the actual damage.
- Angiogenesis inhibitors block growth of new blood vessels needed to supply solid tumors with oxygen and nutrients.
- Because angiogenesis inhibitors affect blood vessels rather than specific cancer cells, they should be active against a wide variety of tumors.
- Bevacizumab, the first angiogenesis inhibitor available, is a monoclonal antibody that binds with VEGF (vascular endothelial growth factor), and thereby prevents VEGF from promoting blood vessel formation. By suppressing angiogenesis, bevacizumab can inhibit further tumor growth, but cannot directly kill existing tumor cells.
- Bevacizumab has clear benefits in colorectal cancer and nonsquamous non-small cell lung cancer, but not in

breast cancer. Accordingly, approval for breast cancer has been withdrawn.

- Bevacizumab can impair wound healing, and can cause hypertension, hemorrhage, GI perforation, and thromboembolism.
- Proteasomes are multienzyme complexes that degrade intracellular proteins, and thereby rid cells of proteins that are not currently needed, including proteins that regulate transcription, cell adhesion, apoptosis, and progression through the cell cycle.
- Bortezomib, a proteasome inhibitor, reduces cell viability, increases apoptosis, and increases sensitivity to the lethal effects of radiation and traditional anticancer drugs.
- Bortezomib can cause bone marrow suppression, GI disturbances, and peripheral neuropathy.
- Glucocorticoids are toxic to cancers of lymphoid origin, including acute and chronic lymphocytic leukemias, Hodgkin's disease, and non-Hodgkin's lymphomas.

- In addition to their use against lymphoid-derived cancers, glucocorticoids are used to manage complications of cancer and cancer therapy. Specific benefits include suppression of chemotherapy-induced nausea and vomiting, reduction of cerebral edema secondary to irradiation of the cranium, reduction of pain secondary to nerve compression or edema, and suppression of hypercalcemia in steroid-responsive tumors. Also, glucocorticoids can improve appetite and promote weight gain, and may impart a generalized sense of well-being.
- When glucocorticoids are used acutely, their toxicities are both mild and manageable. However, when used long term, these drugs can cause many serious toxicities, including osteoporosis, adrenal insufficiency, increased susceptibility to infection, peptic ulcers, and diabetes.

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Drugs for Glaucoma**Pathophysiology and Treatment Overview****Drugs Used to Treat Glaucoma****Cycloplegics and Mydriatics****Anticholinergic Agents****Phenylephrine (an Adrenergic Agonist)****Drugs for Allergic Conjunctivitis****Drugs for Age-Related Macular Degeneration****Pathophysiology of ARMD****Management of Dry ARMD****Management of Wet (Neovascular) ARMD****Additional Ophthalmic Drugs**

The drugs addressed in this chapter are used to diagnose and treat disorders of the eye. Our primary focus is on glaucoma. Many of the drugs considered here are discussed at length in other chapters. Accordingly, discussion here is limited to their ophthalmologic applications.

DRUGS FOR GLAUCOMA

The term *glaucoma* refers to a group of diseases characterized by visual field loss secondary to optic nerve damage. The most common forms of glaucoma are primary open-angle glaucoma and acute angle-closure glaucoma. These forms differ with respect to underlying pathology and treatment. With either form, permanent blindness can result.

In the United States, glaucoma is the leading cause of preventable blindness. Of the 120,000 Americans blinded each year by glaucoma, 90% could have saved their sight with timely treatment. Unfortunately, many afflicted persons are unaware of their condition: Of the 4 million Americans with glaucoma, only 50% are diagnosed.

Before discussing glaucoma, we need to review the role of aqueous humor in maintaining intraocular pressure (IOP). As indicated in Figure 104-1, aqueous humor is produced by the ciliary body and secreted into the posterior chamber of the eye. From there it circulates around the iris into the anterior chamber, and then exits the anterior chamber via the trabecular meshwork and canal of Schlemm. If outflow from the anterior chamber is impeded, back-pressure will develop, and IOP will rise. Conversely, if production of aqueous humor falls, IOP will decline.

Pathophysiology and Treatment Overview**Primary Open-Angle Glaucoma**

Characteristics. Primary open-angle glaucoma (POAG) is the most common form of glaucoma in the United States. About 90% of people with glaucoma have this type. POAG is the leading cause of blindness among African Americans and the second leading cause among whites.

POAG is characterized by progressive optic nerve damage with eventual impairment of vision. Visual loss develops first in the peripheral visual field. As the disease advances, loss occurs in the central visual field. The pathologic process that leads to optic nerve damage is not understood. IOP is often elevated, but it may also be normal. POAG is a painless,

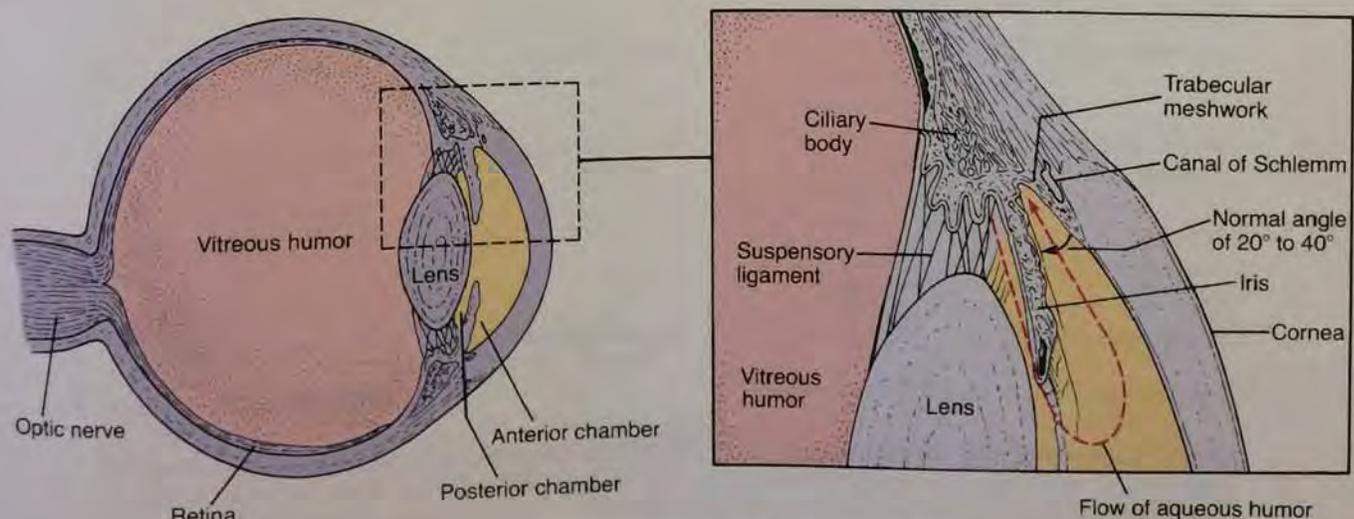


Figure 104-1 ■ Anatomy of the normal eye.

insidious disease in which injury develops over years. Symptoms are absent until extensive optic nerve damage has been produced.

Risk Factors. The major risk factors for POAG are

- Elevated IOP
- Black race
- Family history of POAG
- Advancing age

Of these, elevated IOP is most important. Please note, however, that glaucomatous optic nerve damage can develop even when IOP is normal (ie, below 20 mm Hg). Furthermore, some individuals can have very high IOP (eg, 30 mm Hg) with no associated injury to the optic nerve. These individuals are said to have *ocular hypertension*—not glaucoma.

Among African Americans, the incidence of POAG is 3 times higher than among whites. Also, the age of onset is lower and the course of the disease is more aggressive.

Screening. Since POAG has no symptoms (until significant and irreversible optic nerve injury has occurred), regular testing for early POAG is important—especially among individuals at high risk. With early detection and treatment, blindness can usually be prevented. Diagnosis is based on glaucomatous optic nerve atrophy in association with a characteristic reduction in peripheral vision. Individuals with risk factors for POAG should be tested every 2 years up to age 45, and yearly thereafter. Individuals without risk factors should be tested every 4 years up to age 45, and every 2 years thereafter.

Management. Treatment of POAG is directed at reducing elevated IOP, the only risk factor we can modify. Although POAG has no cure, reduction of IOP can slow or even stop disease progression.

The principal method for reducing IOP is chronic therapy with drugs. Drugs lower IOP by either (1) facilitating aqueous humor outflow or (2) reducing aqueous humor production. As indicated in Table 104-1, the first-line drugs for glaucoma belong to three classes: *beta-adrenergic blocking agents* (beta blockers), *alpha₂-adrenergic agonists*, and *prostaglandin analogs*. Other options—*cholinergic drugs* and *carbonic anhydrase inhibitors*—are considered second-line choices. All of the antiglaucoma drugs are available for topical administration, the preferred route. For more than 25 years, the beta blockers (eg, timolol) have been considered drugs of first choice. However, the alpha₂ agonists (eg, brimonidine) and prostaglandin analogs (eg, latanoprost) are just as effective as the beta blockers, and have a more desirable side effect profile. Accordingly, these drugs have joined the beta blockers as first-choice agents. Because drugs in different classes lower IOP by different mechanisms, combined therapy can be more effective than monotherapy. Because all of these drugs are applied topically, systemic effects are relatively uncommon. Nonetheless, serious systemic reactions *can* occur if sufficient absorption takes place.

If drugs are unable to reduce IOP to an acceptable level, surgical intervention to promote outflow of aqueous humor is indicated. Options include laser trabeculoplasty and trabeculectomy (done with conventional surgical techniques).

Angle-Closure Glaucoma

Angle-closure glaucoma is precipitated by displacement of the iris such that it covers the trabecular meshwork, thereby preventing exit of aqueous humor from the anterior chamber. As a result, IOP increases rapidly and to dangerous levels. This disorder is referred to as *angle-closure* or *narrow-angle*

TABLE 104-1 ■ Topical Drugs for Open-Angle Glaucoma

Class	Drugs	Mechanism	Adverse Effects
First-Line Agents			
Beta Blockers			
Nonselective	Timolol Carteolol Levobunolol Metipranolol	Decreased aqueous formation	Heart block, bradycardia, bronchospasm
Beta ₁ selective	Betaxolol		Heart block, bradycardia, hypotension
Prostaglandin Analogs			
	Latanoprost Travoprost Bimatoprost	Increased aqueous outflow	Heightened brown pigmentation of the iris and eyelid
Alpha₂-Adrenergic Agonists			
	Apraclonidine* Brimonidine	Decreased aqueous formation	Headache, dry mouth, dry nose, altered taste, conjunctivitis, lid reactions, pruritus
Second-Line Agents			
Cholinergic Drugs			
Muscarinic agonists	Pilocarpine	Increased aqueous outflow	Miosis, blurred vision
Cholinesterase inhibitors	Echothiophate		Miosis, blurred vision
Carbonic Anhydrase Inhibitors			
	Dorzolamide Brinzolamide	Decreased aqueous formation	Ocular stinging, bitter taste, conjunctivitis, lid reactions

*Apraclonidine is indicated for short-term use only, and hence is *not* a first-line drug for glaucoma.

glaucoma because the angle between the cornea and the iris is greatly reduced (Fig. 104-2). Angle-closure glaucoma develops suddenly and is extremely painful. In the absence of treatment, irreversible loss of vision occurs in 1 to 2 days. This disorder is much less common than open-angle glaucoma.

Treatment consists of *drug therapy* (to control the acute attack) followed by *corrective surgery*. A combination of drugs (osmotic agents, short-acting miotics, carbonic anhydrase inhibitors, topical beta-adrenergic blocking agents) is employed to suppress symptoms. Once IOP has been reduced with drugs, definitive treatment can be rendered with surgery. Options include *laser iridotomy* and *iridectomy* performed by conventional surgery. Both procedures alter the iris to permit unimpeded outflow of aqueous humor.

Drugs Used to Treat Glaucoma

Beta-Adrenergic Blocking Agents

Actions and Use in Glaucoma. Five beta blockers—*betaxolol*, *carteolol*, *levobunolol*, *metipranolol*, and *timolol*—are approved for use in glaucoma. Dosing is topical. These agents cause minimal disturbance of vision and are considered first-line drugs for glaucoma, although prostaglandin analogs are becoming favored. Formulations and dosages of the beta blockers are summarized in Table 104-2.

The beta-adrenergic blockers lower IOP by decreasing production of aqueous humor. Reductions in IOP occur with “nonselective” beta blockers (drugs that block β_1 and β_2

receptors) as well as with “cardioselective” beta blockers (drugs that block β_1 receptors only).

Beta blockers are used primarily for open-angle glaucoma. They are suitable for initial therapy as well as maintenance therapy. Beta blockers, in combination with other drugs, are also employed for emergency management of acute angle-closure glaucoma.

The basic pharmacology of the beta blockers is discussed in Chapter 18.

Adverse Effects. Local. Local effects are generally minimal, although patients commonly complain of transient ocular stinging. Beta blockers occasionally cause conjunctivitis, blurred vision, photophobia, and dry eyes.

Systemic. Beta blockers can be absorbed in amounts sufficient to cause systemic effects. For example, instilling 1 drop of 0.5% timolol in each eye can produce the same blood level as taking 10 mg of timolol by mouth (the usual starting dose for hypertension). Effects on the heart and lungs are of greatest concern.

Blockade of cardiac β_1 receptors can produce bradycardia and atrioventricular (AV) heart block. Pulse rate should be monitored. Because of their ability to depress cardiac function, beta blockers are contraindicated for patients with AV heart block, sinus bradycardia, and cardiogenic shock. In addition, they should be used with caution in patients with heart failure.

Blockade of β_2 receptors in the lung can cause bronchospasm. Constriction of the bronchi can occur with

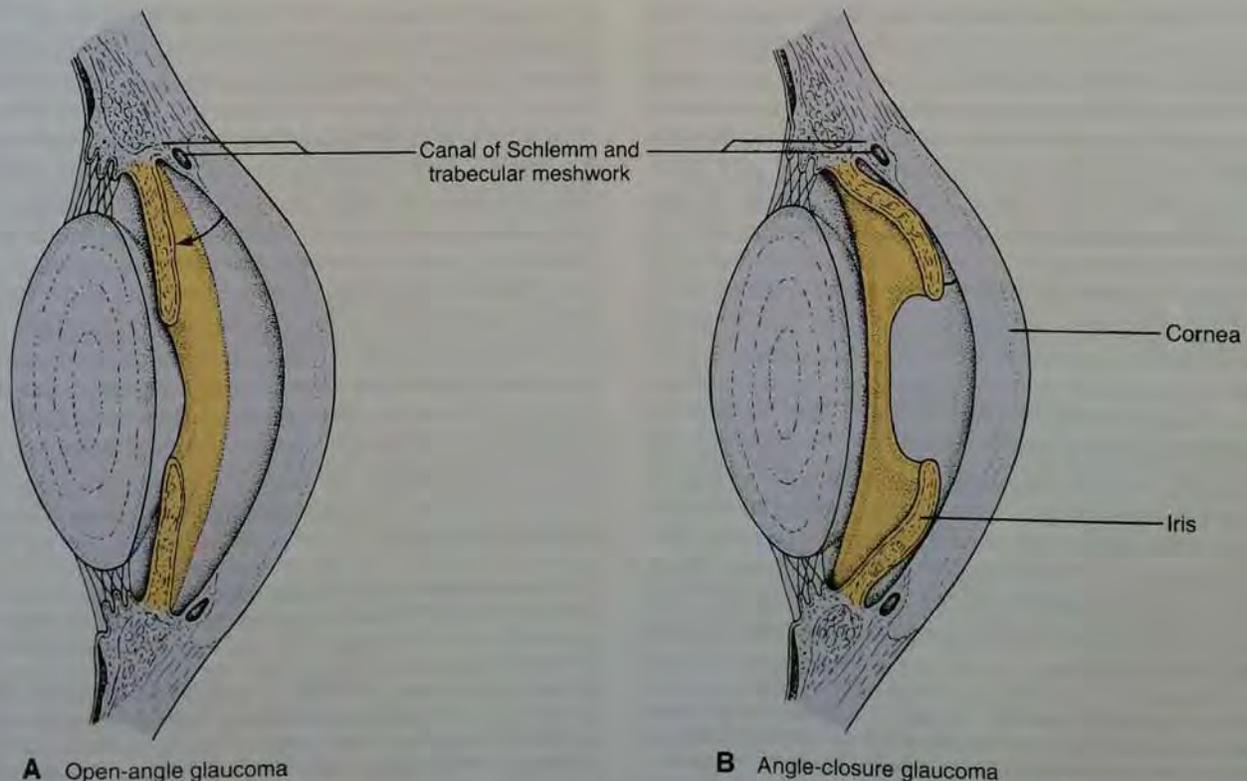


Figure 104-2 Comparative anatomy of the eye in open-angle and angle-closure glaucoma.

A. Note that the angle between the iris and cornea is open in open-angle glaucoma, permitting unimpeded outflow of aqueous humor through the canal of Schlemm and trabecular meshwork. **B.** Note that the angle between the iris and cornea is constricted in angle-closure glaucoma, thereby blocking outflow of aqueous humor through the canal of Schlemm and trabecular meshwork.

TABLE 104-2 ■ Beta Blockers Used in Glaucoma

Drug	Receptor Specificity	Formulation	Usual Dosage
Betaxolol [Betoptic S]	Beta ₁	0.25% suspension	1 drop twice a day
Carteolol	Beta ₁ , beta ₂	1% solution	1 drop twice a day
Levobunolol [Betagan Liquifilm, AKBeta]	Beta ₁ , beta ₂	0.25% solution 0.5% solution	1 drop twice a day 1 drop once or twice a day
Metipranolol [OptiPranolol]	Beta ₁ , beta ₂	0.3% solution	1 drop twice a day
Timolol [Timoptic, Betimol, Istalol]	Beta ₁ , beta ₂	0.25% solution 0.5% solution 0.25% gel 0.5% gel	1 drop once or twice a day 1 drop once or twice a day 1 drop once a day 1 drop once a day

“beta₁-selective” antagonists as well as with “nonselective” beta-adrenergic blockers—although the risk is greatest with the nonselective agents. Only one ophthalmic beta blocker—betaxolol—is beta₁ selective. This drug is preferred to other beta blockers for patients with asthma or chronic obstructive pulmonary disease.

Prostaglandin Analogs

Three prostaglandin analogs are approved for topical therapy of glaucoma. These drugs are as effective as the beta blockers and cause fewer side effects. Accordingly, they are considered first-line medications for glaucoma. Formulations and dosages are summarized in Table 104-3.

Latanoprost. Latanoprost [Xalatan], an analog of prostaglandin F₂ alpha, was the first prostaglandin approved for glaucoma and will serve as our prototype for the group. The drug is applied topically to lower IOP in patients with open-angle glaucoma and ocular hypertension. Latanoprost lowers IOP by facilitating aqueous humor outflow, in part by relaxing the ciliary muscle. The recommended dosage is 1 drop (0.005% solution) applied once daily in the evening. At this dosage, latanoprost produces the same reduction in IOP as does timolol twice daily.

Latanoprost is generally well tolerated, and systemic reactions are rare. The most significant side effect is a harmless heightened brown pigmentation of the iris, which is most noticeable in patients whose irides are green-brown, yellow-brown, or blue/gray-brown. The effect is rare in patients whose irides are blue, green, or blue-green. Heightened pigmentation stops progressing when latanoprost is discontinued, but does not usually regress. Topical latanoprost may also increase pigmentation of the eyelid, and may increase the length, thickness, and pigmentation of the eyelashes. Other side effects include blurred vision, burning, stinging, conjunctival hyperemia, and punctate keratopathy. Rarely, latanoprost may cause migraine.

Other Prostaglandin Analogs. In addition to latanoprost, two other topical prostaglandins are approved for topical therapy of glaucoma. Like latanoprost, these drugs—*travoprost* [Travatan] and *bimatoprost* [Lumigan]—reduce IOP by increasing aqueous humor outflow. In clinical trials, these agents were at least as effective as timolol, a representative beta blocker. Interestingly, one drug—travoprost—was more effective in African Americans than in non-African Americans. Like latanoprost, these prostaglandins can cause a gradual increase in brown pigmentation of the iris, which may be irreversible. In addition, these drugs can increase pigmentation of the eyelid and growth of the eyelashes. In fact, bimatoprost, marketed as *Latisse*, is used for the specific

purpose of increasing eyelash length, darkness, and thickness. With both prostaglandins, the most common adverse effect is ocular hyperemia (engorgement of ocular blood vessels). Less commonly, these drugs cause blurred vision, eye discomfort, ocular pruritus, conjunctivitis, dry eye, light intolerance, and tearing. Dosages for glaucoma are summarized in Table 104-3.

Alpha₂-Adrenergic Agonists

Two alpha₂ agonists are approved for glaucoma. One agent—apraclonidine—is used only for short-term therapy. The other agent—brimonidine—has emerged as a first-line drug for long-term therapy.

Brimonidine. Brimonidine [Alphagan] is the first and only topical alpha₂-adrenergic agonist approved for *long-term* reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The recommended dosage is 1 drop 3 times a day. Effects on IOP are similar to those achieved with timolol. The drug lowers IOP by reducing aqueous humor production, and perhaps by increasing outflow. In addition to lowering IOP, brimonidine may delay optic nerve degeneration and may protect retinal neurons from death. This possibility arises from the ability of alpha₂ agonists to protect neurons from injury caused by ischemia. The most common adverse effects are dry mouth, ocular hyperemia, local burning and stinging, headache, blurred vision, foreign body sensation, and ocular itching. In contrast to apraclonidine (see below), brimonidine can cross the blood-brain barrier, and hence can cause drowsiness, fatigue, and hypotension. (Recall from Chapter 19 that activation of alpha₂ receptors in the brain decreases sympathetic outflow to blood vessels, and thereby lowers blood pressure.) Brimonidine can be absorbed onto soft contact lenses. Accordingly, at least 15 minutes should elapse between drug administration and lens installation.

Apraclonidine. Apraclonidine [Iopidine], a topical alpha₂-adrenergic agonist, lowers IOP by reducing aqueous humor production and possibly by increasing outflow. The drug is indicated only for (1) short-term therapy of open-angle glaucoma in patients who have not responded adequately to maximal doses of other IOP-lowering drugs, and (2) preoperative medication prior to laser trabeculoplasty or iridotomy. Side effects include headache, dry mouth, dry nose, altered taste, conjunctivitis, lid reactions, pruritus, tearing, and blurred vision. Apraclonidine does not cross the blood-brain barrier, and hence does not promote hypotension. For short-term therapy of glaucoma, the dosage is 1 or 2 drops (0.5% solution) 3 times a day.

Alpha₂ Agonist/Beta Blocker Combination

In 2007, the Food and Drug Administration approved a fixed-dose combination of brimonidine (an alpha₂ agonist) and timolol (a nonselective beta blocker) for lowering IOP in patients with glaucoma or ocular hypertension.

TABLE 104-3 ■ Prostaglandin Analogs Used in Glaucoma

Generic Name	Trade Name	Formulation	Usual Dosage
Latanoprost	Xalatan	0.005% solution	1 drop once daily in the evening
Travoprost	Travatan	0.004% solution	1 drop once daily in the evening
Bimatoprost	Lumigan	0.01% solution 0.03% solution	1 drop once daily in the evening 1 drop once daily in the evening

The combination, sold as *Combigan*, contains 0.2% brimonidine and 0.5% timolol. Treatment consists of 1 drop applied to the affected eye twice daily (about every 12 hours). Benefits and adverse effects are about equal to those seen when the two drugs are applied separately.

Pilocarpine, a Direct-Acting Muscarinic Agonist

Pilocarpine is a direct-acting muscarinic agonist (parasympathomimetic agent). Administration is topical. The basic pharmacology of the muscarinic agonists is discussed in Chapter 14. Consideration here is limited to the use of pilocarpine in glaucoma.

Effects on the Eye. By stimulating cholinergic receptors in the eye, pilocarpine produces two direct effects: (1) *miosis* (constriction of the pupil secondary to contraction of the iris sphincter), and (2) *contraction of the ciliary muscle* (an action that focuses the lens for near vision). IOP is lowered indirectly. In patients with *open-angle glaucoma*, IOP is reduced because the tension generated by contracting the ciliary muscle promotes widening of the spaces within the trabecular meshwork, thereby facilitating outflow of aqueous humor. In *angle-closure glaucoma*, contraction of the iris sphincter pulls the iris away from the pores of the trabecular meshwork, thereby removing the impediment to aqueous humor outflow.

Therapeutic Uses. Although used widely in the past, pilocarpine is now considered a second-line drug for open-angle glaucoma. Pilocarpine can also be used for emergency treatment of acute angle-closure glaucoma.

Adverse Effects. The major side effects of pilocarpine concern the eye. Contraction of the ciliary muscle focuses the lens for near vision; corrective lenses can provide partial compensation for this problem. Occasionally, sustained contraction of the ciliary muscle causes retinal detachment. Constriction of the pupil, caused by contraction of the iris sphincter, may decrease visual acuity. Pilocarpine may also produce local irritation, eye pain, and brow ache.

Rarely, pilocarpine is absorbed in amounts sufficient to cause systemic effects. Stimulation of muscarinic receptors throughout the body can produce a variety of responses, including bradycardia, bronchospasm, hypotension, urinary urgency, diarrhea, hypersalivation, and sweating. Caution should be exercised in patients with asthma or bradycardia. Systemic toxicity can be reversed with a muscarinic antagonist (eg, atropine).

Preparations, Dosage, and Administration. Pilocarpine is available in solution and a gel for topical use. Pilocarpine solutions have a relatively short duration of action and must be administered more frequently than the gel.

Pilocarpine Solutions. Pilocarpine hydrochloride [Isopto Carpine, Akarpine♦, Dioicarpine♦] is available in solution for topical application to the conjunctiva. Concentrations range from 0.5% to 8%. For maintenance therapy of open-angle glaucoma, the usual dosage is 1 drop of solution (0.5% to 4%) applied 4 times a day. For patients with acute angle-closure glaucoma, pilocarpine is applied much more frequently (eg, every 5 to 10 minutes for three to six doses, then 1 drop every 1 to 3 hours).

Pilocarpine Gel. Pilocarpine ophthalmic gel [Pilopine HS] consists of 4% pilocarpine hydrochloride in an aqueous gel base. The preparation has a long duration of action, making once-a-day dosing sufficient. For chronic open-angle glaucoma, the usual dosage is 1/2 inch of gel applied to the conjunctiva at bedtime.

Echothiophate, a Cholinesterase Inhibitor

Only one cholinesterase inhibitor—echothiophate [Phospholine Iodide]—is available for glaucoma. The drug has a long duration of action. The basic pharmacology of echothiophate and other cholinesterase inhibitors is discussed in Chapter 15. Consideration here is limited to its use in glaucoma.

Effects on the Eye. Cholinesterase inhibitors inhibit breakdown of acetylcholine (ACh), and thereby promote accumulation of ACh at muscarinic receptors. As a result, they can produce the same ocular effects as pilocarpine (ie, miosis, focusing of the lens for near vision, reduction of IOP).

Use in Glaucoma. Echothiophate is indicated for POAG. However, because of concerns about adverse effects, the drug is not a first-choice agent.

Rather, it is reserved for patients who have responded poorly to preferred medications (eg, beta blockers, alpha₂ agonists, prostaglandins).

Adverse Effects. Like pilocarpine, echothiophate can cause myopia (secondary to contraction of the ciliary muscle) and excessive pupillary constriction. However, of much greater concern is the association between long-acting cholinesterase inhibitors and development of cataracts. Absorption of echothiophate into the systemic circulation can produce typical parasympathomimetic responses, including bradycardia, bronchospasm, sweating, salivation, urinary urgency, and diarrhea.

Preparations, Dosage, and Administration. *Echothiophate iodide* [Phospholine Iodide] is supplied as a powder for reconstitution to solutions that range in strength from 0.03% to 0.25%. For open-angle glaucoma, the 0.03% solution is commonly employed. Administration into the conjunctival sac may be done once daily, twice daily, or every other day.

Carbonic Anhydrase Inhibitors: Topical

Dorzolamide. Introduced in 1995, dorzolamide [Trusopt] was the first carbonic anhydrase inhibitor available for topical administration. The drug is used to reduce IOP in patients with open-angle glaucoma and ocular hypertension. Dorzolamide lowers IOP by decreasing production of aqueous humor. The recommended dosage is 1 drop (2% solution) 3 times a day. Responses are similar to those produced with beta blockers.

Dorzolamide is generally well tolerated. The most common side effects are ocular stinging and bitter taste immediately after dosing. Between 10% and 15% of patients experience allergic reactions, primarily conjunctivitis and lid reactions. If these occur, the patient should stop dorzolamide and contact the prescriber. Other reactions include blurred vision, tearing, eye dryness, and photophobia. In contrast to systemic carbonic anhydrase inhibitors, dorzolamide does not produce acidosis or electrolyte imbalance.

Dorzolamide is also available in a fixed-dose combination with timolol, marketed as *Cosopt*. The combination produces a greater reduction in IOP than either component used alone. The recommended dosage is 1 drop twice a day.

Brinzolamide. Brinzolamide [Azopt] was approved in 1998 for topical treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The drug is as effective as dorzolamide and better tolerated. Like other carbonic anhydrase inhibitors, brinzolamide reduces IOP by slowing production of aqueous humor. The most common adverse effects are bitter aftertaste and transient blurred vision. Brinzolamide causes less ocular stinging and burning than dorzolamide. The recommended dosage is 1 drop (1% solution) 3 times a day.

Carbonic Anhydrase Inhibitors: Systemic

Two carbonic anhydrase inhibitors—*acetazolamide* and *methazolamide*—are available for systemic therapy of glaucoma. Acetazolamide is used more often.

Actions and Uses in Glaucoma. Carbonic anhydrase inhibitors lower IOP by decreasing production of aqueous humor. Maximally effective doses reduce aqueous flow by 50%. Administration is oral.

Carbonic anhydrase inhibitors are employed primarily for long-term treatment of open-angle glaucoma. They are not drugs of first choice. Rather, they should be reserved for patients who have been refractory to preferred medications (eg, beta blockers, alpha₂ agonists, prostaglandin analogs). Carbonic anhydrase inhibitors may also be given (in combination with other antiglaucoma drugs) to produce rapid lowering of IOP in patients with angle-closure glaucoma.

Adverse Effects. Systemic carbonic anhydrase inhibitors can produce a variety of adverse effects. Effects on the central nervous system, which are relatively common, include malaise, anorexia, fatigue, and paresthesias. The sense of malaise causes many patients to discontinue treatment. Reduced appetite, coupled with GI disturbances (nausea, vomiting, diarrhea), may result in weight loss. Carbonic anhydrase inhibitors are teratogenic in animals and should be avoided during pregnancy, especially the first trimester. Additional concerns are acid-base disturbances, electrolyte imbalance, and nephrolithiasis (formation of renal calculi).

Preparations, Dosage, and Administration. *Acetazolamide* is available in immediate-release tablets (125 and 250 mg) and 500-mg sustained-release capsules (sold as Diamox Sequels), and in solution (500 mg/vial) for IM and IV administration. The usual dosage range is 250 mg to 1 gm/day in divided doses.

Methazolamide is available in 25- and 50-mg oral tablets. The usual dosage is 50 to 100 mg 2 or 3 times a day.

Osmotic Agents

In the past, systemic osmotic agents—*mannitol*, *urea*, *glycerin*, and *isosorbide*—were employed for glaucoma. Why? Because they made the plasma hypertonic with respect to intraocular fluid, and hence caused fluid to move from the eye into the plasma, thereby causing a rapid and marked reduction of IOP. Their principal indication was emergency treatment of acute angle-closure glaucoma. Use in open-angle glaucoma was limited to the perioperative period. Glycerin and isosorbide were administered PO; mannitol and urea were administered by IV infusion. Common side effects are headache, nausea, and vomiting. The use of mannitol for osmotic diuresis is discussed in Chapter 40.

CYCLOPLEGICS AND MYDRIATICS

Cycloplegics are drugs that paralyze the ciliary muscle, and *mydriatics* are drugs that dilate the pupil. Cycloplegics and mydriatics are employed primarily to facilitate diagnosis and surgery of ophthalmic disorders. Agents used to produce cycloplegia, mydriasis, or both fall into two classes: (1) *anticholinergic agents* (muscarinic antagonists) and (2) *adrenergic agonists*.

Anticholinergic Agents

Five muscarinic antagonists (Table 104-4) are employed topically for diagnosis and treatment of ophthalmic disorders. The basic pharmacology of the anticholinergic drugs is discussed in Chapter 14. Consideration here is limited to their ophthalmic applications.

Effects on the Eye

The anticholinergic drugs produce mydriasis and cycloplegia. Mydriasis results from blocking muscarinic receptors that promote contraction of the iris sphincter; cycloplegia results from blocking muscarinic receptors that promote contraction of the ciliary muscle. As discussed below, relaxation of the iris can lead to elevation of IOP.

Ophthalmic Applications

Adjunct to Measurement of Refraction. The term *refraction* refers to the bending of light by the cornea and lens. When ocular refraction is proper, incoming light is bent such that a sharp image is formed on the retina.

Errors in refraction can produce nearsightedness, farsightedness, and astigmatism (a visual disturbance caused by irregularities in the curvature of the cornea).

Both the mydriatic and cycloplegic properties of the muscarinic antagonists can be of use in evaluating errors of refraction. Mydriasis (widening of the pupil) facilitates observation of the eye's interior. Cycloplegia (paralysis of the ciliary muscle) prevents the lens from undergoing conformational change during the assessment.

Intraocular Examination. Dilation of the pupil with an anticholinergic agent facilitates observation of the inside of the eye. In addition, by paralyzing the iris sphincter, muscarinic antagonists prevent reflexive constriction of the pupil in response to the light from an ophthalmoscope (the hand-held device used to view the eye's interior). Since adrenergic agonists (eg, phenylephrine) also dilate the pupil, but by a different mechanism, an adrenergic agonist can be combined with a muscarinic antagonist to increase the degree of mydriasis.

Intraocular Surgery. Anticholinergic agents may be employed to facilitate ocular surgery and to reduce postoperative complications. Mydriasis induced by these drugs can aid in cataract extraction and procedures to correct retinal detachment. For these operations, the muscarinic antagonist may be combined with an adrenergic agonist to maximize pupillary dilation. In certain postoperative patients, mydriatics are employed to prevent development of synechiae (adhesions of the iris to neighboring structures in the eye).

Treatment of Anterior Uveitis. Uveitis is an inflammation of the uvea (the vascular layer of the eye). Symptoms include ocular pain and photophobia. Uveitis is treated with a glucocorticoid (to reduce inflammation) plus an anticholinergic agent. By promoting relaxation of the ciliary muscle and the iris sphincter, anticholinergic drugs help relieve pain and prevent adhesion of the iris to the lens.

Adverse Effects

Blurred Vision and Photophobia. The most common side effects of topical anticholinergics are photophobia and blurred vision. Photophobia occurs because paralysis of the iris sphincter prevents the pupil from constricting in response to bright light. Blurred vision occurs because paralysis of the ciliary muscle prevents focusing for near vision.

Precipitation of Angle-Closure Glaucoma. By relaxing the iris sphincter, anticholinergic drugs can induce closure of the filtration angle in individuals whose eyes have a narrow angle to begin with. Angle closure occurs as follows: (1) partial dilation of the pupil maximizes contact between the iris and the lens, thereby impeding egress of aqueous humor from the posterior chamber, and (2) the resultant increase in pressure within the posterior chamber pushes the iris forward, causing blockage of the trabecular meshwork. Caution must be exercised in patients predisposed to angle closure.

Systemic Effects. Topically applied anticholinergic drugs can be absorbed in amounts sufficient to produce systemic toxicity. Symptoms include dry mouth, constipation, fever.

TABLE 104-4 ■ Muscarinic Antagonists Used for Mydriasis and Cycloplegia

Generic Name	Trade Names	Strength of Solution (%)	Time Course			
			Mydriasis		Cycloplegia	
			Peak (min)	Recovery (days)	Peak (min)	Recovery (days)
Atropine	generic only	0.5, 1	30-40	7-12	60-180	6-12
Cyclopentolate	AK-Pentolate, Cyclogyl	0.5, 1, 2	30-60	1	25-76	0.25-1
Homatropine	Isopto Homatropine	2, 5	40-60	1-3	30-60	1-3
Scopolamine	Isopto Hyoscine	0.25	20-30	1-3	30-60	3-7
Tropicamide	Tropicacyl, Opticyl, Mydriacyl*	0.5, 1	20-40	0.25	20-35	<0.25

tachycardia, and central nervous system effects (confusion, hallucinations, delirium, coma). Death can occur. Muscarinic poisoning can be treated with physostigmine (see Chapter 14).

Phenylephrine (an Adrenergic Agonist)

Adrenergic agonists are mydriatic agents. Pupillary dilation results from activating α_1 -adrenergic receptors on the radial (dilator) muscle of the iris. In contrast to anticholinergic drugs, the adrenergic agonists do not cause cycloplegia. Of the adrenergic agents given to induce mydriasis, *phenylephrine* is the most frequently employed. The adrenergic agonists are discussed at length in Chapter 17. Discussion here is limited to the mydriatic use of phenylephrine.

Therapeutic and Diagnostic Applications

The mydriatic applications of phenylephrine are much like those of the anticholinergic drugs. Phenylephrine-induced mydriasis is used as an aid to intraocular surgery, measurement of refraction, and ophthalmoscopic examination. In patients with anterior uveitis, phenylephrine is given to dilate the pupil as part of an overall program of treatment.

Adverse Effects

Effects on the Eye. Like the anticholinergic drugs, phenylephrine can precipitate angle-closure glaucoma secondary to induction of mydriasis. Caution must be exercised in patients whose filtration angle is naturally narrow. Contraction of the dilator muscle may dislodge pigment granules from degenerating cells of the iris. These granules, which appear as "floaters" in the anterior chamber, are usually cleared from the eye within a day. Phenylephrine may also cause ocular pain, corneal clouding, and brow ache.

Systemic Effects. Rarely, topical phenylephrine is absorbed in amounts sufficient to produce systemic toxicity. Cardiovascular responses (eg, hypertension, ventricular dysrhythmias, cardiac arrest) are of greatest concern. Other systemic reactions include sweating, blanching, tremor, agitation, and confusion.

DRUGS FOR ALLERGIC CONJUNCTIVITIS

Pathophysiology

Allergic conjunctivitis (AC) is defined as inflammation of the conjunctiva in response to an allergen. (The conjunctiva is the delicate membrane that surrounds the eyelids.) AC may be seasonal or perennial (chronic). Primary symptoms are itching, burning, and a thin, watery discharge. In addition, the conjunctivae are usually red and congested.

Symptoms of AC result from a biphasic immune response. Initially, symptoms are caused by release of inflammatory mediators—histamine, prostaglandins, leukotrienes, and kinins—from mast cells. These mediators stimulate mucus production (and thereby cause discharge), activate nerve endings (and thereby cause itching and burning sensations), and promote vasodilation and increase capillary permeability (and thereby cause redness and congestion). These symptoms peak about 20 minutes after allergen exposure and abate 20 minutes later. Following this early response, symptoms typically reappear 6 or more hours later. The late phase is due to recruitment of immune cells—eosinophils, neutrophils, and macrophages—that amplify the inflammatory response.

Drug Therapy

AC can be managed with a variety of topical drugs (Table 104-5). *Mast-cell stabilizers* (eg, cromolyn, lodoxamide) prevent release of inflammatory mediators. Patients should be informed that benefits take several days to develop, and several weeks to become maximal. In contrast to mast-cell stabilizers, *histamine₁ (H₁)-receptor antagonists* (antihistamines) can provide immediate symptomatic relief. Some drugs (eg, azelastine, olopatadine) have two actions: They prevent mediator release from mast cells and they block H₁ receptors. Ketorolac, a *nonsteroidal anti-inflammatory drug* (NSAID), reduces symptoms by inhibiting cyclooxygenase, an enzyme required for synthesis of prostaglandins. Like the NSAIDs, *glucocorticoids* (eg, loteprednol) inhibit production of leukotrienes and thromboxane. As a result, these drugs are highly effective. Unfortunately, with prolonged use, they can cause serious adverse effects, including cataracts, eye infection, and elevation of IOP. Accordingly, glucocorticoids are generally reserved for short-term therapy in patients who have not responded adequately to safer drugs. The *ocular decongestants* (eg, naphazoline, phenylephrine) decrease redness and edema by activating α_1 -adrenergic receptors on blood vessels, thereby causing vasoconstriction. Benefits are only symptomatic; these drugs do not interrupt any phase of the immune response. Furthermore, with regular use, rebound congestion is likely.

DRUGS FOR AGE-RELATED MACULAR DEGENERATION

Pathophysiology of ARMD

Age-related macular degeneration (ARMD) is a painless, progressive disease that blurs central vision, and thereby limits perception of fine detail. Symptoms result from injury to the macula, the central part of the retina that contains the highest density of photoreceptors, and hence provides the high-resolution central vision used for reading, driving, sewing, recognizing faces, and so forth. ARMD is the leading cause of blindness in older Americans. About 15 million have the disease.

ARMD has two forms: dry ARMD (atrophic ARMD) and wet ARMD (neovascular ARMD). The disorder begins as dry ARMD, and can later progress to wet ARMD. Dry ARMD is more common than wet ARMD (85% vs. 15%), but wet ARMD is much more severe.

In dry ARMD, macular photoreceptors undergo gradual breakdown, leading to gradual blurring of central vision. The disease is characterized by the appearance of *drusen* (yellow deposits under the retina). Drusen develop before any visual impairment occurs. Whether drusen actually cause visual loss is unknown. However, we do know that an increase in the size or number of drusen increases the risk of symptomatic ARMD. Dry ARMD has three stages of increasing severity:

- *Early*—characterized by a few small or medium-sized drusen and no change of vision
- *Intermediate*—characterized by many medium-sized drusen (or one or more large drusen) and minor visual changes (need for increased light for reading, possible blurred spot in the center of the visual field)

TABLE 104-5 ■ Topical Drugs for Allergic Conjunctivitis

Class and Generic Name	Trade Name	Concentration	Usual Daily Dosage
Mast-Cell Stabilizers			
Cromolyn sodium	Crolom, Opticrom	4%	1–2 drops every 4–6 hr
Lodoxamide tromethamine	Alomide	0.1%	1–2 drops 4 times daily
Nedocromil sodium	Alocril	2%	1–2 drops twice daily
Pemiroloast potassium	Alamast	0.1%	1–2 drops 4 times daily
H₁-Receptor Blockers			
Emedastine difumarate	Emadine	0.05%	1 drop 4 times daily
Mast-Cell Stabilizers/H₁ Blockers			
Alcaftadine	Lastacaft	0.25%	1 drop once daily
Azelastrine hydrochloride	Optivar	0.05%	1 drop twice daily
Epinastine	Elestat	0.05%	1 drop twice daily
Ketotifen fumarate	Zaditor, Alaway	0.025%	1 drop every 8–12 hr
Olopatadine hydrochloride	Patanol	0.1%	1 drop twice daily
	Pataday	0.2%	1 drop once daily
Bepotastine besylate	Bepreve	1.5%	1 drop twice daily
NSAIDs			
Ketorolac tromethamine	Acular LS	0.4%	1 drop 4 times daily
	Acuvail	0.45%	1 drop twice daily
	Acular, Acular PF	0.5%	1 drop 4 times daily
Glucocorticoids			
Loteprednol etabonate	Alrex	0.2%	1 drop 4 times daily
	Lotemax	0.5%	1–2 drops 4 times daily
Dexamethasone sodium phosphate	Various	0.1%	1 drop every 6–8 hr
Prednisolone acetate	Various	1%	2 drops every 6–12 hr
Prednisolone sodium phosphate	Various	1%	1 drop every 6–8 hr
Decongestants (Vasoconstrictors)			
Naphazoline	Clear Eyes, others	0.012%	1–2 drops up to 4 times daily
Oxymetazoline	Visine L.R., OcuClear	0.025%	1–2 drops 4 times daily
Phenylephrine	Neo-Synephrine, others	0.12%	1–2 drops 4 times daily
Tetrahydrozoline	Visine Moisturizing, others	0.05%	1–2 drops 4 times daily
Decongestant/H₁ Blocker			
Naphazoline/pheniramine	Naphcon-A, others	0.025%/0.3%	1–2 drops 1–4 times daily

NSAIDs = nonsteroidal anti-inflammatory drugs.

- **Advanced**—characterized by drusen, breakdown of photoreceptors and supporting tissue, and progressive blurring of central vision

In wet ARMD, macular degeneration is caused by growth of new subretinal blood vessels, which are often fragile and leaky. Fluid leakage lifts the macula from its normal place, which quickly causes permanent injury. As noted, all people with wet ARMD have dry ARMD first. Vision loss occurs only in advanced dry ARMD and in wet ARMD.

Management of Dry ARMD

Although we can't prevent vision loss in people with advanced ARMD, we may be able to slow, or perhaps prevent, progression of intermediate disease. In the *Age-Related Eye Disease Study* (AREDS), sponsored by the National Eye Institute, researchers showed that taking high doses of antioxidants and zinc can significantly reduce the risk of developing advanced ARMD. The regimen employed consisted of vitamin C

(500 mg), vitamin E (400 IU), beta-carotene (15 mg), and zinc (80 mg), all taken once a day. In addition, participants took 2 mg of copper daily to prevent copper deficiency anemia, which can develop when we consume lots of zinc. The AREDS formulation is recommended for people at high risk of developing advanced ARMD, identified as those with (1) intermediate ARMD in one or both eyes or (2) advanced ARMD (dry or wet) in one eye but not the other. In AREDS, the formulation did not benefit people with early ARMD. The AREDS formulation is available commercially as *Ocuvite PreserVision*.

Management of Wet (Neovascular) ARMD

We have three treatments for neovascular ARMD: laser therapy, photodynamic therapy (PDT), and therapy with angiogenesis inhibitors (ie, drugs that suppress growth of new blood vessels). All three treatments can slow disease progression. In some cases, treatment partially reverses vision loss. At this time, treatment with an angiogenesis inhibitor is preferred to the other two options.

TABLE 104-6 • Intravitreal Angiogenesis Inhibitors for Neovascular (Wet) ARMD

Generic Name [Trade Name]	Year Approved for ARMD	Type of Molecule	Dosage	Cost per Injection	Comments
Pegaptanib [Macugen]	2004	Oligonucleotide aptamer	0.3 mg every 6 wk	\$1125	Studies show little or no improvement in visual acuity, and hence use is rare
Ranibizumab [Lucentis]	2006	Antibody fragment	0.5 mg once a month*	\$1950	Studies show significant improvement in visual acuity
Aflibercept [Eylea]	2011	Antibody fragment/ VEGF receptor fragment hybrid	2 mg once a month for 3 months, then 2 mg every 2 months thereafter	\$1850	Studies show significant improvement in visual acuity
Bevacizumab [Avastin]	†	Complete antibody	1.25 mg once a month*	\$50	Studies show significant improvement in visual acuity

ARMD = age-related macular degeneration, VEGF = vascular endothelial growth factor.

*After the first 4 monthly injections, injections may be done once every 3 months, but outcomes are not as good as with monthly injections.

†Bevacizumab is approved for metastatic colorectal cancer, but not for ARMD.

Angiogenesis Inhibitors

Actions and Benefits. Four drugs—*pegaptanib* [Macugen], *ranibizumab* [Lucentis], *aflibercept* [Eylea], and *bevacizumab* [Avastin]—can be used to inhibit growth of new blood vessels in patients with neovascular ARMD. Benefits derive from antagonizing *vascular endothelial growth factor* (VEGF), an endogenous compound that (1) induces angiogenesis, (2) increases vascular permeability, and (3) promotes inflammation—all of which can contribute to neovascular ARMD. Administration is by direct injection into the vitreous humor of the affected eye. Following injection, the drugs penetrate to the subretinal blood vessels and then bind with VEGF, thereby preventing VEGF from binding with its receptors on the vascular endothelium. As a result, VEGF is unable to promote vessel growth. The angiogenesis inhibitors are useful in wet ARMD, but not in dry ARMD. For patients with wet ARMD, treatment reduces the risk of losing visual acuity as well as the risk of progressing to blindness. In some cases, treatment partially reverses vision loss.

Adverse Effects. The biggest concern is *endophthalmitis*, an inflammation inside the eye caused by bacterial, viral, or fungal infection. Fortunately, the incidence is low (less than 1%). Patients who experience symptoms (eg, redness, light sensitivity, pain) should seek immediate medical attention. More common adverse effects (10% to 40% incidence) include blurred vision, cataracts, conjunctival hemorrhage, corneal edema, eye discharge, increased IOP, ocular discomfort, punctate keratitis, vitreous floaters, and reduced visual acuity. Possible long-term effects—ocular or systemic—are not yet known.

Pegaptanib, Ranibizumab, Aflibercept, and Bevacizumab: Comparisons and Contrasts. Properties of the four angiogenesis inhibitors used for ARMD are summarized in Table 104-6. As indicated, these agents differ with regard to structure, approved usage, cost, and efficacy.

Molecular Structure. Two agents—*ranibizumab* and *bevacizumab*—are similar to each other, and both differ from *aflibercept* and *pegaptanib*. *Bevacizumab* is an intact monoclonal antibody that binds with VEGF. *Ranibizumab* is a small fragment of *bevacizumab* that retains full ability to bind VEGF. In contrast, *pegaptanib* is an oligonucleotide aptamer—that is, a polymer of nucleotides designed to bind

with a specific chemical (in this case, VEGF). *Aflibercept* is a hybrid molecule composed of (1) portions of VEGF receptors that have been fused with (2) the Fc portion of human immunoglobulin G1.

Approved Usage and Cost. Three of the drugs—*pegaptanib*, *ranibizumab*, and *aflibercept*—are approved for neovascular ARMD. In contrast, *bevacizumab* is approved for cancer (see Chapter 103), but not for ARMD. Nonetheless, *bevacizumab* is being used off-label for ARMD, largely because of price: A single injection of *bevacizumab* costs only \$50, compared with \$1125 for *pegaptanib*, \$1850 for *aflibercept*, and \$1950 for *ranibizumab*.

Efficacy. All four drugs greatly reduce the risk of further visual impairment and progression to blindness. In addition, studies have shown that three agents—*ranibizumab*, *bevacizumab*, and *aflibercept*—can improve visual acuity that has been impaired. As for *pegaptanib*, studies to date show little evidence of visual improvement. As a result, *pegaptanib* is used only rarely.

How do *ranibizumab* and *bevacizumab* compare with each other? In patients with wet ARMD, both drugs are equally effective, as shown in a large, randomized trial—the Comparison of AMD Treatments Trial (CATT)—in which the drugs were compared side-by-side.

Laser Therapy

In laser therapy, high-energy laser light is used to seal leaky blood vessels. Unfortunately, the procedure has several drawbacks. First, laser light can damage nearby retinal tissue, and hence treatment is limited to regions away from the center of the macula. As a result, only a small percentage of leaky vessels can be sealed. Second, since new vessels continue to grow, repeat treatments are usually needed. Third, although the procedure can retard further vision loss, it cannot reverse existing damage. Fourth, even when the procedure is done with due care, some loss of vision occurs. This loss is justified by arguing that even greater loss would occur if treatment were withheld.

Photodynamic Therapy

Photodynamic therapy (PDT) employs a photosensitive drug in combination with infrared light. The drug—*verteporfin* [Visudyne]—has a high affinity for neovascular tissue. In the procedure, *verteporfin* is delivered by IV infusion, and then an infrared laser is shined on the retina for 90 seconds. The light activates the drug, causing it to seal off leaky vessels. Repeat PDT may be needed because the vessels frequently reopen. Unlike laser therapy, PDT does not injure the retina. PDT reduces the risk of severe vision loss by 30%

to 50%, but only 10% of patients show any vision improvement. For 5 days after the procedure, patients must protect their skin from sunlight and bright indoor light. Why? Because light-mediated activation of verteporfin in the skin could cause a severe burn.

ADDITIONAL OPHTHALMIC DRUGS

Demulcents (Artificial Tears)

Ophthalmic demulcents are isotonic solutions employed as substitutes for natural tears. Most preparations contain *polyvinyl alcohol*, *cellulose esters*, or both. Artificial tears are indicated for relieving dry-eye syndromes and discomfort and dryness caused by irritants, wind, and sun. In addition, demulcents may be used to lubricate artificial eyes. Artificial tears are devoid of adverse effects, and hence may be administered as often and as long as desired.

Ocular Decongestants

Ocular decongestants are weak solutions of adrenergic agonists applied topically to constrict dilated conjunctival blood vessels. These preparations are used to reduce redness of the eye caused by minor irritation. The adrenergic agents employed as decongestants are *phenylephrine*, *naphazoline*, *oxymetazoline*, and *tetrahydrozoline*. When applied to the eye in the low concentrations found in decongestant products, adrenergic agonists rarely cause adverse effects. Local reactions (stinging, burning, reactive hyperemia) may occur with overuse. The adrenergic agonists are discussed at length in Chapter 17.

Glucocorticoids

Glucocorticoids (anti-inflammatory corticosteroids) are used for inflammatory disorders of the eye (eg, uveitis, iritis, conjunctivitis). Administration may be topical or by local injection. Short-term therapy is generally devoid of adverse effects. In contrast, prolonged therapy may cause cataracts, reduced visual acuity, and glaucoma. In addition, there is an increased risk of infection secondary to corticosteroid-induced suppression of host defenses. The glucocorticoids are discussed at length in Chapter 72.

Dyes

Fluorescein is a water-soluble dye that produces an intense green color. This agent is applied to the surface of the eye to detect lesions of the corneal epithelium; intact areas of the cornea remain uncolored while abrasions and other defects turn bright green. Intravenous fluorescein is used to facilitate visualization of retinal blood vessels; IV fluorescein has been employed to help evaluate diabetic retinopathy and other abnormalities of the retinal vasculature. Fluorescein can also be used topically and intravenously to assess flow of aqueous humor. Adverse effects from systemic administration include nausea, vomiting, paresthesias, and pruritus. Severe reactions (anaphylaxis, pulmonary edema, cardiac arrest) are rare.

Rose bengal is applied topically to visualize abrasions of the corneal and conjunctival epithelium. Injured tissue appears rose colored when viewed with a slit lamp. The dye is employed for diagnosis of superficial injury to corneal and conjunctival tissue.

Topical Drugs for Ocular Infections

Topical drugs are available for treating viral and bacterial infections of the eye. Four *antiviral* drugs—trifluridine, vidarabine, ganciclovir, and idoxuridine—are employed. Their pharmacology and specific applications are discussed in Chapter 93. Important *antibacterial* drugs are listed in Table 104-7.

TABLE 104-7 ■ Some Topical Ophthalmic Antibacterial Agents

Class and Generic Name	Trade Name	Formulation
Fluoroquinolones		
Besifloxacin	Besivance	0.6% suspension
Ciprofloxacin	Ciloxan	0.3% solution, 0.3% ointment
Gatifloxacin	Zymar	0.3% solution
	Zymaxid	0.5% solution
Levofloxacin	Quixin	0.5% solution
Moxifloxacin	Moxeza, Vigamox	0.5% solution
Ofloxacin	Ocuflox	0.3% solution
Macrolides		
Azithromycin	Azasite	1% solution
Erythromycin	Ilotycin	0.5% ointment
Aminoglycosides		
Gentamicin	Gentak, Garamycin♦	0.3% solution, 0.3% ointment
Tobramycin	Tobrex	0.3% solution, 0.3% ointment
Sulfonamides		
Sulfacetamide	Bleph-10, Sodium Sulamyd	10% solution
Polymyxin B-Containing Mixtures		
Polymyxin B/ bacitracin	AK-Poly-Bac	Ointment
Polymyxin B/ bacitracin/ neomycin	Neosporin, AK-Spore	Ointment
Polymyxin B/ gramicidin/ neomycin	Neosporin, AK-Spore	Solution
Polymyxin B/ trimethoprim	Polytrim	Solution

These drugs are used to treat serious ophthalmic infections and to prevent infection following ocular surgery. As a rule, anti-infective drugs are not needed for simple conjunctivitis. Patients should be made aware that bacterial and viral infections are contagious. Bacterial infections will remain contagious until treated for 24 to 48 hours. Viral infections may remain contagious until they are completely gone. Patients should not use contact lenses while they have an eye infection, and while they are treating the infection with a topical drug.

KEY POINTS

- The glaucomas are a group of diseases characterized by visual field loss secondary to optic nerve damage.
- In open-angle glaucoma, optic nerve injury develops gradually over years. The cause of nerve damage is unknown.
- In angle-closure glaucoma, there is blockage of aqueous humor outflow, which causes an abrupt rise in IOP. In the absence of treatment, irreversible damage to the optic nerve occurs in 1 or 2 days.
- Drug therapy of open-angle glaucoma is directed at reducing elevated IOP, the major risk factor for this disease.
- Angle-closure glaucoma is treated with drugs to rapidly reduce IOP and then with corrective surgery to allow aqueous humor outflow.
- Drugs reduce IOP by either facilitating aqueous humor outflow or reducing aqueous humor production.
- Three drug families—beta blockers, alpha₂-adrenergic agonists, and prostaglandins—are considered first-line agents for topical therapy of open-angle glaucoma.
- Timolol and other topical beta blockers lower IOP by decreasing aqueous humor production.

- Topical beta blockers can be absorbed in amounts sufficient to cause bronchospasm, bradycardia, and AV heart block.
- Brimonidine, an α_2 agonist, lowers IOP by decreasing aqueous humor production, and possibly by increasing aqueous humor outflow.
- Latanoprost and other prostaglandins lower IOP by facilitating aqueous humor outflow.
- Prostaglandins can increase brown pigmentation of the iris, and can intensify pigmentation of the skin around the eye.
- Cycloplegics are drugs that paralyze the ciliary muscle.
- Mydriatics are drugs that dilate the pupil.
- Atropine and other anticholinergic drugs cause cycloplegia by blocking muscarinic receptors on the ciliary muscle, and cause mydriasis by blocking muscarinic receptors on the iris sphincter.
- By paralyzing the ciliary muscle, anticholinergic drugs prevent the eye from focusing for near vision.
- By paralyzing the iris sphincter, anticholinergic drugs prevent the pupil from constricting in response to bright light; photophobia results.
- Phenylephrine, an adrenergic agonist, causes mydriasis by stimulating alpha-adrenergic receptors on the radial (dilator) muscle of the iris.
- Age-related macular degeneration (ARMD) is a progressive disease that blurs central vision, and thereby limits perception of fine detail.
- ARMD has two forms. The disorder begins as dry ARMD (atrophic ARMD), and may then progress to wet ARMD (neovascular ARMD). Wet ARMD is much less common than dry ARMD, but much more severe.
- In people with dry ARMD, prophylactic treatment with high-dose antioxidants and zinc may prevent the disease from progressing to wet ARMD.
- Wet ARMD can be treated with laser therapy, photodynamic therapy, and angiogenesis inhibitors (drugs that block retinal angiogenesis by neutralizing vascular endothelial growth factor).
- Three angiogenesis inhibitors—afibercept, ranibizumab, and bevacizumab—are highly and equally effective against ARMD. A third agent—pegaptanib—is much less effective.

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- Anatomy of the Skin
- Topical Glucocorticoids
- Keratolytic Agents
- Acne
 - Pathophysiology
 - Overview of Treatment
 - Topical Drugs for Acne
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 - Venereal Warts
 - Common Warts
- Antiperspirants and Deodorants
- Drugs for Seborrheic Dermatitis and Dandruff
- Drugs for Hair Loss
- Eflornithine for Unwanted Facial Hair
- Drugs for Impetigo
- Local Anesthetics

SI Box 105-1. Face Time with Botox

Our objective in this chapter is to discuss some of the more frequently encountered dermatologic drugs. Most are dosed topically; some are given systemically. Before discussing the dermatologic drugs, we review the anatomy of the skin.

ANATOMY OF THE SKIN

The skin is composed of three distinct layers: the epidermis, the dermis, and a layer of subcutaneous fat. These layers and other features of the skin are depicted in Figure 105-1.

Epidermis. The epidermis is the outermost layer of the skin and is composed almost entirely of closely packed cells. As indicated in Figure 105-1B, the epidermis itself consists of

several layers. The deepest, known as the *basal layer* or *stratum germinativum*, contains the only epidermal cells that are mitotically active. All cells of the epidermis arise from this layer. Production of new cells within the basal layer pushes older cells outward. During their migration, these cells become smaller and flatter. As epidermal cells near the surface of the skin, they die and their cytoplasm is converted to *keratin*, a hard, proteinaceous material. Because of its high content of keratin, the outer layer of the epidermis has a rough, horny texture. Because of its texture, this layer is referred to as the *cornified layer* or *stratum corneum*. By a process that is not fully understood, the surface of the stratum corneum undergoes continuous exfoliation (shedding). This shedding completes the epidermal growth cycle.

In addition to germinal cells, the basal layer of the epidermis contains *melanocytes*. These cells, which are few in number, produce *melanin*, the pigment that determines skin color. Following its synthesis within melanocytes, melanin is transferred to other cells of the epidermis. Melanin protects the skin against ultraviolet radiation, which is the principal stimulus for melanin production.

Dermis. The dermis underlies the epidermis and is composed largely of connective tissue, primarily collagen. A major function of the dermis is to provide support and nourishment for the epidermis. Structures found in the dermis include blood vessels, nerves, and muscle. The dermis also contains sweat glands, sebaceous glands, and hair follicles. Sebaceous glands secrete an oily composite known as sebum. Almost all sebaceous glands are associated with hair follicles (see Fig. 105-1A).

Subcutaneous Tissue. Subcutaneous tissue consists largely of fat. This fatty layer provides protection and insulation. In addition, the stored fat constitutes a reserve source of calories.

TOPICAL GLUCOCORTICOIDS

The basic pharmacology of the glucocorticoids (anti-inflammatory corticosteroids) is discussed in Chapter 72. Consideration here is limited to their use for skin disorders.

Actions and Uses. Topical glucocorticoids are employed to relieve inflammation and itching associated with a variety of dermatologic conditions (eg, insect bites, minor burns, seborrheic dermatitis, psoriasis, eczema, pemphigus). The mechanisms by which glucocorticoids suppress inflammation and other symptoms are discussed in Chapter 72.

The vehicle in which a glucocorticoid is dispersed (eg, cream, ointment, gel) can enhance the therapeutic response. How? By helping the glucocorticoid penetrate to its site of action. The vehicle may provide additional benefits by acting as a drying agent or an emollient.

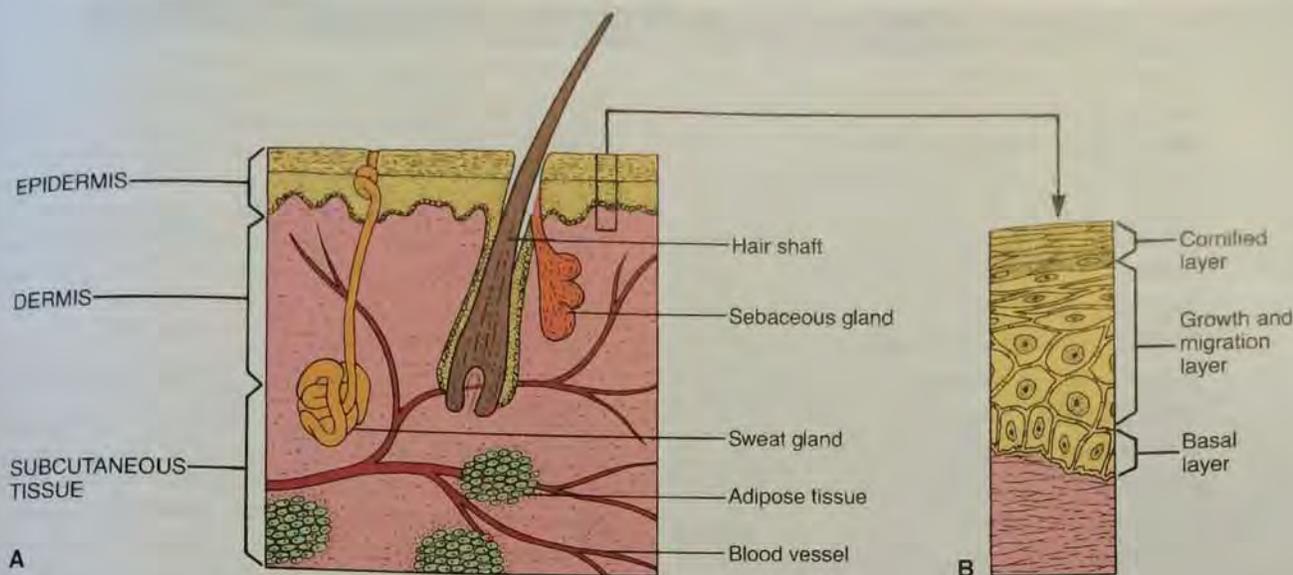


Figure 105-1 • Anatomy of the skin.

A, Major structures of the skin. B, Growth layers of the epidermis.

Relative Potency. Glucocorticoid preparations vary widely in potency. As indicated in Table 105-1, these drugs can be assigned to four groups that range in potency from low to super high. Preparations within each group are equipotent.

It is important to note that the intensity of the response to topical glucocorticoids depends not only on the concentration and inherent activity of the glucocorticoid, but also on the vehicle employed and the method of application. Occlusive dressings can enhance percutaneous absorption by as much as 10-fold, thereby greatly increasing pharmacologic effects.

Absorption. Topical glucocorticoids can be absorbed into the systemic circulation. The extent of absorption is proportional to the duration of use and the surface area covered. Absorption is higher from regions where the skin is especially permeable (scalp, axilla, face, eyelids, neck, perineum, genitalia) and lower from regions where penetrability is poor (back, palms, soles). Absorption through intact skin is lower than through inflamed skin. As noted, absorption is influenced by the vehicle, and can be greatly increased by an occlusive dressing.

Adverse Effects. Adverse effects may be local or systemic. Factors that increase the risk of adverse effects include use of a high-potency glucocorticoid, use of an occlusive dressing, prolonged therapy, and application over a large area.

Local Reactions. Glucocorticoids increase the risk of local infection, and may also produce irritation. With prolonged use, glucocorticoids can cause atrophy of the dermis and epidermis, resulting in thinning of the skin, striae (stretch marks), purpura (red spots caused by local hemorrhage), and telangiectasia (red, wart-like lesions caused by capillary dilation). Long-term therapy may induce acne and hypertrichosis (excessive growth of hair, especially on the face).

Systemic Toxicity. Topical glucocorticoids can be absorbed in amounts sufficient to produce systemic toxicity. Principal concerns are growth retardation (in children) and adrenal suppression (in all age groups). Systemic toxicity is more likely under extreme conditions of use (prolonged ther-

apy in which a large area is treated with big doses of a high-potency agent covered with an occlusive dressing). When these conditions are present, the hypothalamic-pituitary-adrenal axis should be monitored. Systemic toxicity of the glucocorticoids is discussed at length in Chapter 72.

Administration. Topical glucocorticoids should be applied in a thin film and gently rubbed into the skin. Patients should be advised not to use occlusive dressings (bandages, plastic wraps) unless the prescriber tells them to. Tight-fitting diapers and plastic pants can act as occlusive dressings and should not be worn when glucocorticoids are applied to the diaper region of infants.

KERATOLYTIC AGENTS

Keratolytic agents are drugs that promote shedding of the horny layer of the skin. Effects range from peeling to extensive desquamation of the stratum corneum. Two keratolytic compounds—*salicylic acid* and *sulfur*—are considered below. A third agent—*benzoyl peroxide*—is discussed later under *Topical Drugs for Acne*.

Salicylic Acid. Salicylic acid promotes desquamation by dissolving the intracellular cement that binds scales to the stratum corneum. Keratolytic effects are achieved with concentrations between 3% and 6%. At concentrations above 6%, tissue injury is likely. Low (3% to 6%) concentrations are used to treat dandruff, seborrheic dermatitis, acne, and psoriasis. Higher concentrations (up to 40%) are used to remove warts and corns.

Salicylic acid is readily absorbed through the skin, and systemic toxicity (salicylism) can result. Symptoms include tinnitus, hyperpnea, and psychologic disturbances. Systemic effects can be minimized by avoiding prolonged use of high concentrations over large areas.

Sulfur. Sulfur promotes peeling and drying. The compound has been used to treat acne, dandruff, psoriasis, and

TABLE 105-1 • Relative Potency of Topical Glucocorticoids

Potency Class and Drug	Formulation	Concentration
Super-High Potency		
Betamethasone dipropionate [Diprolene]	Ointment, lotion	0.05%
Clobetasol propionate [Clobex, Temovate, others]	Cream, ointment, gel, spray, foam, lotion, shampoo	0.05%
Fluocinonide [Vanos]	Cream	0.1%
Halobetasol propionate [Ultravate]	Cream, ointment	0.05%
High Potency		
Amcinonide	Cream, ointment, lotion	0.1%
Betamethasone dipropionate [Diprolene AF]	Cream, ointment	0.05%
Betamethasone valerate	Ointment	0.1%
Desoximetasone [Topicort]	Cream, ointment	0.25%
Diflorasone diacetate [ApexiCon, Florone, Maxiflor]	Cream, ointment	0.05%
Fluocinonide [Fluonex, Lidex]	Cream, ointment, gel, solution	0.05%
Halcinonide [Halog]	Cream, ointment	0.1%
Triamcinolone acetonide	Ointment	0.5%
Medium Potency		
Betamethasone dipropionate	Lotion	0.05%
Betamethasone valerate [Beta-Val, Valisone]	Cream, ointment, lotion	0.1%
Clocortolone pivalate [Cloderm]	Cream	0.1%
Desoximetasone [Topicort LP]	Cream	0.05%
Fluocinolone acetonide	Cream, ointment	0.025%
Flurandrenolide [Cordran, Cordran SP]	Cream, lotion	0.05%
Fluticasone propionate [Cutivate]	Ointment	0.005%
	Cream	0.05%
Hydrocortisone butyrate [Locoid, Locoid Lipocream]	Cream, ointment, solution	0.1%
Hydrocortisone valerate [Westcort]	Cream, ointment	0.2%
Mometasone furoate [Elocon]	Cream, ointment, lotion	0.1%
Prednicarbate [Dermatop]	Cream, ointment	0.1%
Triamcinolone acetonide [Kenalog]	Cream, ointment, lotion	0.1%
Low Potency		
Alclometasone dipropionate [Aclovate]	Cream, ointment	0.05%
Desonide [DesOwen, LoKara, Verdeso Foam]	Cream, ointment, lotion, foam	0.05%
Fluocinolone acetonide [Capex]	Cream, shampoo, solution	0.01%
Hydrocortisone [Anusol-HC, Cortaid, Hytone]	Cream, ointment, lotion	2.5%
Hydrocortisone [Ala-Cort, Cortaid, Cortizone-10, Hytone]	Cream, ointment, lotion	1%
Hydrocortisone acetate [Lanacort 10, U-Cort]	Cream, ointment	1%

seborrheic dermatitis. Sulfur is available in lotions, gels, and shampoos. Concentrations range from 2% to 10%.

ACNE

Acne is the most common dermatologic disease. About 85% of teenagers develop acne, which often persists into adulthood. Acne accounts for more visits to dermatologists than any other disorder. In the United States, the direct costs of acne exceed \$1 billion a year, including about \$100 million spent on acne products sold over the counter.

Pathophysiology

Acne is a chronic skin disorder that usually begins during puberty. The disease is more common and more severe in males. Lesions typically develop on the face, neck, chest, shoulders, and back. In mild acne, *open comedones* (blackheads) are the most common lesion. A comedo forms when sebum combines with keratin to create a plug within a pore (oxidation of the sebum causes the exposed surface of the plug to turn black). *Closed comedones* (whiteheads) develop when pores become stuffed with sebum and scales below the skin surface. In its most severe form, acne is characterized by abscesses and inflammatory cysts. As a rule, acne begins to resolve after

puberty and clears entirely during the early 20s. However, with some people, the disease continues for decades.

Onset of acne is initiated by increased production of androgens during adolescence. Under the influence of androgens, sebum production and turnover of follicular epithelial cells are increased, leading to plugging of pores. Symptoms are intensified by the activity of *Propionibacterium acnes*, a microbe that converts sebum into irritant fatty acids. This bacterium also releases chemotactic factors that promote inflammation. Oily skin and a genetic predisposition also contribute.

Overview of Treatment

Because acne is a chronic disease, treatment is prolonged. Fortunately, almost all patients respond well. Effective treatment will prevent scarring and limit the duration of symptomatic disease, and will thereby minimize the psychologic impact of acne.

Nondrug Therapy

Nondrug measures can help minimize lesions, especially in patients with milder acne. Surface oiliness should be reduced by gentle cleansing 2 or 3 times a day. Care should be taken to avoid irritation from vigorous scrubbing or use of abrasives. Oil-based moisturizing products should not be used. Additional nondrug measures (eg, comedo extraction, dermabrasion) may be indicated for some individuals. Dietary measures don't help.

Drug Therapy

Drugs for acne fall into two major groups: topical drugs and oral drugs (Table 105-2). The topical drugs have two principal subgroups: antimicrobial agents and retinoids. Likewise, the oral drugs have two principal subgroups: antibiotics and retinoids.

Drug selection is based on symptom severity. For patients with relatively mild symptoms, topical therapy can suffice. When symptoms are more severe, oral therapy is required. *Mild* acne can be managed with topical antimicrobials and topical retinoids. *Moderate* acne can be treated with oral antibiotics (eg, doxycycline, minocycline) and comedolytics (retinoids and azelaic acid). In addition, hormonal agents—combination oral contraceptives (OCs) and spironolactone—can be used in young women. The principal agent for severe acne is isotretinoin.

Topical Drugs for Acne

Antibiotics

Benzoyl Peroxide. Benzoyl peroxide is a first-line drug for mild to moderate acne. Improvement can be seen within days of starting treatment. Benefits derive primarily from suppressing growth of *P. acnes*. The presumed mechanism is release of active oxygen. In addition to suppressing *P. acnes*, benzoyl peroxide can reduce inflammation and promote keratolysis (peeling of the horny layer of the epidermis). In one study, topical benzoyl peroxide was at least as effective as oral minocycline.

Unlike other topical antimicrobials, benzoyl peroxide does not promote emergence of resistant *P. acnes*. In fact, the drug

TABLE 105-2 • Drugs for Acne

Topical Drugs

Antibiotics

Benzoyl peroxide (generic only)
Clindamycin [Cleocin, others]
Erythromycin [Eryderm, others]
Dapsone [Aczone]
Benzoyl peroxide/clindamycin [Benzac/Cl]
Benzoyl peroxide/erythromycin [Benzamycin]

Retinoids

Tretinoin [Atralin, Avita, Retin-A, Retin-A Micro]
Adapalene [Differin]
Tazarotene [Avage, Tazorac]

Retinoid/Antibiotic Combinations

Tretinoin/clindamycin [Vibin Gel, Ziana]
Adapalene/benzoyl peroxide [Epiduo]

Others

Azelaic acid [Azela, Finacea ♦]

Oral Drugs

Antibiotics

Doxycycline [Vibramycin, others]
Minocycline [Dynacin, Minocin, others]
Tetracycline [Sumycin, others]
Erythromycin [Ery-Tab, others]

Retinoids

Isotretinoin [Accutane ♦, Amnestrom, Claravis, Sotret]

Hormonal Agents

Combination oral contraceptives
Spironolactone [Aldactone]

is often combined with clindamycin or erythromycin to protect against resistance, which can occur when those antibiotics are used alone.

Benzoyl peroxide may produce drying and peeling of the skin. If signs of severe local irritation occur (eg, burning, blistering, scaling, swelling), the frequency of application should be reduced.

Some formulations contain sulfites, which can cause potentially serious allergic reactions. The incidence is highest in patients with asthma. Otherwise, the incidence is low.

Benzoyl peroxide is available in a variety of formulations (eg, lotions, creams, gels). Concentrations range from 2.5% to 10%. For initial therapy, once-daily application is recommended. Over time, the frequency of administration can be increased (to a maximum of 3 times a day) as tolerance permits. Patients should be advised to keep the drug away from the eyes, mouth, and mucous membranes, as well as inflamed or denuded skin.

Clindamycin and Erythromycin. Like benzoyl peroxide, topical clindamycin [Cleocin, others] and erythromycin [Eryderm, others] suppress growth of *P. acnes*. In addition, these drugs can decrease inflammation. Monotherapy with either drug quickly leads to resistance. To protect against emergence of resistance, these drugs can be combined with benzoyl peroxide. Two fixed-dose combinations are available: clindamycin/benzoyl peroxide, sold as *Benzac/Cl* and *Clindoxyl* ♦; and erythromycin/benzoyl peroxide, sold as *Benzamycin*.

Dapsone. Dapsone [Aczone], approved for topical therapy of acne in 2008, has been used for oral therapy of leprosy for decades (see Chapter 90). In patients with acne, the drug yields a modest decrease in inflammation and number of lesions. The mechanism underlying benefits has not been established. Comparative trials with other topical agents have not been conducted. Dapsone is available as a 5% gel in 30-gm tubes for twice-daily application. The site should be washed and dried before applying the drug, and the hands should be washed afterward. The most common side effects—oiliness (19%), peeling (19%), dryness (16%), and erythema (13%)—are caused primarily by the gel vehicle, and not by dapsone. Unlike oral dapsone, topical dapsone does not pose a risk of hemolytic anemia or peripheral neuropathy. Combining dapsone with benzoyl peroxide can turn the skin yellow or orange, and hence should be avoided. Until more is known, dapsone should be reserved for patients who can't tolerate traditional topical treatments.

Retinoids

The topical retinoids—derivatives of vitamin A (retinol)—are a cornerstone of acne therapy. These drugs can unplug existing comedones and prevent development of new ones. In addition, they can reduce inflammation and improve penetration of other topical agents. The retinoids may be used alone or in combination with other drugs, including topical and oral antimicrobials.

Tretinoin. Tretinoin [Atralin, Avita, Retin-A, Retin-A Micro, Renova], a derivative of vitamin A, is used for acne and to remove fine wrinkles. Formulations for acne are marketed as Atralin, Avita, Retin-A, and Retin-A Micro. The formulation for wrinkles, which is nearly identical to one of the formulations for acne, is marketed as Renova. Tretinoin should not be confused with isotretinoin, a powerful oral antiacne medicine (see below).

Use for Acne. Tretinoin is approved for topical treatment of mild to moderate acne. Benefits derive from normalizing hyperproliferation of epithelial cells within hair follicles. By doing so, retinoids can unplug existing comedones and suppress formation of new plugs. Tretinoin also causes thinning of the stratum corneum, and can thereby facilitate penetration of other drugs. Therapeutic effects can be enhanced by combining tretinoin with benzoyl peroxide, topical antibiotics, and oral antibiotics.

Use for Fine Wrinkles. Tretinoin is approved for reducing fine wrinkles, tactile roughness, and mottled hyperpigmentation (liver spots, age spots) in facial skin. Benefits may derive from suppressing genes that code for specific proteases that break down collagen and elastin. In clinical trials, responses to tretinoin were modest. In fact, many patients achieved equivalent effects with a program of comprehensive skin care and sun protection. It is important to appreciate that tretinoin does *not* repair deep, coarse wrinkles and other damage caused by chronic sun exposure. Furthermore, the drug does not reverse photoaging or restore the microscopic structure of skin to a more youthful pattern. Lastly, benefits in patients over the age of 50 have not been established.

Adverse Effects. Tretinoin can cause *localized* reactions, but absorption is insufficient to cause systemic toxicity. In patients with sensitive skin, tretinoin may induce blistering, peeling, crusting, burning, and edema. These effects can be intensified by concurrent use of abrasive soaps and keratolytic agents (eg, sulfur, resorcinol, benzoyl peroxide, salicylic acid). Accordingly, these preparations should be discontinued prior to tretinoin therapy. Skin reactions with two formulations—Avita and Retin-A Micro—may be less intense than those caused by Retin-A, an older formulation.

Tretinoin increases susceptibility to sunburn. Patients should be warned to apply a sunscreen (sun protection factor

[SPF] of 15 or greater) and wear protective clothing. Patients with existing sunburn should not apply the drug.

Preparations, Dosage, and Administration. For treatment of *acne*, tretinoin is available under four trade names: Retin-A, Retin-A Micro, Atralin, and Avita. Products marketed as *Retin-A* are available in two formulations: cream (0.025%, 0.05%, and 0.1%) and gel (0.01% and 0.025%). *Retin-A Micro* is supplied as a gel (0.04% and 0.1%), *Atralin* as a 0.05% gel, and *Avita* as a 0.025% cream or gel. All products are administered topically, usually once a day at bedtime. Before application, the skin should be washed, toweled dry, and allowed to dry fully for 15 to 30 minutes. Tretinoin should not be applied to open wounds or to areas of sunburn or windburn. Contact with the eyes, nose, and mouth should be avoided.

For *fine wrinkles of the face*, tretinoin is available in a 0.05% cream, sold as *Renova*. Application is done once daily at bedtime. Cosmetics should be washed off before use. Up to 6 months of treatment may be needed to see a response, and treatment must continue to maintain the response.

Adapalene. Adapalene [Differin] is a topical antiacne drug similar to tretinoin. Through actions in the cell nucleus, adapalene modulates inflammation, epithelial keratinization, and differentiation of follicular cells. As a result, the drug reduces formation of comedones and inflammatory lesions. Benefits take 8 to 12 weeks to develop. During the early weeks, adapalene may appear to exacerbate acne by affecting previously invisible lesions. In clinical trials, 0.1% adapalene gel was as effective as 0.025% tretinoin gel in reducing the total number of comedones, and was more effective than tretinoin in reducing the total number of acne lesions and inflammatory lesions.

Adverse effects are limited to sites of application. The drug is not absorbed, and hence systemic effects are absent. Common side effects include burning (10% to 40%), pruritus or burning immediately after application (20%), erythema, dryness, and scaling. These are most likely during the first 2 to 4 weeks of treatment and tend to subside as treatment continues.

Adapalene increases the risk of developing sunburn and can intensify existing sunburn. Accordingly, all patients should apply a sunscreen and wear protective clothing. In addition, adapalene should not be used until existing sunburn has resolved.

Adapalene, by itself, is available in four 0.1% formulations—gel, cream, lotion, and solution—for once-daily application in the evening. In addition, adapalene is available in a fixed-dose combination with benzoyl peroxide. Contact with the eyes, lips, and mucous membranes should be avoided.

Tazarotene. Tazarotene [Avage, Tazorac] is indicated for topical therapy of acne, wrinkles, and psoriasis. Like tretinoin and adapalene, tazarotene is a derivative of vitamin A. For treatment of acne, tazarotene is available in a gel (0.05%, 0.1%) and cream (0.05%, 0.1%). The gel or cream is applied to affected areas of the face each evening. The face should be cleaned and dried before application. The most common side effects—itching, burning, and dry skin—occur more often with tazarotene than with tretinoin or adapalene. Like other retinoids, tazarotene sensitizes the skin to ultraviolet light, and hence patients should be advised to use a sunscreen and wear protective clothing. The basic pharmacology of tazarotene is discussed below under *Topical Drugs for Psoriasis*.

Azelaic Acid

Azelaic acid [Azelex, Finacea] is a topical drug for mild to moderate acne. It appears to work by suppressing growth of *P. acnes* and by decreasing proliferation of keratinocytes, thereby decreasing the thickness of the stratum corneum. In clinical trials, topical azelaic acid (20% cream) was as effective as 5% benzoyl peroxide, 0.05% tretinoin, or 2% erythromycin. For severe acne, azelaic acid was much less effective than oral isotretinoin. Adverse effects—which are uncommon and less intense than with tretinoin or benzoyl peroxide—include pruritus, burning, stinging, tingling, and erythema. Azelaic acid may reduce pigmentation in patients with dark complexions. Hence, these people should be monitored for hypopigmentation. Azelaic acid is applied twice daily by gently massaging a thin film into the affected area. Contact with the eyes, nose, and mouth should be avoided. Before application, the skin should be washed and patted dry.

Oral Drugs for Acne

Antibiotics

Oral antibiotics are used for moderate to severe acne. These drugs suppress growth of *P. acnes* and directly suppress inflammation. As a rule, oral antibiotics are combined with a topical retinoid.

At this time, doxycycline [Vibramycin, others] and minocycline [Minocin, Dynacin, others] are considered agents of

choice. Tetracycline [Sumycin, others] and erythromycin [Ery-Tab, others] are alternatives, but resistance to these drugs is common. With all antibiotics, benefits develop slowly, taking 3 to 6 months to become maximal. After symptoms have been controlled with an oral antibiotic, patients should switch to a topical antibiotic for long-term maintenance.

Isotretinoin

Actions and Use. Isotretinoin [Accutane[®], Amnesteem, Claravis, Sotret], a derivative of vitamin A, is used to treat severe *nodulocystic acne vulgaris*, a condition for which this drug is highly effective. For most patients, a single course of therapy can produce complete and prolonged remission. Because isotretinoin can cause serious side effects, use is restricted to patients with severe, disfiguring acne that has not responded to more conventional agents, including oral antibiotics. Isotretinoin is highly teratogenic, and hence must not be used during pregnancy.

Isotretinoin has several actions that may contribute to anti-acne effects. The drug decreases sebum production, sebaceous gland size, inflammation, and keratinization. In addition, by decreasing availability of sebum, a nutrient for *P. acnes*, isotretinoin lowers the skin population of this microbe.

Pharmacokinetics. Absorption from the GI tract is rapid but incomplete. Food greatly increases absorption. In the blood, isotretinoin is nearly 100% bound to albumin. The drug undergoes metabolism in the liver and possibly in cells of the intestinal wall. Excretion is by renal and biliary processes. The drug's half-life is 10 to 20 hours.

Adverse Effects. Common Effects. The most common reactions are nosebleeds (80%), inflammation of the lips (90%), inflammation of the eyes (40%), and dryness or itching of the skin, nose, and mouth (80%). About 15% of patients experience pain, tenderness, or stiffness in muscles, bones, and joints. Among pediatric patients, nearly 30% experience back pain. Less common reactions include skin rash, headache, hair loss, and peeling of skin from the palms and soles. Reduction in night vision has occurred, sometimes with sudden onset. The skin may become sensitized to ultraviolet light; patients should be advised to wear protective clothing or a sunscreen if responses to sunlight become exaggerated. Rarely, isotretinoin causes cataracts, optic neuritis, papilledema (edema of the optic disk), and pseudotumor cerebri (benign elevation of intracranial pressure).

Triglyceride levels may become elevated. Blood triglyceride content should be measured prior to treatment and periodically thereafter until effects on triglycerides have been evaluated. Alcohol can potentiate hypertriglyceridemia and should be avoided.

Although the above adverse effects occur frequently, they usually reverse upon stopping treatment.

Rare Effect: Depression. Isotretinoin may pose a small risk of depression and suicide, although proof of a causal relationship is lacking. With some patients, depression developed while taking isotretinoin, resolved when the drug was discontinued, and then recurred when treatment was resumed. Between 1982 and January 2005, 190 suicides were reported. However, there is no definitive proof that isotretinoin was the cause, and no mechanism for inducing depression has been established. Nonetheless, because the potential consequences of depression are severe, steps should be taken to minimize risk. Accordingly, clinicians should ask patients to report signs of depression (eg, depressed mood, loss of interest or pleasure) or thoughts of suicide. If these occur, isotretinoin

should be withdrawn. Psychiatric evaluation should be obtained as indicated.

Drug Interactions. Adverse effects of isotretinoin can be increased by *tetracyclines* and *vitamin A*. Tetracyclines increase the risk of pseudotumor cerebri and papilledema. Vitamin A, a close relative of isotretinoin, can produce generalized intensification of isotretinoin toxicity. Because of the potential for increased toxicity, tetracyclines and vitamin A supplements should be discontinued prior to isotretinoin therapy.

Contraindication: Pregnancy. *Isotretinoin is teratogenic and must not be used during pregnancy.* The drug is classified in Food and Drug Administration (FDA) Pregnancy Risk Category X: The risks of use during pregnancy clearly outweigh any possible benefits. Major fetal abnormalities that have occurred include hydrocephalus, microcephaly, facial malformation, cleft palate, cardiovascular defects, and abnormal formation of the outer ear.

iPLEDGE Program. iPLEDGE is the name of a very strict risk management program designed to ensure that no woman starting isotretinoin is pregnant and that no woman taking isotretinoin becomes pregnant. The iPLEDGE program, which went into effect December 31, 2005, replaced S.M.A.R.T. (System to Manage Accutane-Related Teratogenicity) and all other programs designed to guard against use of isotretinoin during pregnancy. The principal difference between iPLEDGE and S.M.A.R.T. is that, under iPLEDGE, all transactions involving isotretinoin must be processed through a *central automated system*, which tracks and verifies critical elements that control access to the drug. The program has rules that apply to the prescriber, patient, pharmacist, and wholesaler. Details regarding iPLEDGE are available online at www.ipledgeprogram.com.

Requirements for Female Patients. Each patient must receive oral and written warnings about the high risk of fetal harm if isotretinoin is taken during pregnancy.

Pregnancy must be ruled out before the initial prescription, and again before each monthly refill. Prior to the initial prescription, the patient must undergo *two* pregnancy tests, both of which must be negative. For the monthly refills, only one negative test result is required.

Each patient must use *two* effective forms of birth control, even if one of them is tubal ligation or vasectomy of the male partner. In addition, the patient must review educational material, provided through iPLEDGE, on contraceptive methods, possible reasons for contraceptive failure, and the importance of using effective contraception while taking a teratogenic drug. Birth control measures must be implemented at least 1 month before starting isotretinoin, and must continue at least 1 month after stopping. Birth control is not required following hysterectomy or for women who commit to total abstinence from sexual intercourse.

Each patient must sign a Patient Information/Informed Consent document, designed to reinforce the benefits and risks of isotretinoin use.

Each patient must be registered with iPLEDGE by her prescriber, and must contact iPLEDGE (through the Internet or by phone) before starting treatment, once a month during treatment, and, finally, 1 month after stopping treatment. At each contact, the patient must answer questions on program requirements and must indicate her two chosen methods of birth control.

Requirements for Prescribers. Prescribers must register with iPLEDGE and must agree to follow key points of the

iPLEDGE program, as described in the *iPLEDGE Program Guide to Best Practices for Isotretinoin*. Also, the prescriber must register each patient with iPLEDGE, enter the results of each monthly pregnancy test, and indicate what methods of contraception the patient is using. The initial prescription for isotretinoin and each monthly refill must be entered into the iPLEDGE system.

Requirements for Pharmacists. To dispense isotretinoin, pharmacists must be registered with iPLEDGE, and must obtain the drug through an iPLEDGE-registered wholesaler. Every time a prescription for isotretinoin is filled, the pharmacist must

- Contact iPLEDGE for authorization
- Confirm with iPLEDGE that the prescription is no more than 7 days old
- Dispense no more than a 30-day supply
- Write the risk management authorization (RMA) number on the prescription

Preparations, Dosage, and Administration. Isotretinoin is available in standard capsules (10, 20, 30, and 40 mg) sold as Accutane, Amnesteem, and Claravis, and in soft-gel capsules (10, 20, 30, and 40 mg) sold as Sotret. The usual course of treatment is 0.5 to 1 mg/kg/day (taken in two divided doses with food) for 15 to 20 weeks. If needed, a second course may be given, but no sooner than 2 months after completing the first course.

Hormonal Agents

Hormonal therapies can be used for acne in young women. Combination oral contraceptives and spironolactone are the main agents employed. In both cases, benefits derive from decreasing androgen activity, leading to decreased production of sebum.

Oral Contraceptives. Three combination oral contraceptives (OCs)—Elostep, Ortho Tri-Cyclen, and YAZ—are approved for managing acne in women. Treatment is limited to females at least 15 years old who want contraception, have reached menarche, and have not responded to topical drugs. Acne may take 6 or more months to improve. Benefits are due primarily to the *estrogen* in combination OCs—not the progestin. Two mechanisms are involved: suppression of ovarian androgen production, and increased production of *sex hormone-binding globulin*, a protein that binds androgens and thereby renders them inactive. By decreasing androgen availability, estrogens decrease production of sebum. Although only three OCs are approved for acne, all estrogen-containing OCs should work. Accordingly, selection among them should be based primarily on tolerability.

Spironolactone. Spironolactone [Aldactone] blocks a variety of steroid receptors, including those for aldosterone and sex hormones. Blockade of aldosterone receptors underlies the drug's use as a diuretic (see Chapter 41) as well as its use in heart failure (see Chapter 48). Blockade of androgen receptors underlies benefits in females with acne. As a rule, spironolactone is *added* to the regimen after an oral contraceptive has proved inadequate. This sequence makes sense. Why? Because spironolactone is teratogenic, and hence contraception should be implemented before taking the drug. Adverse effects include menstrual irregularities, breast tenderness, and hyperkalemia.

SUNSCREENS

Sunlight has multiple effects on the skin. In addition to promoting tanning, solar radiation can cause burns, premature aging of the skin, skin cancer, and immunosuppression. Sun

TABLE 105-3 • Properties of UVB and UVA Radiation

Property	Type of UV Radiation	
	UVB	UVA
Wavelength (nm)	290–320	320–400
Can penetrate glass	No	Yes
Skin penetration	Epidermis only	Epidermis/dermis
Effects on the skin:		
Burning	Major cause	Minor cause
Tanning	Major cause	Minor cause
Cancer	Major cause	Major cause
Photoaging		Sole cause
Photosensitive drug reactions		Sole cause

exposure can also induce photosensitivity reactions to drugs. All of these effects are caused by ultraviolet (UV) radiation, and all can be greatly reduced by using a sunscreen.

Types of Ultraviolet Radiation: UVB and UVA

Solar UV radiation that reaches the earth's surface is classified by wavelength into two basic types: UVB (290 to 320 nm) and UVA (320 to 400 nm). UVA can be further subdivided into UVA2 (320 to 340 nm) and UVA1 (340 to 400 nm). Most (95%) of terrestrial UV radiation is UVA; only 5% is UVB. The intensity of UVA is fairly constant from morning to evening and from one day to the next throughout the year. In contrast, UVB is significant only between late spring and early fall, and, on any given day, is moderate in the morning and evening, and most intense around noon. UVA can penetrate glass; UVB can't.

The dermatologic effects of UVA and UVB differ. UVA penetrates the epidermis and deep into the dermis. In contrast, UVB penetrates into the epidermis but goes no deeper. Tanning and sunburn are caused primarily by UVB. Because UVA penetrates much deeper than UVB, UVA is the primary cause of immunosuppression, photosensitive drug reactions, and photoaging of the skin (wrinkling, thickening, yellowing, breakdown of elastic fibers). Both UVA and UVB promote damage to DNA, and hence both can cause premalignant actinic keratoses, basal cell carcinoma, squamous cell carcinoma, and malignant and nonmalignant melanoma. Properties of UVA and UVB are summarized in Table 105-3.

Benefits of Sunscreens

Sunscreens impede penetration of UV radiation to viable cells of the skin. As a result, sunscreens can protect against sunburn, photoaging of the skin, and photosensitivity reactions to certain drugs (eg, tricyclic antidepressants, phenothiazines, sulfonamides, sulfonyleureas). Sunscreens can also decrease the risk of actinic keratoses, squamous cell carcinoma, and melanoma. Whether sunscreens protect against basal cell carcinoma is unclear.

Compounds Employed as Sunscreens

There are two categories of sunscreens: *organic* screens (also known as *chemical* screens) and *inorganic* screens (also known as *physical* screens). Organic screens *absorb* UV radiation and then dissipate it as heat. Inorganic screens *scatter*

	Range of UV Protection		
	UVB	UVA2	UVA1
ORGANIC (CHEMICAL) SUNSCREENS			
Aminobenzoic Acid Derivatives			
PABA (<i>para</i> -aminobenzoic acid)	■		
Padimate O (octyl dimethyl PABA)	■		
Cinnamates			
Cinoxate	■		
Octinoxate (octyl methoxycinnamate)	■		
Salicylates			
Homosalate	■		
Octisalate (octyl salicylate)	■		
Trolamine salicylate	■		
Benzophenones			
Dioxybenzone (benzophenone-8)	■	■	
Oxybenzone (benzophenone-3)	■	■	
Sulisobenzone (benzophenone-4)	■	■	
Others			
Avobenzone (Parsol 1789)			■
Ecamsule	■	■	
Ensulizole	■	■	
Meradimate (methyl anthranilate)	■	■	
Octocrylene	■		
INORGANIC (PHYSICAL) SUNSCREENS			
Titanium dioxide	■	■	■
Zinc oxide	■	■	■

Figure 105-2 ■ Range of UVB and UVA protection conferred by FDA-approved sunscreens.

UV radiation. At this time, 17 compounds are FDA approved for use as sunscreens (Fig. 105-2).

Organic (Chemical) Screens. Most (15) of the approved sunscreens are organic. Almost all of them absorb UVB, but only six absorb UVA. Of these six, five absorb UVA2, and only one—*avobenzone*—absorbs UVA1. Therefore, in order to provide protection against the full range of UV radiation, products must contain a mixture of compounds, one of which must be *avobenzone*. Products formulated with *avobenzone* include Aveeno Continuous Protection, Neutrogena Ultra Sheer Dry-Touch SPF 45, Sea & Ski Advanced Sunscreen, and Coppertone Sport.

Inorganic (Physical) Screens. Physical screens act primarily as barriers to the sun's rays. Hence, rather than absorbing solar radiation, they *reflect and scatter* sunlight, thereby preventing penetration to the skin. Only two agents are employed as physical screens: *titanium dioxide* and *zinc oxide*. Preparations containing these compounds are especially useful for protecting limited areas (eg, nose, lips, tips of ears). In the formulations used today, titanium dioxide and zinc oxide are "micronized." As a result, they are clear when applied to the skin, unlike older formulations, which were white.

Sun Protection Factor

All sunscreen products are labeled with a sun protection factor (SPF). The SPF is an index of protection against UVB. The SPF says nothing about protection against UVA.

The SPF is determined by shining UV light on adjacent regions of protected and unprotected skin and recording the time required for erythema (redness) to develop in both areas. The SPF is calculated by dividing the time required for erythema to develop in the protected region by the time required for erythema to develop in the unprotected region. For example, if the

unprotected region developed erythema in 15 minutes, and the protected region developed erythema in 150 minutes, the sunscreen would have an SPF of 10 (150 divided by 15). Be aware that the methods for determining the SPF are not very precise. Hence, all products labeled with the same SPF may not provide an equal degree of protection.

You should appreciate that the relationship between SPF and protection against sunburn is not linear. That is, an SPF of 30 does not indicate twice as much protection as an SPF of 15. In fact, as the SPF increases, the increment in protection gets progressively smaller. For example, SPF 15 indicates 93% block of UVB, SPF 30 indicates 96.7% block, and SPF 40 indicates 97.5% block. Because SPF values above 30 provide only a small additional benefit, the FDA no longer allows companies to advertise high SPF values (eg, SPF 80). Instead products with an SPF greater than 50 can only be labeled as SPF 50+.

Adverse Effects of Sunscreens

Contact dermatitis and photosensitivity reactions can occur, especially with products that contain *para*-aminobenzoic acid (PABA) derivatives. PABA-containing products should be avoided by people with allergies to benzocaine, sulfonamides, or thiazides, all of which can cross-react with PABA.

New Rules for Sunscreen Labeling

In 2011, at long last, the FDA released new rules for labeling sunscreens. Under these rules, the label will now have to indicate (1) the range of UV radiation protection, and (2) the degree of water/sweat resistance. As in the past, labels will continue to indicate the SPF.

Range of UV Protection and SPF. All sunscreens protect against UVB radiation, but only some protect against UVA too. Products that protect against UVA *and* UVB will now be labeled BROAD SPECTRUM. The label will also show the SPF, indicating the degree of UVB protection. Broad-spectrum sunscreens that have an SPF of 15 or higher can claim to protect against skin cancer and photoaging. Broad-spectrum agents with an SPF below 15 cannot make this claim. In fact, these products must carry a warning that they do *not* protect against skin cancer or photoaging. Products that only protect against UVB must carry the same warning. In summary, the new labels will allow consumers to distinguish between three basic groups of sunscreens:

- **Highly Protective**—BROAD SPECTRUM sunscreens with an SPF of 15 or higher. These protect against sunburn, skin cancer, and photoaging.
- **Moderately Protective**—BROAD SPECTRUM sunscreens with an SPF of 2 to 14. These protect against sunburn, but do not protect against skin cancer and photoaging.
- **Least Protective**—Sunscreens with UVB protection only. These protect against sunburn, but do not protect against skin cancer and photoaging.

Water/Sweat Resistance. Sunscreens can no longer claim to be *waterproof* or *sweatproof*. Rather, they can claim to be *water resistant* or *sweat resistant*. Furthermore, they must indicate how long the resistance lasts, as determined by laboratory testing. Products that retain their SPF after 40 minutes of water exposure will be labeled *Water Resistant 40 Minutes*. Products that retain their water resistance after 80 minutes will be labeled *Water Resistant 80 Minutes*. Regardless of the stated

duration of water/sweat resistance, the label must advise reapplication after swimming or sweating.

Safe Sunning

To protect against skin damage from sunlight, we should use a sunscreen, protective clothing, and common sense.

Using a Sunscreen Effectively. Sunscreens must be used properly to achieve maximum benefit. The American Academy of Dermatology recommends using a sunscreen with coverage against both UVB and UVA. The SPF should be at least 15. Individuals who burn easily should use a higher SPF product. Protection is greatest when a sunscreen has been allowed to penetrate the skin in advance of exposure to the sun. Accordingly, sunscreens should be applied at least 30 minutes prior to going outdoors; sunscreens containing PABA or padimate O should be applied up to 2 hours in advance. The amount applied is an important determinant of protection; 2 mg/cm² is considered adequate. Sunscreens should be reapplied after swimming and profuse sweating; failure to do so reduces the duration of protection. However, it is important to note that reapplication will not extend the period of protection beyond that indicated by the SPF. That is, if treated skin can be expected to burn when sun exposure exceeds 2 hours, no amount of reapplication can prevent burning if the duration of exposure exceeds the limit.

Environmental factors play a part in sunscreen use. The intensity of UVB radiation is greatest between the hours of 10:00 AM and 4:00 PM. Accordingly, the need for a sunscreen is correspondingly high during this time. Ultraviolet radiation can be reflected by painted surfaces, white sand, and snow, thereby augmenting total UV exposure. Accordingly, the contribution of reflected radiation should be considered when choosing a sunscreen. Clouds can filter out UV radiation. Nonetheless, the amount of UV light reaching the ground on a bright day with thin cloud cover can be as much as 80% of that reaching the ground on days that are sunny and clear. Ultraviolet radiation can penetrate at least several centimeters of clear water; swimmers should be made aware of this fact.

Other Protection Measures. Sunscreens alone cannot completely protect against sun damage. Accordingly, to further reduce risk, you should wear sunglasses, protective clothing, and a wide-brimmed hat. In addition, common sense dictates avoiding sun exposure in the middle of the day, especially between 10:00 AM and 4:00 PM. If you must be outside at these times, try to stay in the shade.

PSORIASIS

Pathophysiology

Psoriasis is a common, chronic inflammatory disorder that follows an erratic course. The initial episode usually develops in early adulthood. Subsequent attacks may occur spontaneously or may be triggered by emotional stress, streptococcal pharyngitis (sore throat), or certain drugs, including lithium, beta blockers, antimalarials, and angiotensin-converting enzyme inhibitors. There is no cure for psoriasis, but symptoms can usually be controlled with medication. Drug-induced remission is common and may last from a few weeks to many years.

Psoriasis has varying degrees of severity. Mild disease manifests as red patches covered with silvery scales; lesions typically appear on the scalp, elbows, knees, palms, and soles. Severe disease may involve the entire skin surface and mucous membranes; patients may develop superficial pustules, high fever, leukocytosis, and painful fissuring of the skin.

Symptoms result from two processes: accelerated maturation of epidermal cells (keratinocytes) and excessive activity of inflammatory cells. In re-

TABLE 105-4 ■ Treatments for Psoriasis

TOPICAL DRUGS

Glucocorticoids
Vitamin D₃ analogs
Tazarotene [Tazorac]
Anthralin
Salicylic acid
Tars

SYSTEMIC DRUGS

Conventional Agents

Methotrexate [Trexall, Rheumatrex]
Acitretin [Soriatane]
Cyclosporine [Neoral, Gengraf, Sandimmune]

Biologic Agents

T-Cell Antagonist

Alefacept [Amevive]

Tumor Necrosis Factor Antagonists

Adalimumab [Humira]
Etanercept [Enbrel]
Infliximab [Remicade]

Interleukin Antagonist

Ustekinumab [Stelara]

PHOTOTHERAPY

Coal tar plus UVB irradiation
Photochemotherapy (PUVA therapy)

cent years, it has become clear that inflammatory T cells (T lymphocytes) play a central role in the development and maintenance of psoriatic plaques. Hence, it now appears that psoriasis is primarily an inflammatory disorder, and that excessive proliferation of keratinocytes is a secondary response.

Overview of Treatment

Psoriasis can be treated with topical drugs, systemic drugs, or phototherapy. Several of the drugs employed suppress proliferation of keratinocytes. However, most antipsoriatic drugs suppress the activity of inflammatory cells. Treatment options are summarized in Table 105-4.

Treatment is based on symptom severity. For mild psoriasis, topical glucocorticoids are usually adequate; keratolytic agents (eg, salicylic acid) may be useful adjuncts to steroid therapy. A vitamin D₃ analog (eg, calcipotriene) may also be tried. For patients with moderate symptoms, coal tar or anthralin may be added to the regimen. Topical therapy with tar and anthralin can be enhanced by exposing the skin to UVB light. Treatment options for moderate to severe psoriasis include phototherapy or systemic treatment with methotrexate, acitretin, alefacept, and other drugs.

Topical Drugs for Psoriasis

Glucocorticoids

In the United States, glucocorticoids are the most commonly used topical drugs for psoriasis. Benefits derive from suppressing the activity of inflammatory cells. Preparations with super-high potency are employed where plaques are thickest. However, super-high-potency agents should not be applied to the face, groin, axilla, or genitalia. Why? Because skin in these regions is especially vulnerable to glucocorticoid-induced atrophy.

Vitamin D₃ Analogs

Two synthetic analogs of vitamin D₃—*calcipotriene* [Dovonex] and *calcitriol* [Vectal, Silkis♦]—are approved for topical therapy of mild to moderate psoriasis. Benefits derive from inducing differentiation of epidermal cells and from inhibiting proliferation of keratinocytes. Responses take a month or more to develop, and equal those seen with medium-potency topical glucocorticoids.

Adverse effects are generally mild. Local reactions—itching, irritation, and erythema—are most common. Unlike the glucocorticoids, the vitamin D₃ analogs do not cause thinning of the skin. With topical use, calcipotriene and

calcitriol can cause moderate hypercalcemia, although the clinical significance is unclear. Both drugs are classified in FDA Pregnancy Risk Category C (fetal risk cannot be ruled out). In animal studies, topical calcitriol has caused skeletal defects in the developing fetus. Animal data suggest that the vehicle used for calcitriol may enhance the ability of UV radiation to induce skin cancer. Accordingly, patients using calcitriol should minimize exposure of treated skin to natural and artificial sunlight.

Calcipotriene [Dovonex] is supplied as a 0.005% solution, cream, and ointment. Application is done twice daily. The solution is applied to affected areas of the scalp. The cream and ointment are applied to affected areas other than the scalp.

Calcitriol [Vectal, Silkis] is supplied as a 0.0003% ointment in 5- and 100-gm tubes. Application is made twice daily to affected areas, but not to the face. The maximum daily dose is 200 gm.

Tazarotene

Tazarotene [Tazorac] is a vitamin A derivative indicated for topical therapy of mild to moderate psoriasis. Following application to the skin, tazarotene is rapidly converted to tazarotenic acid, its active form. Tazarotenic acid binds with specific retinoic acid receptors, and thereby normalizes differentiation and proliferation of epidermal cells. In clinical trials, application of a 0.1% tazarotene gel once daily for 12 weeks produced a significant reduction in lesions in 50% to 70% of patients. Benefits were about equivalent to those seen with 0.05% fluocinonide, a high-potency topical glucocorticoid. Tazarotenic acid stays in the skin long after application of tazarotene has stopped. As a result, benefits may persist for several months. Use of tazarotene for acne is discussed above.

Adverse effects are limited largely to the skin. The most common local reactions (10% to 30%) are itching, burning, stinging, dry skin, and redness. Less common effects (1% to 10%) include rash, desquamation, contact dermatitis, inflammation, fissuring, and bleeding. Tazarotene sensitizes the skin to sunlight. Accordingly, patients should be advised to use a sunscreen and wear protective clothing.

Tazarotene gel is available in two concentrations: 0.05% and 0.1%. The gel is applied once daily in the evening. No more than 20% of the body surface area should be covered. Wet skin should be dried before application.

Anthralin

Anthralin has only one indication: topical treatment of psoriasis. The drug inhibits DNA synthesis and thereby suppresses proliferation of hyperplastic epidermal cells.

Anthralin may cause local irritation, especially when applied in concentrations above 1%. Erythema (redness) may develop in normal skin adjacent to areas of treatment. Severe conjunctivitis can develop following contact with the eyes. Systemic toxicity has not been documented. Anthralin preparations can stain clothing, skin, and hair.

Anthralin is supplied as a 0.5% and 1% cream. In conventional therapy, the drug is applied to lesions at bedtime and allowed to remain in place overnight. Stains can be avoided by wearing old clothing and by covering treated areas with a dressing.

Tars

Tars suppress DNA synthesis, mitotic activity, and cell proliferation. Coal tar is the tar employed most frequently. Preparations that contain juniper tar, birch tar, and pine tar are also available. Tar-containing products (eg, shampoos, lotions, and creams) are used to treat psoriasis and other chronic disorders of the skin. Tars have an unpleasant odor and can cause irritation, stinging, and burning. They may also stain the skin and hair. Systemic toxicity does not occur.

Systemic Drugs for Psoriasis: Conventional Agents

The conventional systemic drugs—methotrexate, acitretin, and cyclosporine—are oral agents that provide effective therapy for psoriasis, but also pose a risk of serious harm. Accordingly, these drugs are reserved for patients with moderate to severe psoriasis that has not responded to safer treatments. To reduce risk, systemic drugs can be alternated with phototherapy.

Methotrexate

The basic pharmacology of methotrexate [Trexall, Rheumatrex] is discussed in Chapter 102 (Anticancer Drugs I: Cytotoxic Agents). Consideration here is limited to treatment of psoriasis.

Actions and Use in Psoriasis. Methotrexate is a cytotoxic agent that shows some selectivity for tissues with a high growth fraction (ie, tissues with a large percentage of actively dividing cells). Benefits in psoriasis result from reduced proliferation of epidermal cells. The biochemical mechanisms under-

lying suppression of cell growth and division are discussed in Chapter 102. Methotrexate is highly toxic and should be used only in patients with severe, debilitating psoriasis that has not responded to safer therapy.

Adverse Effects. Methotrexate is administered systemically, and toxicity can be severe. Death has occurred. Patients should be fully informed of the risks of treatment. Close medical supervision is required. Gastrointestinal effects (diarrhea, ulcerative stomatitis) are the most frequent reasons for interrupting therapy. Blood dyscrasias (anemia, leukopenia, thrombocytopenia) from bone marrow suppression are an additional major concern. With prolonged use, even at relatively low doses, methotrexate can cause significant harm to the liver. Accordingly, hepatic function must be monitored; a liver biopsy is the best method for assessing injury. Methotrexate can cause congenital anomalies and fetal death, and hence is contraindicated during pregnancy.

Dosage and Administration. Methotrexate may be administered PO, IM, or IV. Various dosing schedules have been developed. In one schedule, the drug is administered once a week as a single large dose (10 to 25 mg). In another schedule, three smaller doses (2.5 to 5 mg) are administered at 12-hour intervals; this dosing sequence is repeated weekly. Regardless of the schedule chosen, dosage must be individualized.

Acitretin

Acitretin [Soriatane] is the principal active metabolite of etretinate, a highly toxic drug that has been withdrawn. The major difference between the two drugs is pharmacokinetic: Whereas etretinate has a very long half-life (120 days), the half-life of acitretin is much shorter (only 49 hours). Accordingly, acitretin is cleared from the body much faster than etretinate. Although acitretin is less dangerous than etretinate, it still can cause serious harm, especially injury to the liver and developing fetus.

Mechanism of Action. Acitretin acts on epithelial cells to inhibit keratinization, proliferation, and differentiation. These actions probably contribute to its beneficial effects. Benefits may also derive from anti-inflammatory and immunomodulatory actions.

Therapeutic Use. Acitretin is indicated for severe psoriasis, including erythrodermic and generalized pustular types. Efficacy is equivalent to that of etretinate. In clinical trials, the drug produced a 60% to 70% reduction in the severity and area of symptoms. The relapse rate was 40% at 12 weeks after termination of treatment. Because side effects are very common and sometimes severe, acitretin should be reserved for patients who have not responded to safer drugs.

Pharmacokinetics. Administration is oral, and absorption is enhanced by food. In the blood, acitretin is 99.9% bound to plasma proteins. The drug undergoes extensive metabolism followed by excretion in the urine and bile. Its half-life is 49 hours. If taken with alcohol, acitretin will be converted to etretinate.

Adverse Effects. Adverse effects are very common. Hair loss and skin peeling occur in 50% to 75% of patients. Other dermatologic effects (dry skin, nail disorders, pruritus) occur in 25% to 50% of patients. Mucous membranes are affected, causing rhinitis (25% to 50%), inflammation of the lips (25% to 50%), dry mouth (10% to 25%), nosebleed (10% to 25%), and gingival bleeding, gingivitis, and stomatitis (1% to 10%). Other common reactions include erythematous rash (10% to 25%), bone and joint pain (10% to 25%), spinal hyperostosis (10% to 25%), dry eyes (10% to 25%), and paresthesias (10% to 25%). In addition, acitretin can elevate plasma triglycerides and reduce levels of HDL cholesterol (good cholesterol). Signs of liver damage (elevation of aminotransferase activity) develop in one-third of patients, but normally resolve when treatment is stopped.

Drug Interactions. Alcohol promotes conversion of acitretin to etretinate, and can thereby greatly prolong the risk of teratogenic effects (see below). Accordingly, women of child-bearing age should be warned against drinking alcohol. Acitretin can reduce the efficacy of progestin-only oral contraceptives, and hence other forms of contraception are preferred. Because acitretin is a derivative of vitamin A, combining it with vitamin A supplements may pose a risk of vitamin A toxicity. Both acitretin and tetracycline can cause pseudotumor cerebri (intracranial hypertension), therefore combining the drugs is not recommended. In addition, acitretin should not be combined with methotrexate and other drugs that can damage the liver.

Contraindication: Pregnancy. Acitretin is embryotoxic and teratogenic, and therefore must not be used during pregnancy. The drug is classified in FDA Pregnancy Risk Category X: The risks of use during pregnancy clearly outweigh any possible benefits. Major human fetal abnormalities that have been reported include encephalocele (hernia of the brain through a skull defect), reduced cranial volume, facial malformation, cardiovascular defects, absence of terminal phalanges, and malformations of the hip, ankles, and forearms.

Before acitretin is given to women of reproductive age, pregnancy should be ruled out and two reliable methods of contraception implemented. Contraception should be initiated at least 1 month prior to treatment and should continue for at least 3 years after treatment has ceased. Women should be thoroughly counseled about the potential for fetal harm. If pregnancy occurs, acitretin should be discontinued immediately, and termination of pregnancy should be considered.

Preparations, Dosage, and Administration. Acitretin [Soriatane] is available in 10- and 25-mg capsules for oral dosing. The dosage for psoriasis is 25 or 50 mg once daily, taken with a meal to facilitate absorption. As a rule, administration should cease when lesions have sufficiently resolved.

Cyclosporine

Cyclosporine [Neoral, Sandimmune, Gengraf] is a powerful immunosuppressant that inhibits proliferation of B cells and T cells. In patients with psoriasis, the drug produces rapid improvement. Unfortunately, cyclosporine can cause kidney damage and other serious harm, and hence should be used only after safer drugs have failed. The basic pharmacology of cyclosporine is presented in Chapter 69 (Immunosuppressants).

Systemic Drugs for Psoriasis: Biologic Agents

Like the conventional systemic drugs, the biologic agents are reserved for patients with moderate to severe psoriasis that has not responded to other treatments. In the United States, five biologic agents are available. One of these drugs—alefacept—decreases the activity of T cells. Three others—etanercept, infliximab, and adalimumab—block tumor necrosis factor (TNF). The fifth drug—ustekinumab—inhibits interleukin-12 (IL-12) and interleukin-23 (IL-23). All five drugs suppress immune function, and thereby increase the risk of serious infection. However, these drugs don't cause the serious acute toxicities—hepatotoxicity and nephrotoxicity—seen with the conventional systemic drugs. All of the biologic agents are administered by injection.

Alefacept, a T-Cell Antagonist

Alefacept [Amevive], approved in January 2003, was the first biologic therapy for psoriasis. The drug is moderately effective, and has produced prolonged remission in some patients. Alefacept causes few immediate adverse effects, but over time may increase the risk of serious infections and perhaps cancer. Although alefacept is fairly effective, it is also expensive (treatment costs \$12,000 or more a year) and inconvenient (treatment requires IM injections and weekly blood tests), and possible long-term toxicity is still unclear. Another T-cell antagonist—*efalizumab* [Raptiva]—was withdrawn in 2009, owing to a risk of progressive multifocal leukoencephalopathy (PML).

Actions and Therapeutic Use. Alefacept reduces the number and activity of memory CD4+ T lymphocytes, which are the principal mediators of inflammation in psoriasis. Benefits take about 2 months to develop, and correlate directly with reduced T-cell counts. Alefacept is approved for adults with moderate to severe psoriasis. In one trial, two courses of IV therapy reduced symptom intensity by 50% or more in 71% of patients, and by 75% or more in 40% of patients. Response duration ranged from about 7 months to more than 12 months. Alefacept has not been compared directly with conventional systemic agents (eg, methotrexate, acitretin).

Adverse Effects. The most common adverse effect is chills, which develop in about 6% of patients receiving alefacept IV (versus 1% of patients receiving IV placebo). Less common effects are pharyngitis, dizziness, cough, pruritus, myalgia, chills, inflammation, and injection-site pain.

Alefacept produces a dose-dependent decrease in circulating T cells, and can thereby cause *lymphopenia*, a condition that increases the risk of *infection*. Accordingly, alefacept should be avoided in patients with clinically important infections, and should be used with caution in patients with chronic infection or a history of recurrent infection. If a serious infection develops, the drug should be discontinued. To minimize infection risk, CD4+ T lymphocyte counts must be monitored (see below).

Alefacept may increase the risk of *cancer*. In studies with monkeys, the drug was associated with B-cell hyperplasia and B-cell lymphoma. In one clinical trial, the incidence of malignancy was 1.3% in patients receiving alefacept, versus 0.5% in those receiving placebo. Alefacept should be avoided in patients with a history of systemic malignancy, and should be discontinued if malignancy develops.

Alefacept is contraindicated for people with HIV infection. Why? Because HIV and alefacept both decrease CD4+ T-cell counts. Hence, there is concern that alefacept may accelerate progression of HIV disease.

Drug Interactions. There have been no formal studies on the interaction of alefacept with other drugs. However, common sense dictates that alefacept not be combined with other drugs that reduce T-cell number.

Monitoring. Counts of CD4+ T cells must be determined at baseline and before each alefacept dose. If the count is below 250 cells/mL, dosing should be postponed. If the count remains below 250 cells/mL for more than 1 month, alefacept should be discontinued.

Preparations, Dosage, and Administration. Alefacept [Amevive] is supplied as a 15-mg powder to be reconstituted with the supplied diluent for IM administration. The initial dosing schedule is 15 mg once a week for 12 weeks. If needed, the 12-dose series can be repeated—but no sooner than 12 weeks after completing the first series, and provided T-cell counts are in the normal range. There is no experience with giving a third series.

Tumor Necrosis Factor Antagonists

Drugs that inhibit tumor necrosis factor (TNF) can suppress immune function, and can thereby reduce inflammation in psoriasis. Three TNF antagonists are approved for the disease: *adalimumab* [Humira], *etanercept* [Enbrel], and *infliximab* [Remicade]. These drugs are very effective and have become first-line treatments for moderate to severe psoriasis. When compared with methotrexate in a 4-month study, one of these drugs—adalimumab—was more effective and less toxic. However, since the duration of this study was relatively short, and since psoriasis requires treatment lifelong, we don't know which drug would prove safer in actual practice. Furthermore, because of their immunosuppressant actions, the TNF antagonists pose a risk of serious opportunistic infections, and possibly cancer. Dosages for psoriasis are as follows: adalimumab, 80 mg subQ initially, then 40 mg subQ weekly thereafter; etanercept, 25 mg subQ twice a week; and infliximab, 3 mg/kg, infused IV over 2 or more hours, on days 0, 2, and 6, and then once every 8 weeks thereafter. The basic pharmacology of the TNF antagonists is presented in Chapter 73 (Drug Therapy of Rheumatoid Arthritis).

Ustekinumab, an Interleukin Antagonist

Actions and Uses. Ustekinumab [Stelara] is a first-in-class interleukin antagonist. In 2009, the drug was approved for adults with moderate to severe plaque psoriasis. Benefits derive from blocking the actions of interleukin-12 and interleukin-23, cytokines that promote inflammatory responses, immune responses, and overproduction of skin cells. Interleukin-12 and -23 work in part by promoting the differentiation of CD4+ T lymphocytes into helper T cells, essential components of the immune system. Ustekinumab is very effective: About two-thirds of patients experience at least a 75% reduction in symptoms. Furthermore, in a trial comparing ustekinumab with etanercept (a TNF antagonist), more patients responded to ustekinumab. Like the other biologic therapies for psoriasis, ustekinumab is administered by injection. However, since injections are made just once every 12 weeks, ustekinumab is more convenient than the other agents.

Adverse Effects. Ustekinumab is generally well tolerated. In short-term clinical trials, adverse effects were usually mild and self-limited, and their incidence was no greater than with placebo. However, because ustekinumab suppresses immune function, it may pose a risk of serious infection and cancer (just like the TNF antagonists and T-cell antagonists). Accordingly, patients should be checked for latent tuberculosis before starting treatment, and should be advised to report serious infections that develop during treatment. Since experience with ustekinumab is limited, long-term safety is unknown.

Preparations, Dosage, and Administration. Ustekinumab [Stelara] is supplied in solution (45 mg/0.5 mL, 90 mg/mL) for subQ injection. Dosage depends on body weight. For adults who weigh 100 kg or less, dosing consists of 45 mg on days 1 and 28, followed by 45 mg every 12 weeks thereafter. For adults who weigh more than 100 kg, dosing consists of 90 mg on days 1 and 28, followed by 90 mg every 12 weeks thereafter. At this time, ustekinumab must be administered by a healthcare provider. The drug is not approved for self-injection by patients.

Phototherapy

Coal Tar Plus Ultraviolet B Irradiation

This procedure involves sequential treatment with coal tar followed by UV radiation. In the first step, affected regions are covered with 1% coal tar ointment for 8 to 10 hours, after which the coal tar is washed off. In the second step, the area is exposed to short-wave UV radiation (ultraviolet B, UVB). This procedure is very safe and produces remission in 80% of patients. Unfortunately, treatment is expensive and time consuming (up to 30 treatments are needed), and patients dislike being coated with smelly coal tar.

Photochemotherapy (PUVA Therapy)

Photochemotherapy combines the use of long-wave UV radiation (ultraviolet A, UVA) with *methoxsalen*, an orally administered photosensitive drug. Methoxsalen belongs to a chemical family known as *psoralens*. In response

to UVA light shined on the skin, methoxsalen is thought to undergo a photochemical reaction with DNA, resulting in the formation of a DNA-psoralen complex. This alteration in DNA structure is thought to underlie the ability of photochemotherapy to decrease proliferation of epidermal cells. Adverse effects associated with the procedure include pruritus, nausea, and erythema. In addition, the process may accelerate aging of the skin and may increase the risk of skin cancer. Photochemotherapy is indicated for patients with extensive, active psoriasis who have not responded adequately to more conventional therapy. An alternative name for photochemotherapy is *PVU therapy* (PVU is an abbreviation derived from *psoralen* and *ultraviolet A*).

DRUGS FOR ACTINIC KERATOSES

Actinic keratoses (AKs) are rough, scaly, red or brown papules caused by chronic exposure to sunlight. Lesions typically develop on the face, scalp, forearms, and backs of the hands. A small percentage (0.25% to 1% per year) evolve into squamous cell carcinoma. However, although the *percentage* is small, the *absolute amount* is large: In the United States, nearly half of all skin cancers (about 500,000 cases) begin as AKs. AK treatment consists of topical drugs—fluorouracil, diclofenac, imiquimod, and aminolevulinic acid—and physical interventions: cryotherapy, curettage, excision, and laser resurfacing. Of these options, cryotherapy (freezing with liquid nitrogen) is used most, owing to its speed, simplicity, and effectiveness.

Fluorouracil

The basic pharmacology of fluorouracil [Carac, Fluoroplex, Efudex[®]] is discussed in Chapter 102 (Anticancer Drugs I: Cytotoxic Agents). Discussion here is limited to treatment of dermatologic disorders.

Actions and Uses in Dermatology. Fluorouracil is indicated for topical treatment of *multiple actinic keratoses* and *superficial basal cell carcinoma*. Cytotoxic effects result from disruption of DNA and RNA synthesis. A course of topical treatment elicits the following sequence of responses: (1) mild inflammation; (2) severe inflammation, often with burning, stinging, and vesicle formation; (3) tissue disintegration, characterized by erosion, ulceration, and necrosis; and (4) healing. Although fluorouracil is only applied for 2 to 6 weeks, the events just described may require 3 or more months for completion. Treatment is effective in over 90% of those who can tolerate a full course.

Adverse Effects. Among the more frequent reactions are itching, burning, rash, inflammation, and increased sensitivity to sunlight. Intense, burning pain develops occasionally. Darkening of the skin is rare. Absorption is insufficient to cause systemic toxicity.

Preparations and Administration. Topical fluorouracil is available under three trade names: *Carac* (microspheres in a 0.5% cream), *Fluoroplex* (1% cream), and *Efudex*[®] (5% cream). *Carac* is applied once daily; *Efudex* and *Fluoroplex* are applied twice daily. Treatment should continue until a stage-three response (tissue disintegration) develops, usually within 2 to 6 weeks. Complete healing may not occur for another 1 to 2 months.

Diclofenac Sodium

Diclofenac sodium [Solaraze], in a 3% gel, was the first nonsteroidal anti-inflammatory drug (NSAID) approved for topical use. The only indication for Solaraze is AK.* Topical diclofenac is better tolerated than fluorouracil, but is less effective and treatment takes longer. In clinical trials, twice-daily application for 60 to 90 days produced complete clearing in 50% of patients. The mechanism underlying benefits is unknown. The most common side effects are dry skin, itching, redness, and rash at the application site. Diclofenac may sensitize the skin to UV radiation, and hence patients should avoid sunlamps and minimize exposure to sunlight. Systemic absorption is low (10%), and therefore the risk of GI injury is much less than with oral diclofenac and other NSAIDs.

Imiquimod

Imiquimod cream [Aldara, Zyclara], originally developed for venereal warts (see below), was approved for AK in 2004. Benefits derive from stimulating innate and cell-mediated immunity. Imiquimod requires a prescription, but is applied at home. Imiquimod is better tolerated than fluorouracil, but less effective, causing complete clearance in only 45% of patients, compared with 90% for fluorouracil. Also, treatment takes much longer (16 weeks vs. 2 to 6 weeks with fluorouracil). In clinical trials, 33% of patients experienced local reac-

tions: redness, swelling, sores, blisters, itching, burning, scabbing, and crusting. Of note, lesion clearance correlated with the intensity of side effects, suggesting that an inflammatory reaction is needed to produce a clinical response. Imiquimod increases sensitivity to UV radiation, and hence patients should minimize sun exposure, use a sunscreen, and wear protective clothing. For treatment of actinic keratoses, imiquimod is available in three formulations, a 2.5% cream [Zyclara], a 3.75% cream [Zyclara], and a 5% cream [Aldara].

Aminolevulinic Acid Plus Blue Light

Topical aminolevulinic acid [Levulan Kerastick], in conjunction with blue light photoactivation, is an alternative therapy for AKs of the face and scalp. Treatment takes place in two steps. First, the prescriber applies a 20% solution of aminolevulinic acid to AK lesions. Fourteen to 18 hours later, the prescriber photoactivates the drug by exposing lesions to 1000 seconds of blue light, using the Blu-B Blue Light supplied by the manufacturer. In clinical trials, 66% of patients experienced complete clearing by 8 weeks after a single treatment, and 77% of patients experienced clearing of 75% or more. The mechanism underlying benefits is complex and incompletely understood. Local effects—burning, stinging, redness, and edema—occur in nearly all patients. Because aminolevulinic acid is light sensitive, patients should protect treated areas from exposure to sunlight and bright indoor light prior to blue light exposure. The best protection is a wide-brimmed hat; sunscreens won't help.

DRUGS FOR ATOPIC DERMATITIS (ECZEMA)

Atopic dermatitis, also known as eczema, is a chronic inflammatory skin disease seen primarily in children. The condition is characterized by dry, scaly skin and intense pruritus that often leads to scratching and rubbing, which in turn can lead to erythema, abrasions, rash, erosions with an exudate, and increased susceptibility to skin infection. The underlying cause is abnormal activity of T lymphocytes. First-line therapy consists of *moisturizers* (eg, Cetaphil Moisturizing Cream, Eucerin Original Cream) and *topical glucocorticoids*. Unfortunately, the glucocorticoids can cause skin atrophy, hypopigmentation, telangiectasis (permanent focal red lesions), and, in high doses, possible systemic effects, including adrenal suppression. If topical glucocorticoids are insufficient, patients may be treated with a *topical immunosuppressant* (see below). A *sedating antihistamine* can help control itching and can facilitate sleeping at night.

Topical Immunosuppressants

Two topical immunosuppressants—tacrolimus and pimecrolimus—are approved for atopic dermatitis. Both drugs are *calcineurin inhibitors* (see Chapter 69). Although effective against atopic dermatitis, both drugs may pose a risk of skin cancer and lymphoma. Because of this potential for serious harm, tacrolimus and pimecrolimus are considered second-line drugs for atopic dermatitis, and should be reserved for patients who have not responded to glucocorticoids.

Tacrolimus Ointment. Tacrolimus [Protopic], available as Prograf for preventing organ transplant rejection (see Chapter 69), is available as an ointment for moderate to severe atopic dermatitis. The drug relieves symptoms by attenuating local immune responses. Specifically, the drug inhibits calcineurin, and thereby suppresses the activity of T cells and decreases the release of inflammatory mediators from cutaneous mast cells and basophils. The result is reduced inflammation.

Systemic absorption of topical tacrolimus is low, and gets even lower as the skin heals. Absolute bioavailability is less than 0.05%. Blood levels of tacrolimus are usually low.

Tacrolimus ointment is generally well tolerated. The most common side effects are erythema, pruritus, and burning sensations at the application site. As the skin heals, these local reactions abate. In children, tacrolimus may increase the risk of varicella-zoster virus infection. Adverse effects associated with *systemic* tacrolimus (nephrotoxicity, neurotoxicity, hypertension, diarrhea, nausea) have not occurred with topical therapy. Unlike topical glucocorticoids, tacrolimus does not cause thinning of the skin.

There is concern that tacrolimus may pose a risk of *cancer*. The drug increases the incidence of skin cancer in laboratory animals exposed to UV light. In mice, tacrolimus increases the incidence of lymphoma. There have been reports of skin cancer and lymphoma in humans, although a causal relationship has not been established. To reduce any risk of skin cancer, patients should protect treated areas from direct sunlight, and should avoid sunlamps and tanning beds.

Tacrolimus ointment [Protopic] is available in two concentrations: 0.03% and 0.1%. Adults may use either formulation; children ages 2 years to

*Two other topical formulations of diclofenac, sold as Voltaren Gel and Flector, are available to relieve musculoskeletal pain (see Chapter 71).

16 years should use the 0.03% formulation; and children under 2 years should not use the drug. All patients should apply a thin layer twice daily. Occlusive dressings should be avoided. Treatment should be intermittent or short term.

Pimecrolimus Cream. Pimecrolimus 1% cream [Elidel] is a topical immunosuppressant approved for mild to moderate atopic dermatitis. The drug is very similar to tacrolimus with regard to mechanism, therapeutic effects, and adverse effects. In clinical trials, twice-daily application for 3 weeks reduced signs and symptoms of eczema by 72%. Initial improvement could be seen in 2 days. Pimecrolimus may be less effective than topical glucocorticoids. Although studies comparing pimecrolimus directly with tacrolimus have not been done, clinical efficacy of the drugs appears similar.

Pimecrolimus is generally well tolerated. The most common adverse effects are erythema, pruritus, and burning sensations at the application site, especially during the first few days of treatment. As with tacrolimus, there have been reports of skin cancer and lymphoma, but a causal relationship has not been established. Like tacrolimus, pimecrolimus sensitizes the skin to UV light, and hence patients should use a sunscreen and should limit exposure to natural and artificial sunlight. Systemic absorption of pimecrolimus is minimal; in clinical trials, blood levels were at or below the limit of detection. As with tacrolimus, prolonged treatment should be avoided.

AGENTS USED TO REMOVE WARTS

Warts are small, benign tumors that form in the skin and mucous membranes. They are caused by infection of squamous epithelial cells with human papillomavirus (HPV), of which there are roughly 100 types. Most warts resolve spontaneously within a few months, but some can last for years. Discussion below focuses primarily on management of venereal warts.

Venereal Warts

Venereal warts form around the cervix, vulva, urethra, glans penis, and anus and anal canal. The majority are caused by two types of HPV, known as HPV-6 and HPV-11. Two other types—HPV-16 and HPV-18—are responsible for most cervical cancers. As discussed in Chapter 68 (Childhood Immunization), an HPV vaccine, sold as *Gardasil*, can protect against all four HPV types, and hence can help prevent venereal warts as well as cancer of the cervix. Another HPV vaccine, sold as *Cervarix*, only protects against HPV-16 and 18, and hence can help prevent cervical cancer but not venereal warts.

Infection with HPV can be transmitted by sexual contact. Individuals with anogenital warts should be warned that they can transmit the infection to sexual partners. Partners of infected individuals should be examined for warts. Using a condom can reduce the risk of transmission.

Genital warts can be removed in two basic ways: with *topical drugs* or with *physical measures*: cryotherapy (freezing), electrodesiccation, laser surgery, and conventional surgery. Physical measures are much faster than drugs but also more painful. Neither approach—drugs or physical measures—can eradicate the virus. Hence, even after successful wart removal, the virus remains. Treatments for genital warts are summarized in Table 105-5.

The drugs used to remove venereal warts can be divided into two groups: agents that must be administered by a healthcare provider and agents that can be applied at home. With both groups, application is done repeatedly until the warts disappear. Provider-applied drugs are *podophyllin*, *trichloroacetic acid*, and *bichloroacetic acid*. Drugs for home application are *podofilox*, *imiquimod*, and *kunecatechins*. All of these drugs act slowly, and they all cause local irritation. The pharmacology of six topical drugs is discussed below.

Provider-Applied Drugs

Podophyllin. Podophyllin (podophyllum resin) [Podocon-25, Podofin] is used primarily for perianal and venereal warts. The drug is not very effective against common warts. Podophyllin is a mixture of resins from the May apple or mandrake (*Podophyllum peltatum* Linne). The active ingredient in the resin is *podophyllotoxin*, a compound that inhibits DNA synthesis and mitosis. These actions eventually lead to cell death and erosion of warty tissue. Formulations employed to remove warts contain 25% podophyllum resin. These preparations are highly caustic and should be applied only by a trained clinician. To minimize the risk of toxicity from systemic absorption, the resin should be washed off with alcohol or soap and water a few hours after application. Each treatment should be limited to a small surface area and to a small number of warts.

Podophyllin can be absorbed in amounts sufficient to cause systemic toxicity. Potential reactions include central and peripheral neuropathy, kidney damage, and blood dyscrasias. These effects are most likely when the drug is

TABLE 105-5 • Treatment and Prevention of Venereal Warts

Treatment	
External Genital	<i>Patient administered:</i> Podofilox 0.5% solution or gel (topical) or Imiquimod 3.75% or 5% cream (topical) or Kunecatechins (Sinecatechins) 15% ointment (topical)
	<i>Provider administered:</i> Cryotherapy with liquid nitrogen or cryoprobe or Podophyllin 10%–25% (topical) or TCA or BCA 80%–90% (topical) or Surgical excision
Anal	Cryotherapy with liquid nitrogen or TCA or BCA (80%–90%) applied to warts or Surgical excision
Vaginal	Cryotherapy with liquid nitrogen or TCA or BCA (80%–90%) applied to warts
Urethral Meatus	Cryotherapy with liquid nitrogen or Podophyllin resin 10%–25% (topical)
Prevention	
All Sites	<i>Gardasil</i> vaccine; protects against HPV-6 and HPV-11, which cause 90% of venereal warts, as well as HPV-16 and HPV-18, which cause 70% of cervical cancers

BCA = bichloroacetic acid, TCA = trichloroacetic acid.

applied to large areas in excessive amounts. Podophyllin is teratogenic and must not be used during pregnancy.

Podophyllin is supplied in a 25% solution for topical use. Application should be limited to small areas. The drug should not be applied to moles or birthmarks, nor should it be applied to warts that are bleeding or friable (easily crumbled) or that have undergone recent biopsy. When used to remove venereal warts, podophyllin should be washed off 1 to 4 hours after application. Treatment may be repeated at weekly intervals for up to 4 weeks.

Bichloroacetic Acid (BCA) and Trichloroacetic Acid (TCA). When applied in high concentration (80% to 90%), BCA and TCA can destroy warts by chemical coagulation. Application is repeated weekly if needed. Solutions of these acids are very watery, and hence can easily spread to and thereby injure surrounding tissue. To minimize spread, the solution should be allowed to dry before the patient sits or stands. If pain develops, BCA and TCA can be neutralized with liquid soap or sodium bicarbonate (baking soda). If too much solution is applied, it should be neutralized with soap or sodium bicarbonate, or removed by applying talc.

Patient-Applied Drugs

Patient-applied drugs are used for topical therapy of external genital and perianal warts. Like podophyllin, these drugs require a prescription. Because they are applied at home, these drugs are more convenient than the provider-applied drugs.

Imiquimod. Imiquimod cream [Aldara, Zyclara] stimulates production of interferon alpha, tumor necrosis factor, and several interleukins, and thereby intensifies immune responses to HPV, the virus that causes venereal warts. Imiquimod has no direct antiviral effects of its own. Principal adverse effects are erythema, erosion, and flaking at the site of administration. Local itching, burning, and pain may occur too. Imiquimod undergoes minimal absorption, and hence systemic effects are usually absent.

Imiquimod cream is available in two formulations, a 3.75% cream sold as Zyclara, and a 5% cream sold as Aldara. Zyclara is applied once a day for up to 8 weeks; Aldara is applied 3 times a week for up to 16 weeks. Both formulations are applied at bedtime and washed off in the morning. Imiquimod use for actinic keratoses is discussed above.

Podofilox. Like podophyllin, podofilox [Condylox] inhibits mitosis. Whether this action underlies beneficial effects (erosion of warty tissue) is

unknown. Podofilox is supplied as a 0.5% gel or 0.5% solution to be applied twice daily for 3 consecutive days followed by 4 days off. This pattern is repeated 4 times or until the warts are gone—whichever comes first. Patients should wash their hands before and after applying the drug. However, unlike imiquimod, podofilox needn't be washed from the site of application. Treatment frequently causes local inflammation, burning, erosion, pain, itching, and bleeding. These can be minimized by limiting the application area to 10 cm², applying no more than 0.5 gm/day, and avoiding application to normal skin. Podofilox causes more discomfort than imiquimod, but works faster and costs less.

Kunecatechins (Sinocatechins) Ointment. Kunecatechins [Veregen] is made by extraction from the leaves of *Camellia sinensis* (green tea). The primary active component in this extract is epigallocatechin, a compound in the catechin family. The extract also contains small amounts of gallic acid and three methylxanthines: caffeine, theophylline, and theobromine. Although the mechanism of action has not been determined, possibilities include antioxidative effects, induction of apoptosis (programmed cell death), and inhibition of telomerase (an enzyme cells use to extend the telomere cap on DNA). Kunecatechins is supplied as a 15% ointment to be applied 3 times daily until all warts clear, or for 16 weeks, whichever comes first. In one trial, treatment for 16 weeks produced complete wart removal in 53.6% of patients, compared with 35.3% in those treated with placebo. Adverse effects, which are common, include erythema (70%), pruritus (69%), burning (67%), pain (56%), erosion or ulceration (49%), edema (45%), induration (35%), and rash (2%). Moderate reactions develop in 37% of patients, and severe reactions develop in 30%. Kunecatechins should not be applied to the vagina, rectum, or open wounds. Patients should avoid sexual contact while the ointment is present. Kunecatechins is not recommended for HIV-infected patients, immunocompromised patients, or patients with genital herpes infection. Why? Because safety and efficacy in these patients has not been established.

Common Warts

Common warts—also known as verruca vulgaris—manifest as hard, rough, horny nodules. These benign lesions may appear anywhere on the body, but are most common on the hands and feet. The majority of common warts are caused by just three types of HPV, known as HPV-1, HPV-2, and HPV-3.

Like venereal warts, common warts may be removed by physical procedures and with topical drugs. The physical methods are cryotherapy, electrodesiccation (destruction with an electric current), curettage (surgical removal with a loop-shaped cutting tool), and laser therapy. Pharmacologic agents include salicylic acid, podophyllin, podofilox, imiquimod, trichloroacetic acid, and topical fluorouracil.

ANTIPERSPIRANTS AND DEODORANTS

Perspiration is produced by two types of sweat glands: *eccrine glands* and *apocrine glands*. The eccrine glands secrete profuse, watery perspiration. The apocrine glands secrete a small volume of fluid rich in organic compounds. The unpleasant odor associated with sweating results from chemical and bacterial degradation of the compounds in apocrine sweat. Eccrine glands contribute to odor by creating a moist environment that favors bacterial growth. Perspiration odor can be reduced with *antiperspirants* (agents that decrease flow of eccrine sweat) and *deodorants* (antiseptics that suppress growth of skin-dwelling bacteria).

Antiperspirants. The principal compounds employed as antiperspirants are *aluminum chlorohydrate*, *aluminum chloride*, and *buffered aluminum sulfate*. These agents can decrease flow of eccrine sweat by 20% to 50%. Reduced flow appears to result from inhibition of sweat production and from partial occlusion of sweat glands. Topical antiperspirants can cause stinging, burning, itching, and irritation. Dermatitis and ulceration occur rarely.

Severe sweating can be reduced with *botulinum toxin type A* [Botox], the same drug used to smooth facial wrinkles (Box 105-1). Botulinum toxin inhibits release of acetylcholine from sympathetic neurons that innervate sweat glands, and thereby reduces sweat volume. To treat axillary hyperhidrosis (severe underarm sweating), 10 to 15 intradermal injections (0.1 to 0.2 mL) are made into each armpit. The needle employed is very fine (30 gauge) to minimize discomfort. One set of injections can markedly decrease sweating for 6 or more months.

Deodorants. Deodorants inhibit growth of the surface bacteria that degrade components of apocrine sweat into malodorous products; deodorants do not suppress sweat formation. Agents employed as deodorants include *carbanilide*, *triclocarban*, and *triclosan*. These antiseptics are the active ingredients in deodorant soaps, such as Dial, Lifebuoy, Safeguard, and Zest.

DRUGS FOR SEBORRHEIC DERMATITIS AND DANDRUFF

Seborrheic dermatitis is a chronic, relapsing condition characterized by inflammation and scaling of the scalp and face. Skin of the underarms, chest, and anogenital region may also be affected. Symptoms result from an inflammatory reaction to infection with *Pityrosporum ovale*, a microbe in the yeast family.

Symptoms respond rapidly to topical treatment with *ketoconazole*, an antifungal drug with activity against yeast (see Chapter 92). For treatment of seborrhea, ketoconazole is available in a 2% cream [Kuric, Ketoderm[®]], 2% foam [Extina], 2% gel [Xolegel], and 1% and 2% shampoos [Nizoral]. The cream and foam formulations are applied twice daily for 4 weeks. The gel is more convenient, being applied just daily and for only 2 weeks. Concurrent use of topical glucocorticoids can accelerate initial responses. Once the yeast infection has been controlled, remission can be maintained by periodic use of a shampoo that contains a yeast-suppressing drug, such as *ketoconazole* (in Nizoral), *pyrithione zinc* (in Head & Shoulders), or *selenium sulfide* (in Selsun Blue and Head & Shoulders Intensive Treatment).

DRUGS FOR HAIR LOSS

Two drugs are available to promote hair growth: minoxidil and finasteride. Minoxidil is applied topically; finasteride is taken orally. Neither drug was originally developed for baldness: Minoxidil was developed for hypertension, and finasteride for benign prostatic hyperplasia.

Topical Minoxidil

Minoxidil is a direct-acting vasodilator used primarily to treat severe hypertension. The drug's basic pharmacology is discussed in Chapter 46. Consideration here is limited to its use against patterned hair loss in men and women.

Minoxidil for baldness is available in three formulations, a 2% solution (generic only), a 5% solution [Rogaine Extra Strength for Men], and a 5% foam [Rogaine Men's Extra Strength]. All formulations are approved for men, but only the 2% solution is approved for women. Nonetheless, all formulations are routinely prescribed for women. All formulations are applied to the scalp twice a day.

The mechanism by which minoxidil promotes hair growth is unknown. One possibility is that it causes resting hair follicles to enter a state of active growth. Improved cutaneous blood flow secondary to vasodilation does not seem to be involved.

Minoxidil can retard loss of hair and stimulate hair growth. Benefits take several months to develop. Unfortunately, response rates are somewhat disappointing: Only about one-third of patients experience significant restoration of hair to regions of baldness. Hair regrowth is most likely when baldness has developed recently and has been limited to a small area. Responses with the 5% solution are only 50% greater than with the 2% solution. When minoxidil is discontinued, newly gained hair is lost in 3 to 4 months, and the natural progression of hair loss resumes. In some cases, beneficial effects may decline even with uninterrupted treatment.

Topical minoxidil is generally devoid of adverse effects. A few patients have reported pruritus and local allergic responses (eg, rash, swelling, burning sensation). Absorption is low, and hence systemic reactions (eg, hypotension, headache, flushing) are rare.

Finasteride

Finasteride is an oral drug with two indications: androgenic alopecia (male-pattern baldness) and benign prostatic hyperplasia (BPH). For treatment of androgenic alopecia, finasteride is sold in 1-mg tablets under the trade name *Propecia*. For treatment of BPH, the drug is sold in 5-mg tablets under the trade name *Proscar* (see Chapter 66).

Male-pattern baldness is caused by dihydrotestosterone (DHT), a powerful androgenic hormone formed from testosterone. In balding men, the scalp has high levels of DHT, which act on hair follicles to induce shrinkage. Finasteride promotes hair growth by inhibiting the enzyme that converts testosterone into DHT. A 1-mg dose reduces serum levels of DHT by 65% after 24 hours. In the prostate gland, levels of testosterone increase by sixfold (because conversion of testosterone into DHT has been suppressed).

Regrowth of hair with finasteride is very modest. The drug has been evaluated in men 18 to 41 years old. Only 50% grew any hair. Furthermore, even when hair growth did occur, the amount was small: One year of treatment with 1 mg/day increased hair count by only 12% (in a 5.1-cm² circle on the scalp, the average hair count rose by 107 hairs, up from a baseline of 867

FACE TIME WITH BOTOX

Frown ridges got you down? Brow lines make you whine? Don't mind injecting your face with a deadly poison? If you answered "Yes" to these questions, then you may be a candidate for Botox—the hottest thing in cosmetic medicine since the nose job. How hot? In 2001, over 1.6 million Americans underwent Botox treatment, making it the number 1 nonsurgical cosmetic procedure in the United States—and that was *before* the drug was approved for cosmetic use. By 2008, the number of procedures exceeded 2.5 million.

Why do people love Botox? Because it makes them look younger. By making facial lines go away. Without surgery. And it's cheaper and less traumatic than a face-lift.

Just what is Botox? Well, Botox is a trade name for *botulinum toxin type A*, a protein produced by the gram-negative bacterium *Clostridium botulinum*. And yes, Botox is the same powerful toxin that causes botulism, a potentially fatal condition brought on by eating foods contaminated with *C. botulinum*. (In case you're curious: Common signs and symptoms include double vision, dysphagia, generalized weakness, urinary retention, and respiratory impairment—all without any decrease in mentation. Death results from respiratory arrest secondary to paralysis of the muscles of respiration.) You're probably asking, "Can Botox do all of that?" Not really. The doses approved for cosmetic use are *much* too small to produce these widespread effects. However, if a *huge* dose were injected inadvertently, botulism could indeed result (see below).

How does Botox work? Botulinum toxin type A is a neurotoxin that acts on cholinergic neurons to block release of acetylcholine. Following injection, the drug is taken up by cholinergic nerve terminals, where it inactivates SNAP-25, a protein critical to the function of acetylcholine-containing vesicles. In the absence of SNAP-25, the vesicles are unable to fuse with the terminal membrane, and hence cannot release their acetylcholine. Restoration of neuronal function requires sprouting of new terminals, a process that can take several months. Botulinum toxin blocks transmission at neuromuscular junctions and at cholinergic synapses of the autonomic nervous system, including synapses in autonomic ganglia.

What are the cosmetic uses of Botox? On April 15, 2002, the Food and Drug Administration (FDA) approved Botox for reducing frown lines, known formally as "glabellar" lines (because they appear on the glabella—the smooth area located between your eyebrows, directly above your nose). At this time, reduction of frown lines is the only cosmetic use approved by the FDA. Nonetheless, Botox is also used widely to soften lines on the forehead and neck, and to diminish "crow's-feet" (lines that form near the outer corners of our eyes when we squint).

How is cosmetic Botox applied? With a needle. In the face. To be precise, to reduce frown lines, Botox is injected directly into the small muscles that produce a frown when they contract. Five injections are made, each consisting of 4 units of botulinum toxin in 0.1 mL of fluid. Two injections go into each corrugator muscle and one into the procerus muscle. The whole procedure takes just a few minutes. Discomfort can be reduced by pretreatment with a topical anesthetic cream.

What's the time course of Botox effects? Results are neither instantaneous nor permanent. Rather, muscle paralysis develops slowly—over 3 to 10 days—and then fades within 3 to 6 months. Botox injections may be repeated to maintain cosmetic benefits. However, at least 3 months should separate treatments. At this time, there are no data on long-term effects.

Does Botox have side effects? Of course—It's a drug, isn't it? The most common side effects are headache, respiratory infection, and a flu-like syndrome. Treatment may also cause facial pain, swelling, and bruising. Swelling and bruising can be reduced by applying ice to the site, and by avoiding alcohol, vitamin E, and aspirin (and related nonsteroidal anti-inflammatory drugs) for the week preceding treatment. There are no data on side effects with repeated use.

Injection into the wrong site, or diffusion from the right site into surrounding tissues, can weaken muscles that were not intended as targets, thereby causing multiple undesired effects. Ptosis (droopy eyelids) occurs in about 5% of patients, and can persist for 3 to 6 months. Injections in the lower face can result in drooling, an asymmetric smile, drooping mouth, and biting the inside of the cheek. Injections in the neck can make swallowing difficult and can change vocal pitch. In extreme cases, Botox has caused urinary incontinence, generalized muscle weakness, and breathing impairment. All of these problems can be reduced by taking steps to minimize Botox displacement. Accordingly, for at least 4 hours after the injections, patients should avoid lying down, rubbing the injection site, and washing their hair. Of course, it also helps to have Botox administered by a highly trained expert, preferably a dermatologist or plastic surgeon.

Excessive cosmetic doses can cause loss of facial expression. Patients can lose the ability to frown, raise their eyebrows, or squint. This may be fine if you're a professional poker player, but can be a disaster if you're an actor—or just an ordinary person who doesn't want to spend a few months projecting Buddha-like calm (rather than the anger you're really feeling because an incompetent physician froze your face).

Who should *not* use Botox? The drug should be avoided by women who are pregnant or breast-feeding, and by patients who may be allergic to human albumin, a protein in Botox preparations. In addition, Botox should be avoided by people using aminoglycoside antibiotics or any other agent that has neuromuscular blocking properties. The drug should be used with caution in patients with myasthenia gravis and other neuromuscular disorders that can intensify muscle paralysis. Lastly, Botox should be avoided by people over 65. Why? Because it's unlikely to help: In older people, the major cause of lines and wrinkles is loss of elasticity in the skin—a phenomenon that can't be reversed by neuromuscular blockade.

Over time, some patients develop antibodies against botulinum toxin type A. The only consequence is a reduction in Botox benefits. The risk of antibody production may be increased by using high doses and short dosing intervals. If antibodies do develop, patients may still respond to a product known as Myobloc, which consists of botulinum toxin type B (as opposed to botulinum toxin type A).

How is cosmetic Botox supplied? The drug is available as a powder in 100-unit vials under the name Botox. Immediately before use, the powder is reconstituted with 2.5 mL of preservative-free normal saline to form a clear, colorless solution. According to the package label, reconstituted botulinum toxin is unstable, and hence should be stored cold and used within 4 hours. However, there are data indicating that, if the drug is diluted in normal saline that contains the preservative benzyl alcohol, it retains its potency for 5 weeks—and causes less pain when injected.

How much does Botox cost? About \$300 to \$500 for each area treated (frown lines, forehead, crow's-feet, etc.). The cost to the doctor is about \$500 for a 100-unit vial—enough for five treatments. Although labeling prohibits using the same vial for more than one patient, this regulation is often disregarded, thereby saving money for patient and doctor alike.

In the United States, we have two licensed Botox products, sold as Botox and Botox Cosmetic. Botox Cosmetic is approved only for treating frown lines, whereas plain Botox is approved for treating cervical dystonia, strabismus, and other disorders (see below). However, except for the packaging, both Botox products are identical.

Patients should never ever allow a physician to inject them with an unlicensed botulin toxin product. Why? Because the result could be catastrophic. In 2004, four people became paralyzed with botulism after receiving cosmetic injections at a clinic in Oakland Park, Florida. Turns out the doc in charge wanted to boost profits. So, instead of using the Botox Cosmetic his patients had paid for, Doctor Greedy used a less expensive, highly concentrated preparation intended for laboratory use only. Which might have been OK, if Dr. G had diluted

the toxin properly. Which he hadn't. As a result, the amount of botulinum toxin his patients received was 2857 times the lethal dose. (The vial he used had enough toxin to kill over 14,000 people). Fortunately, all four patients survived, and Dr. G. was given a fat fine and sent to jail. The moral of the story? Select a doctor who doesn't need the biggest boat in the marina, and, just to be safe, be sure to see the vial your Botox is actually coming from.

Not Just a Pretty Face

Does botulinum toxin have any noncosmetic uses? Yes. And some precede its cosmetic use by more than a decade. In 1989, the FDA approved Botox for two ocular disorders: strabismus (misaligned eye, aka "lazy eye") and blepharospasm (involuntary, intermittent forced closure of the eyelid). In 2000, botulinum toxin type B was approved for cervical dystonia, a neurologic disorder characterized by painful, sustained contraction of muscles in the neck. In 2004, Botox was approved for primary axillary hyperhidrosis (excessive underarm sweating). And in 2010, Botox was approved for chronic migraine (injections are made into the scalp), and for spasticity in the flexor muscles of the elbow, wrist, and fingers. Unlabeled uses of botulinum toxins include drooling (injections are made into the parotid gland), spasmodic torticollis (clonic twisting of the head), hemifacial spasms (unilateral contraction of facial muscles in any combination), hand dystonia, hyperhidrosis of the palms, and overactive bladder syndrome. Licensed botulinum toxin products and their approved uses are shown in the table below.

A final note: Because botulinum toxin is the most powerful poison known, terrorists might use it as a weapon. This disturbing possibility is discussed in Chapter 110.

Approved Uses of Botulinum Toxin Products

	Botox Cosmetic	Botox	Dysport	Xeomin	Myobloc
Botulinum Toxin Type	A	A	A	A	B
Approved Uses					
Glabellar lines	✓		✓		
Cervical dystonia		✓	✓	✓	✓
Blepharospasm		✓		✓	
Strabismus		✓			
Migraine		✓			
Axillary hyperhidrosis		✓			
Upper limb spasticity		✓			

EFLORNITHINE FOR UNWANTED FACIAL HAIR

Eflornithine [Vaniqa] is an old drug with a new indication and new formulation. As discussed in Chapter 99, eflornithine has been available since 1990 for systemic therapy of African trypanosomiasis (sleeping sickness). Now, the drug is also available in a 13.9% cream, for use by women to remove facial hair. Topical eflornithine acts on cells in hair follicles to inhibit ornithine decarboxylase, an enzyme required for synthesis of polyamines, which in turn are required for cell division and subsequent hair growth.

hairs). In older men taking 5 mg/day to treat BPH, no hair growth has been reported.

At the dosage employed to treat baldness (1 mg/day), adverse effects are uncommon. About 4% of men experience reduced libido, erectile dysfunction, impaired ejaculation, and reduced ejaculate volume. Finasteride is a teratogen that can cause genitourinary abnormalities in males exposed to the drug *in utero*. Accordingly, women who are or may become pregnant should not take finasteride, nor should they handle tablets that are crushed or broken.

TABLE 105-6 ■ Some Antibiotics for Impetigo

Generic Name	Trade Name	Formulation	Dosage	
			Pediatric	Adult
Topical				
Mupirocin	Bactroban	Ointment, cream	Apply 3 times a day for 3–10 days	Apply 3 times a day for 3–10 days
Retapamulin	Altabax	Ointment	Apply 2 times a day for 5 days	Apply 2 times a day for 5 days
Oral				
Cephalexin	Keflex	Capsules, suspension	3 mg/kg 4 times a day	250 mg 4 times a day
Dicloxacillin	generic only	Capsules	6.25 mg/kg 4 times a day	250 mg 4 times a day
Clindamycin	Cleocin	Capsules, suspension	10–20 mg/kg/day in three doses	300–450 mg 3 times a day
Amoxicillin/ clavulanate	Augmentin	Tablets, suspension	12.5 mg amoxicillin twice daily	875 mg amoxicillin/ 125 mg clavulanate twice daily

In clinical trials, eflornithine cream was moderately effective in some women and had no effect in others. All subjects had beards or mustaches that required removal (by shaving, waxing, tweezing, etc.) at least twice a week. Participants were randomized to receive either (1) eflornithine cream twice a week or (2) the vehicle alone (ie, the cream without eflornithine). What happened? Substantial hair reduction occurred in 40% of treated women in one study and 20% of treated women in another, compared with a 10% response in women receiving the vehicle alone. Among the women who did respond, benefits developed slowly—over 4 to 8 weeks or more—and then faded entirely within 8 weeks of stopping treatment. It should be noted that eflornithine does not remove facial hair entirely. Rather, it retards hair growth, causes hair to be finer and lighter, and decreases (but does not eliminate) the need for shaving and other hair-removal procedures. Because effects are not permanent, continuous treatment is required.

Very little of topical eflornithine gets absorbed: about 1% of each dose reaches the systemic circulation. Absorbed drug is eliminated intact in the urine. No metabolism occurs.

Eflornithine cream is generally well tolerated—although there is some concern about possible fetal harm. The most common reactions are transient stinging, burning, tingling, or rash at the application site. Although eflornithine absorption is minimal, it may still be sufficient to cause fetal injury. In animal studies, there was no evidence that topical eflornithine is teratogenic or fetotoxic. However, of the 19 pregnancies that occurred during clinical trials, there were four spontaneous abortions and one birth defect (Down's syndrome). Until more is known, avoiding pregnancy would seem prudent.

Eflornithine is supplied in 30-gm tubes (a 2-month supply). Applications are made twice daily, 8 hours apart. Women should rub the cream in thoroughly and should not wash the treated area for at least 4 hours. Cosmetics and sunscreens can be applied as soon as the cream dries.

DRUGS FOR IMPETIGO

Impetigo is the most common bacterial infection of the skin. The usual pathogen is *Staphylococcus aureus*. Most cases are seen in children 2 to 5 years old, although all age groups are susceptible. Impetigo is highly contagious and usually spread by person-to-person contact. Fortunately, the infection is superficial, and usually self-limited.

Impetigo has two forms: bullous and nonbullous. Bullous impetigo is caused by a toxin from *Staph. aureus*, and manifests as rapidly spreading papules that may evolve into large, thin-walled vesicles. The usual location is a warm, moist area of the skin. Nonbullous impetigo, also known as crusted impetigo, is caused by *Staph. aureus* and/or *Streptococcus pyogenes*. This infection typically manifests as a single small macule or papule that evolves into a vesicle that oozes a yellow-brown exudate, which then dries into a honey-colored crust. The usual location is skin of the hands, feet, and legs. The majority (70%) of impetigo cases are nonbullous.

Impetigo is treated with antibiotics. Mild to moderate infection can be treated with topical agents. More serious infection is treated with oral agents. Dosages for representative antibiotics are summarized in Table 105-6.

LOCAL ANESTHETICS

Local anesthetics (eg, benzocaine, lidocaine, pramoxine) can be applied topically to relieve pain and itching associated with various skin disorders, including sunburn, plant poisoning, fungal infection, diaper rash, and eczema. Selection of a topical anesthetic is based on duration of action, desired vehicle (cream, ointment, solution, gel), and prior history of hypersensitivity reactions. The pharmacology of the local anesthetics is discussed in Chapter 26. Agents available for application to the skin are listed in Table 26-2.

KEY POINTS

- Topical glucocorticoids are employed to relieve inflammation and itching associated with a variety of dermatologic disorders.
- Preparations of topical glucocorticoids are classified into four potency groups: low, medium, high, and super-high.
- Prolonged use of topical glucocorticoids can cause atrophy of the dermis and epidermis.
- Topical glucocorticoids can be absorbed in amounts sufficient to cause systemic toxicity. Principal concerns are growth retardation and adrenal suppression.
- Keratolytic agents—salicylic acid, sulfur, and benzoyl peroxide—promote shedding of the horny layer of the skin.
- Topical antibiotics—benzoyl peroxide, clindamycin, and erythromycin—help clear mild to moderate acne by suppressing growth of *P. acnes*.
- Topical retinoids—tretinoin, adapalene, and tazarotene—help clear mild to moderate acne by normalizing hyperproliferation of epithelial cells in hair follicles.
- Oral antibiotics, including doxycycline and minocycline, are reserved for moderate to severe acne. Benefits derive

from suppressing growth of *P. acnes* and from anti-inflammatory actions.

- Isotretinoin is an oral drug reserved for severe acne.
- Isotretinoin causes multiple adverse effects, including nosebleeds; inflammation of the lips and eyes; and pain, tenderness, or stiffness in muscles, bones, and joints.
- Isotretinoin is highly teratogenic. Accordingly, all parties involved with the drug—prescribers, patients, pharmacists, and wholesalers—must participate in iPLEDGE, a risk management program designed to ensure that isotretinoin is not used during pregnancy.

- Excessive sun exposure can cause sunburn, premature aging of the skin, and skin cancer.
- Sunscreens can protect against sunburn and aging of the skin, and some cancers.
- To be most effective, a sunscreen product should offer protection against the full range of UVB and UVA radiation.

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Anatomy of the Ear**Otitis Media and Its Management****Acute Otitis Media****Recurrent Otitis Media****Otitis Media with Effusion****Otitis Externa and Its Management****Acute Otitis Externa****Necrotizing Otitis Externa****Fungal Otitis Externa (Otomycosis)**

In this chapter, we discuss drugs for disorders of the middle ear and external ear. In preparation, we review relevant anatomy of the ear.

ANATOMY OF THE EAR

The ear has three major divisions: the external ear, middle ear, and inner ear (Fig. 106–1). Their primary features are as follows:

- The *external ear* consists of (1) the auricle or pinna (the cartilaginous flap visible on the side of the head that serves to collect sound waves); and (2) the external auditory canal (EAC), a skin-lined tube that directs sound waves from the auricle to the tympanic membrane (eardrum). The surface of the EAC is coated with cerumen (earwax), a hydrophobic substance that blocks penetration of water and helps protect against bacterial and fungal infection.
- The *middle ear* is the chamber that houses the malleus, incus, and stapes—three tiny bones that transmit sound vibrations from the eardrum to the inner ear. The middle ear is bounded laterally by the tympanic membrane, which walls off the middle ear from the external ear. The eustachian tube (auditory tube) connects the middle ear with the nasopharynx, and thereby allows air pressure within the middle ear to equalize with air pressure in the environment. The mucociliary epithelium that lines the eustachian tube sweeps bacteria out of the middle ear into the nasopharynx.
- The *inner ear* consists of the semicircular canals and the cochlea. The canals provide our sense of balance. The cochlea houses the apparatus of hearing.

OTITIS MEDIA AND ITS MANAGEMENT

Otitis media (OM), defined as an inflammation of the middle ear, is the most prevalent disorder of childhood. The condition affects more than 75% of children by the age of 3 years, and

about 95% by the age of 12. In the United States, OM is responsible for more than 30 million clinic visits a year.

Otitis media may result from bacterial infection, viral infection, or noninfectious causes. Only bacterial OM responds to antibiotics. Furthermore, most cases resolve spontaneously, making antibiotics largely unnecessary—even when bacteria are the cause. Nonetheless, antibiotics have been used routinely. In fact, OM is the most common reason for giving these drugs to kids—at an estimated cost of \$3.5 billion a year.

Acute Otitis Media**Characteristics, Pathogenesis, and Microbiology**

Acute otitis media (AOM) is defined by *inflammation and fluid in the middle ear*. Otalgia (ear pain) is characteristic, often causing the child to tug at the ear or just hold it. Other symptoms include fever, vomiting, irritability, impaired hearing, sleeplessness, and otorrhea (discharge from the ear, usually purulent [pus containing]).

AOM may be bacterial, viral, or both. In children with full-blown bacterial AOM, the inner ear is filled with purulent fluid, which can cause the tympanic membrane to bulge outward. If the membrane is perforated, otorrhea results. In children with nonbacterial AOM or with mild bacterial AOM, the tympanic membrane does not bulge. Of the two presentations—bulging or nonbulging eardrum—nonbulging is the more common.

How does AOM develop? As a rule, the process begins with a viral infection of the nasopharynx, which can cause blockage of the eustachian tube, which in turn can cause negative pressure in the middle ear. When the eustachian tube opens, causing pressure equalization, bacteria and viruses can be sucked in. If the mucociliary system is sufficiently impaired, it will be unable to transport these pathogens back to the nasopharynx. Otitis media results when bacteria colonize the fluid of the middle ear and/or when viruses colonize cells of the middle-ear mucosa. As indicated in Table 106–1, bacteria are present in 70% to 90% of fluid samples taken from the middle ear of children with AOM, and viruses are present in nearly 50%. The most common bacterial pathogens are *Streptococcus pneumoniae* (40% to 50%), *Haemophilus influenzae* (20% to 25%), and *Moraxella catarrhalis* (10% to 15%).

Diagnosis

To diagnose AOM, three elements must be present: (1) acute onset of signs and symptoms, (2) middle-ear effusion (MEE), and (3) middle-ear inflammation. The patient history will reveal whether onset of signs and symptoms has been both recent and rapid. The presence of MEE is indicated by any of the following: bulging tympanic membrane (the best predictor of MEE), limited mobility of the tympanic membrane, and otorrhea (fluid in the EAC following perforation of the tym-

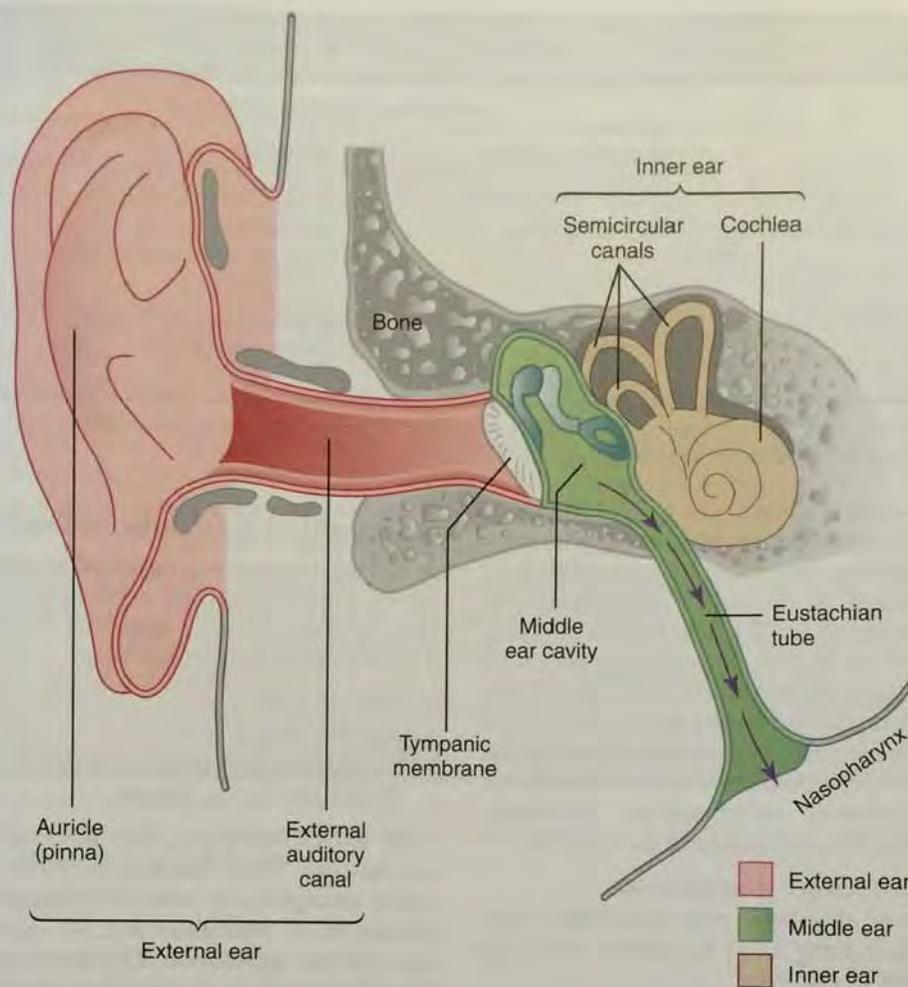


Figure 106-1 ■ Anatomy of the ear.

The purple arrows indicate flow of the mucociliary system, which can transport bacteria out of the middle ear.

TABLE 106-1 ■ Primary Pathogens Found in Fluid from the Middle Ear of Children with Acute Otitis Media

Pathogen	Children with the Pathogen (%)
<i>Streptococcus pneumoniae</i>	40–50
<i>Haemophilus influenzae</i>	20–25
<i>Moraxella catarrhalis</i>	10–15
No bacteria found	20–30
Respiratory viruses (with or without bacteria)	48

panic membrane). Middle-ear inflammation is indicated by either (1) distinct erythema of the tympanic membrane or (2) distinct otalgia (discomfort, clearly referable to the ear, that disrupts normal activity or sleep).

Frequently, the diagnosis of AOM is somewhat uncertain. Why? Because in many cases, MEE can't be confirmed. When the presence of MEE is questionable, a diagnosis of AOM may be considered, but cannot be deemed certain.

It is important to distinguish between AOM and otitis media with effusion (OME). As discussed below, children with OME have fluid in the middle ear but no signs of local or systemic illness. Prolonged OME is common following resolution of AOM.

Standard Treatment

All children with AOM should receive required pain medication (eg, acetaminophen, ibuprofen, codeine), and *some* should receive antibiotics. Prescribing antibiotics for *all* children should be discouraged. Why? Because the vast majority (over 80%) of AOM episodes resolve spontaneously within a week. Hence, if antibiotics are prescribed routinely, most recipients will be taking drugs they don't really need. Not only does this generate unnecessary expense, worse yet, it puts children at needless risk of adverse drug effects, increases their risk of recurrent AOM, and accelerates the emergence of antibiotic-resistant bacteria.

In 2004, two organizations—the American Academy of Pediatrics and the American Academy of Family Physicians—released guidelines for treating AOM in children. The guidelines stress the need for an accurate diagnosis, and they recommend basing treatment on three factors: age, illness severity, and the degree of diagnostic certainty.

TABLE 106-2 • Criteria for Choosing Initial Antibacterial Therapy Versus Observation in Children with AOM

Age	Management Recommendation	
	Certain Diagnosis	Uncertain Diagnosis
Less than 6 months	Antibacterial therapy	Antibacterial therapy
6 months to 2 years	Antibacterial therapy	Antibacterial therapy if illness is severe; observation if illness is not severe*
2 years and older	Antibacterial therapy if illness is severe; observation if illness is not severe*	Observation, regardless of symptom severity

*Severe illness = moderate to severe otalgia or fever of 39°C or higher, nonsevere illness = mild otalgia and fever below 39°C in the past 24 hours.

For some patients, the guidelines include an important option—*observation*—rather than immediate treatment with antibacterial drugs. Observation is defined as management by symptomatic relief alone for 48 to 72 hours, thereby allowing time for AOM to resolve on its own. If symptoms persist or worsen, antibacterial therapy is then started. As part of this strategy, parents are informed about (1) the high probability of spontaneous AOM resolution, and (2) the drawbacks of giving antibiotics when they are not needed. Observation is considered appropriate only when follow-up can be ensured. The recommendation for observation is based on studies showing that:

- Most episodes of AOM resolve spontaneously.
- Immediate antibacterial therapy is only marginally superior to observation at causing AOM resolution, and is no better at relieving pain or distress.
- Parents find the observation approach acceptable.
- Delaying antibacterial therapy does not significantly increase the risk of mastoiditis, which can occur when bacteria invade the mastoid bone.

Criteria for choosing between observation and initial antibacterial therapy are summarized in Table 106-2. The choice is based on patient age, how certain the diagnosis is, and severity of symptoms. As indicated, all children less than 6 months old should receive antibiotics, regardless of diagnostic certainty or symptom severity. Among children 6 months to 2 years old, antibiotics are indicated whenever the diagnosis is certain. If the diagnosis is uncertain, antibiotics are indicated only if symptoms are severe. For children age 2 years and older, antibacterial therapy is indicated only if the diagnosis is certain, and then only if symptoms are severe. In all other cases, observation is the preferred strategy.

When antibacterial drugs are indicated, *high-dose amoxicillin* (40 to 45 mg/kg PO twice a day) is the treatment of choice (Table 106-3). Benefits of amoxicillin are efficacy, safety, low cost, acceptable taste, and narrow microbiologic spectrum. The duration of treatment ranges from 5 to 10 days, depending on patient age and illness severity.

For patients with penicillin allergy, drug selection depends on allergy severity. If the allergy is *not* severe (type II allergy), a cephalosporin may be used (eg, cefdinir, cefuroxime). However, if the allergy is *severe* (type I allergy, causing urticaria or anaphylaxis), cephalosporins should be avoided, owing to concerns of cross-reactivity. In this case, azithromycin and clarithromycin are recommended.

Treatment of Antibiotic-Resistant AOM

Antibiotic resistance is indicated by persistence of symptoms (fever; earache; otorrhea; a red, bulging tympanic membrane) for 2 to 3 days despite antibiotic therapy. Major risk factors for developing resistant AOM are

- Attending day care
- Age less than 2 years
- Exposure to antibiotics in the prior 1 to 3 months
- Winter and spring seasons

In the United States, the incidence of resistant AOM is on the rise. Why? Because overuse of antibiotics has favored emergence of resistant pathogens. Resistance among strains of *H. influenzae* and *M. catarrhalis* is limited to beta-lactam antibiotics. The mechanism is production of beta-lactamase, an enzyme that inactivates amoxicillin and certain other beta-lactam antibiotics. In contrast, strains of *S. pneumoniae* are resistant to multiple antibiotics, including erythromycin and trimethoprim/sulfamethoxazole, as well as amoxicillin and other beta-lactam antibiotics. Interestingly, resistance to amoxicillin does not result from beta-lactamase production. Rather, it results from synthesis of altered penicillin-binding proteins (PBPs), whose affinity for amoxicillin is much lower than that of normal PBPs.

How should resistant AOM be treated? The preferred approach is oral therapy with *high-dose amoxicillin/clavulanate*. The clavulanate (clavulanic acid) in the combination inhibits beta-lactamase, and thereby increases activity against resistant *H. influenzae* and *M. catarrhalis*. Using a high dose of amoxicillin increases activity against resistant *S. pneumoniae*. Because the clavulanate in the combination can cause diarrhea, we want to keep its dosage low. This is best accomplished by using *Augmentin ES-600* (600 mg amoxicillin/42.9 mg clavulanate), a formulation that contains less clavulanate per milligram of amoxicillin than any other amoxicillin/clavulanate product. To treat resistant AOM, the dosage is 45 mg/kg amoxicillin PO twice a day for 7 days. Alternatives to amoxicillin/clavulanate include *IM or IV ceftriaxone* (50 mg/kg once a day for 3 days) and *oral clindamycin* (30 to 40 mg/kg/day in three divided doses). All three regimens are recommended for (1) children with acute AOM that has not responded to standard antibiotic therapy, and (2) initial therapy of AOM in children with risk factors for resistant infection.

TABLE 106-3 ■ Recommended Antibacterial Drugs for Acute Otitis Media

Patient Group and Illness Severity	Recommended Drugs	
	For Most Patients	For Patients with Penicillin Allergy*
Patients Receiving Immediate Antibiotic Therapy		
Nonsevere illness	Amoxicillin, 40–45 mg/kg twice daily	<i>Non-type I allergy:</i> Cefdinir, 14 mg/kg/day in 1 or 2 divided doses <i>or</i> Cefuroxime, 15 mg/kg twice daily <i>or</i> Cefpodoxime, 10 mg/kg once daily <i>Type I allergy:</i> Azithromycin, 10 mg/kg on day 1, then 5 mg/kg on days 2, 3, 4, and 5 <i>or</i> Clarithromycin, 7.5 mg/kg twice daily Ceftriaxone, 50 mg/kg IM for 1 or 3 days
Severe illness	Amoxicillin, 45 mg/kg twice daily <i>plus</i> clavulanate, 3.2 mg/kg twice daily [†]	
Patients with Persistent Symptoms After 48–72 hr of Observation (with No Antibiotic Therapy)		
Same as for patients receiving immediate antibiotic therapy		
Patients with Persistent Symptoms After 48–72 hr of Antibiotic Therapy (Indicating Drug Resistance)		
Nonsevere illness	Amoxicillin, 45 mg/kg twice daily <i>plus</i> clavulanate, 3.2 mg/kg twice daily [†]	<i>Non-type I allergy:</i> Ceftriaxone, 50 mg/kg IM or IV for 3 days <i>Type I allergy:</i> Clindamycin, 30–40 mg/kg/day in 3 divided doses
Severe illness	Ceftriaxone, 50 mg/kg IM for 3 days	Clindamycin, tympanocentesis

*Type I allergy is severe (urticaria or anaphylaxis); type II is less severe.

[†]This ratio of amoxicillin to clavulanate can be achieved with Augmentin ES-600, a fixed-dose combination containing amoxicillin and clavulanic acid.

Prevention

The risk of acquiring AOM can be decreased in several ways. Breast-feeding for at least 6 months seems to reduce early episodes of AOM. During infancy and early childhood, AOM can be significantly reduced by avoiding child care centers when respiratory infections are prevalent. Measures of unproved benefit include eliminating exposure to tobacco smoke, reducing pacifier use in the second 6 months of life, and avoiding supine bottle feeding. Two additional measures—prevention and treatment of influenza, and vaccination against pneumococcal infection—are discussed below.

Prevention and Treatment of Influenza. As noted, influenza and other viral infections of the respiratory tract predispose children to developing bacterial and viral OM. Accordingly, measures that reduce influenza can reduce OM risk. Two methods are available: (1) vaccination against influenza and (2) treatment of active influenza infection. In one study, day care attendees over the age of 2 years were vaccinated against influenza. The result was a 36% reduction in diagnosed cases of AOM during the 6-week interval when influenza virus was circulating in the community. However, in a study of younger children (ages 6 months to 2 years), influenza vaccination failed to reduce AOM occurrence. In a study involving children with active influenza, treatment with oseltamivir (an antiviral drug) decreased cases of AOM by 40%. Although both approaches—immunization and treatment—can help during the flu season, they do nothing to alter AOM risk the rest of the year.

Vaccination Against *Streptococcus pneumoniae*. Vaccination with *pneumococcal conjugate vaccine* (PCV) [Prevnar] can slightly reduce the risk of AOM. Although the

vaccine is highly active against the strains of *S. pneumoniae* that cause pneumonia and meningitis, it is only moderately active against the strains that cause AOM. In a study involving 37,868 children in Northern California, the benefits of PCV immunization were significant but modest: office visits for AOM were reduced by 7.8%, and the need for tympanostomy tubes was reduced by 24%.

Recurrent Otitis Media

Recurrent AOM can be defined as AOM that occurs 3 or more times within 6 months, or 4 or more times within 12 months. Four management strategies are available: (1) short-term antibacterial therapy, (2) prophylactic antibacterial therapy, (3) prevention and treatment of influenza, and (4) placement of a tympanostomy tube.

Short-Term Antibacterial Therapy. There is disagreement regarding antibacterial therapy. Some authorities would prescribe antibiotics for each recurrent episode, regardless of presentation. Others would reserve antibiotics for episodes in which symptoms are severe. In both cases, high-dose amoxicillin is the treatment of choice. If resistance is suspected, amoxicillin/clavulanate can be used.

Prophylactic Antibacterial Therapy. Antibacterial prophylaxis is *not* generally recommended. An analysis of several studies indicates that, for each year of prophylaxis (with sulfisoxazole, trimethoprim/sulfamethoxazole, or amoxicillin), only 1.3 episodes of AOM would be prevented. This small benefit is largely outweighed by the risk of promoting resistance. If prophylaxis is elected, it should be conducted only

during the head-cold season. The preferred drug for prophylaxis is amoxicillin. Why? Because, compared with sulfonamides, amoxicillin is more active against multidrug-resistant strains of *S. pneumoniae*.

Prevention and Treatment of Influenza. As discussed above, we can reduce OM occurrence by vaccinating against the influenza virus and by treating active influenza infection. However, benefits are seen only during the flu season.

Tympanostomy Tubes. A tympanostomy tube is a small tube that is placed into an incision in the eardrum, thereby permitting drainage and aeration of the middle ear. Tube insertion is performed under general anesthesia and costs about \$3000. In children with recurrent AOM, the procedure can significantly reduce AOM episodes. Complications of the procedure include obstruction of the tube, secondary infection with otorrhea, and premature tube extrusion.

Otitis Media with Effusion

Otitis media with effusion is seen in many children following an episode of AOM. The condition is characterized by fluid in the middle ear but without evidence of local or systemic illness. OME may cause mild hearing loss, but not pain. The condition can persist for weeks to months after AOM has resolved. Antibiotics have minimal effect on OME and should not be used.

OTITIS EXTERNA AND ITS MANAGEMENT

Otitis externa (OE) is an inflammation of the external auditory canal. The usual cause is bacterial infection, which may be limited to the EAC, or may spread to adjacent tissues. Most cases of OE respond to topical drugs.

Acute Otitis Externa

Characteristics, Pathogenesis, and Microbiology

Acute OE, also known as “swimmer’s ear,” is a bacterial infection of the EAC. The most common pathogens are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Other pathogens include *Staphylococcus epidermidis* and *Microbacterium otitidis*. Patients who have acute OE present with rapid-onset ear pain associated with pruritus, impaired hearing, purulent discharge, and pronounced tenderness of the auricle upon manipulation.

Susceptibility to acute OE is precipitated primarily by two factors: abrasion and excessive moisture. Both facilitate bacterial colonization. Abrasion of the epithelium creates a site for bacterial entry. Most often, abrasion results from cleaning the EAC with a cotton-tipped swab or some other foreign object (finger, pencil, toothpick, etc.). Abrasion can also be caused by hearing aids and earplugs. Moisture can wash away the protective layer of cerumen. As a result, keratin debris in the EAC is able to absorb water, thereby creating a nourishing medium for bacterial growth. Moisture in the EAC may come from swimming, perspiration, and even high humidity.

Treatment

Acute OE usually responds well to simple treatment. The goal is to eradicate the pathogen and reduce pain. For most patients, cleaning and use of topical antimicrobials will suffice. If the infection is extensive, oral antibiotics may be needed. To facilitate healing, the ear should be kept as dry as possible.

Most infections begin to improve in 3 days, and resolve completely by 10 days.

Topical Medications. Topical antimicrobials are generally preferred to systemic drugs. There are two reasons why. First, because topical agents achieve very high local concentrations (often 100 to 1000 times the concentration achieved with systemic drugs), antibacterial effects are superior: disease persistence is lower, and recurrence is less likely. Second, with topical therapy, systemic side effects are absent.

A variety of topical medications can be used. A 2% solution of acetic acid is safe, effective, and cheap. Furthermore, because bactericidal activity results from simply reducing pH, there is no risk of encouraging resistance. A solution of alcohol plus acetic acid offers the additional benefit of promoting tissue drying. For many patients, acidification and drying are all that is needed.

If the infection cannot be cleared with acetic acid and alcohol, a topical antibiotic should be employed. In the past, a three-drug combination—hydrocortisone, neomycin, and polymyxin B—was considered standard therapy. The hydrocortisone reduces inflammation and edema; neomycin and polymyxin kill bacterial pathogens. Unfortunately, although this combination is effective and inexpensive, it does have drawbacks. Specifically, the neomycin component is ototoxic, and causes local swelling and erythema in about 15% of patients. Today, fluoroquinolones (eg, ciprofloxacin) are preferred. Why? Because these drugs are highly effective, don’t cause local reactions, and are not ototoxic. Options include Cipro HC (ciprofloxacin plus hydrocortisone), Ciprodex (ciprofloxacin plus dexamethasone), and Floxin Otic (ofloxacin alone). Principal drawbacks of these preparations are expense and promotion of resistance to all fluoroquinolone antibiotics.

Applying ear drops correctly can improve outcomes and reduce drug-related discomfort. Instillation of cold solutions can cause dizziness, and hence ear drops should be warmed prior to administration. Wiggling the earlobe can facilitate transit of solutions down the EAC. If edema of the EAC is sufficient to impede drug penetration, insertion of a sponge wick can help. Drug solutions are absorbed into the wick, which then delivers them to the epithelium of the entire canal. The wick should be removed every 48 hours to allow cleaning and to determine if further wicking is still needed.

Oral Medications. Oral antibacterials are indicated if the infection extends beyond the EAC to involve the pinna. For adults, ciprofloxacin [Cipro] is a good choice. For children, cephalexin [Keflex], is preferred. Why? Because oral ciprofloxacin and other fluoroquinolones can cause tendon rupture in younger patients. Accordingly, these drugs should not be given to patients under the age of 18.

Prevention

The best way to prevent bacterial OE is to keep the natural defenses of the EAC healthy. Ear hygiene can be promoted by following these rules:

- Don’t put *anything* in the ear, including cotton-tipped swabs, fingers, pencils, paper clips, toothpicks, liquids, or sprays, all of which can remove cerumen and/or damage the epithelium.
- Dry the EAC after swimming and showering. How? By towel-drying off and promoting water drainage (by tipping the head to each side while pulling the auricle in different directions).

- Don't remove cerumen (earwax).
- Don't use earplugs (except when swimming).

Necrotizing Otitis Externa

Necrotizing OE is a rare but potentially fatal complication of acute OE that develops when bacteria in the EAC invade the mastoid or temporal bone. Spread of infection to the skull base can affect cranial nerves, and spread to the dura mater can cause meningitis and possibly lateral sinus thrombosis. The usual pathogen is *P. aeruginosa*. Patients typically present with progressive severe otic pain, purulent discharge from the ear, and granulation of tissue in the EAC. Necrotizing OE occurs almost exclusively in two groups of high-risk people, specifically, older people with diabetes and anyone who is immunocompromised, especially people with HIV infection. Most cases can be managed by thorough cleansing of the EAC followed by treatment with antipseudomonal drugs; surgery is rarely needed. All patients should receive antipseudomonal ear drops (eg, ofloxacin solution). Patients with mild

disease should also receive oral ciprofloxacin. Patients with severe disease should receive IV antipseudomonal therapy (eg, *imipenem/cilastatin* [Primaxin], *meropenem* [Merrem IV], or *ciprofloxacin*). The usual duration of IV therapy is 4 to 6 weeks.

Fungal Otitis Externa (Otomycosis)

In about 10% of patients, OE is caused by fungi and not bacteria. The two most common pathogens are *Aspergillus*, which causes 80% to 90% of otomycoses, and *Candida*. Fungal OE typically manifests as intense pruritus and erythema, with or without pain or hearing loss. As a rule, otomycosis can be managed with thorough cleansing and application of acidifying drops (eg, 2% acetic acid solution applied 3 to 4 times a day for 7 days). If these measures are inadequate, the patient can apply a solution that contains an antifungal drug (eg, 1% *clotrimazole* [Lotrimin] twice daily for 7 days). If the infection fails to respond, oral antifungal therapy may be needed. Options include *itraconazole* [Sporanox] and *fluconazole* [Diflucan].

KEY POINTS

- Otitis media (OM), defined as inflammation of the middle ear, is among the most prevalent disorders of childhood.
- Acute otitis media (AOM) is characterized by rapid onset, middle-ear effusion, and middle-ear inflammation.
- AOM may be bacterial, viral, or both.
- Over 80% of AOM cases resolve spontaneously within a week.
- All children with AOM should receive pain medication (eg, acetaminophen, ibuprofen, codeine) as needed.
- Clinical guidelines recommend antibacterial therapy for some children, and observation for others. (Observation for 48 to 72 hours allows time for AOM to resolve on its own. If it doesn't resolve, then antibacterial therapy is implemented.)
- The decision to treat immediately or to wait is based on three factors: patient age, illness severity, and the degree of diagnostic certainty (see Table 106-2).
- When antibiotics are used for AOM (either immediately or after a period of observation), high-dose amoxicillin is the treatment of choice.
- For children with antibiotic-resistant AOM, high-dose amoxicillin/clavulanate (available as Augmentin ES-600) is the treatment of choice.
- The risk of acquiring AOM can be reduced by vaccination against the influenza virus, treatment of active influenza infection, and, to a lesser degree, vaccination against *Streptococcus pneumoniae* (using the pneumococcal conjugate vaccine [Prevnar]).
- Otitis media with effusion (OME) is characterized by fluid in the middle ear but without evidence of local or systemic illness. The condition may cause mild hearing loss, but not pain.
- OME is seen in many children following an episode of AOM, and may persist for weeks to months.
- Antibiotics have minimal effect on OME and should not be used.
- Otitis externa (OE) is an inflammation of the external auditory canal (EAC).
- Acute OE, also known as "swimmer's ear," is a bacterial infection of the EAC.
- In most cases, acute OE can be treated by cleaning and use of ear drops, which may contain 2% acetic acid (to kill bacteria), alcohol (to promote drying), hydrocortisone (to reduce inflammation and edema), or an antibacterial drug (ciprofloxacin and certain other fluoroquinolones are preferred).
- If acute OE progresses to the pinna, oral antibiotics should be used. Ciprofloxacin is a good choice for adults; cephalexin is a good choice for children.
- Necrotizing OE is a rare but potentially fatal complication of acute OE that develops when bacteria in the EAC invade the mastoid or temporal bone. The usual pathogen is *Pseudomonas aeruginosa*.
- Necrotizing OE can be managed by thorough cleansing and use of antipseudomonal drugs. All patients should receive antipseudomonal ear drops (eg, ofloxacin solution). Patients with mild disease should receive oral ciprofloxacin. Patients with severe disease should receive IV therapy (eg, *imipenem/cilastatin* [Primaxin]).
- In about 10% of patients with OE, the infection is due to fungi and not bacteria. The most common fungal pathogen is *Aspergillus*.
- Fungal OE (otomycosis) can usually be managed by thorough cleansing and application of acidifying drops (eg, 2% acetic acid solution). If needed, a topical antifungal drug (eg, 1% *clotrimazole*) can be used. Unresponsive infections can be treated with an oral antifungal drug (eg, *itraconazole*, *fluconazole*).

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Drugs for Pulmonary Arterial Hypertension**Prostacyclin Analogs****Endothelin-1 Receptor Antagonists****Phosphodiesterase Type 5 Inhibitors****Drugs for Neonatal Respiratory Distress Syndrome****Prenatal and Postnatal Glucocorticoids****Lung Surfactant****Drugs for Cystic Fibrosis****Pathophysiology of Cystic Fibrosis****Drug Therapy****Drugs for Sickle Cell Anemia****Analgesics and Glucocorticoids****Hydroxyurea****Drugs for Hyperuricemia Caused by Cancer****Chemotherapy****Phosphate Binders for Patients on Dialysis****Gamma-Hydroxybutyrate for Cataplexy in Patients with Narcolepsy****Riluzole for Amyotrophic Lateral Sclerosis****Tetrabenazine for Chorea of Huntington's Disease****Drugs for Fibromyalgia Syndrome****Antidepressants and Related Drugs****Anticonvulsants****Analgesics****Drugs for Sleep Disturbances****Drugs for Hereditary Angioedema****Old Drugs for HAE****New Drugs for HAE****Belimumab for Systemic Lupus Erythematosus****DRUGS FOR PULMONARY ARTERIAL HYPERTENSION**

Pulmonary arterial hypertension (PAH) is a rare, progressive, and potentially fatal disease of the small pulmonary arteries. The condition is defined by a sustained elevation of pulmonary arterial pressure of more than 25 mm Hg at rest or more than 30 mm Hg during exercise, with a mean pulmonary capillary wedge pressure and left ventricular end-diastolic pressure of less than 15 mm Hg. The primary vascular changes in PAH are vasoconstriction, proliferation of smooth muscle cells and endothelial cells, and pulmonary thrombosis. Cell proliferation and vascular remodeling lead to a progressive increase in pulmonary vascular resistance. The ultimate result is right ventricular failure and death. Although the pathogenesis of PAH is not fully understood, a hormone known as endothelin-1 may play a critical role (see below).

Traditional treatment consists of three drugs: warfarin, a diuretic, and a calcium channel blocker. Warfarin prevents thrombosis. Diuretics reduce fluid retention, and thereby reduce cardiac preload, which in turn reduces symptoms of right-heart failure. Calcium channel blockers dilate constricted pulmonary arteries, and can thereby reduce pulmonary hypertension. However, only 20% of patients respond to calcium channel blockers, hence use of these drugs is limited to this small group.

For many patients, PAH becomes progressively worse despite drug therapy, and hence surgical intervention may be required. Options include single-lung, double-lung, and heart-lung transplantation. These surgeries are high risk, with a mortality rate of 16% to 29%. Five-year survival is 40% to 45%.

Since 1995, seven new drugs for PAH have been approved: epoprostenol, treprostinil, iloprost, bosentan, ambrisentan, sildenafil, and tadalafil (Table 107-1). All seven promote pulmonary vasodilation. In addition, they may delay or reverse pulmonary vascular remodeling. Also, all seven are very expensive. Discussion below is limited to these seven drugs.

Prostacyclin Analogs

Three derivatives of prostacyclin are approved for PAH: epoprostenol, treprostinil, and iloprost. All three mimic the actions of endogenous prostacyclin, a compound that promotes vascular relaxation, suppresses growth of vascular smooth muscle cells, and inhibits platelet aggregation. Like prostacyclin itself, the analogs bind with cell-membrane receptors and thereby stimulate synthesis of cyclic AMP, an intracellular second messenger that mediates prostacyclin effects. In patients with PAH, the prostacyclin analogs lower pulmonary arterial resistance, decrease pulmonary arterial pressure, increase exercise tolerance, and improve short-term survival.

Epoprostenol

Epoprostenol [Flolan], approved in 1995, was the first prostacyclin available for PAH. Administration is complex and inconvenient, and adverse effects are common. The drug has a very short half-life (less than 6 minutes) and is unstable at room temperature. As a result, it must be given by continuous IV infusion, using a portable pump that can keep the drug cold. Administration is done through a central venous catheter. The infusion rate is low initially, and then gradually increased to a typical maintenance rate of 20 to 40 ng/kg/min. The most common side effects are flushing (58%), headache (49%), and nausea and vomiting (32%). These responses are dose dependent and generally mild. Of greater concern, patients are at risk of catheter-related sepsis. Also, if the pump fails or the catheter becomes dislodged, the resulting interruption of drug delivery can be life threatening.

TABLE 107-1 ■ Drugs for Pulmonary Arterial Hypertension

Drug	Year Approved	Administration	Principal Adverse Effects
Prostacyclin Analogs			
Epoprostenol [Flolan]	1995	Continuous IV infusion through a central venous catheter	Catheter-related sepsis, headache, flushing, nausea
Treprostinil [Remodulin]	2002	Continuous subQ infusion	Local pain and other local reactions in most patients
[Remodulin]	2002	Continuous IV infusion through a central venous catheter	Catheter-related sepsis
[Tyvaso]	2009	Oral inhalation, 4 times a day	Cough, headache, throat irritation, nausea, flushing
Iloprost [Ventavis]	2004	Inhalation, 6–9 times a day	Hypotension and fainting, cough, headache, flushing
Endothelin-1 Receptor Blockers			
Bosentan [Tracleer]	2001	Oral, twice a day	Hepatotoxicity, major birth defects, anemia
Ambrisentan [Letairis, Volibris♣]	2007	Oral, once a day	Major birth defects, anemia (Unlike bosentan, ambrisentan does <i>not</i> injure the liver.)
Phosphodiesterase Type 5 Inhibitors			
Sildenafil [Revatio]*	2005*	Oral or IV bolus, 3 times a day	Headache, flushing, dyspepsia
Tadalafil [Adcirca]†	2009†	Oral, once a day	Headache, dyspepsia, back pain, muscle pain

*Sildenafil is also sold as Viagra for treating erectile dysfunction (ED). Approval for ED was granted in 1998.

†Tadalafil is also sold as Cialis for treating ED. Approval for ED was granted in 2003.

Treprostinil

Treprostinil was approved for parenteral therapy of PAH in 2002, and then for inhalation therapy of PAH in 2009. Products for parenteral therapy are marketed as *Remodulin*, and products for inhalation therapy are marketed as *Tyvaso*. For parenteral therapy, treprostinil is usually administered by continuous subQ infusion, but if needed, it can be infused through a central venous line instead. Treprostinil has a much longer half-life than epoprostenol (4 hours vs. 6 minutes) and much greater heat stability.

Compared with infused epoprostenol, infused treprostinil [Remodulin] has three major advantages. First, because treprostinil is heat stable, it doesn't require cooling during the infusion. Second, because treprostinil has a prolonged half-life, maintaining a precise infusion rate is less critical. And third, because treprostinil can be infused subQ, the risk of sepsis associated with a central venous catheter is obviated. However, subQ treprostinil is not free of problems: local pain occurs in 85% of patients, and other local reactions (eg, erythema, induration, rash) occur in 83% of patients. Local pain is often dose limiting. Other side effects include jaw pain, diarrhea, edema, and nausea.

For inhalation therapy, treprostinil [Tyvaso] is dosed using the Tyvaso Inhalation System, which delivers 6 mcg with each inhalation. The initial dosage is 18 mcg (3 inhalations) 4 times a day (at 4-hour intervals during waking hours), for a total of 72 mcg/day. The target maintenance dosage is 54 mcg (9 inhalations) 4 times a day, for a total of 216 mcg/day. The most common adverse effects of inhaled treprostinil are cough (54%), headache (41%), throat irritation (25%), nausea (19%), flushing (17%), and dizziness (6%).

Iloprost

Iloprost [Ventavis], approved for PAH in 2004, was the first prostacyclin that did not require continuous infusion. Instead, the drug is administered by oral inhalation. The usual dosage

is 5 mcg inhaled 6 to 9 times a day, using either the *Prodose AAD* system or the *I-neb AAD* system. The most common side effects are cough (39%), headache (30%), flushing (27%), and spasm of the jaw muscles (12%). More importantly, about 11% of patients are at risk of fainting owing to hypotension, which can occur secondary to peripheral vasodilation. To reduce risk, iloprost should be avoided in patients with systolic blood pressure below 85 mm Hg.

Endothelin-1 Receptor Antagonists

Endothelin-1 (ET-1) is a small peptide hormone that promotes vasoconstriction and proliferation of endothelial cells. In patients with PAH, the level of ET-1 in the pulmonary vasculature is elevated as much as 10-fold. Furthermore, the degree of ET-1 elevation corresponds with the degree of PAH severity. Endothelin-1 acts through two types of receptors, known as endothelin type A (ET_A) receptors and endothelin type B (ET_B) receptors. Activation of ET_A receptors causes vasoconstriction and cell proliferation, whereas activation of ET_B receptors causes vasodilation.

Endothelin-1 receptor antagonists (ERAs) can reduce the adverse impact of ET-1 on lung function. Two ERAs are available: *bosentan* [Tracleer] and *ambrisentan* [Letairis, Volibris♣]. In patients with PAH, these drugs can improve exercise tolerance and delay symptom progression. Unfortunately, the drugs can also cause serious adverse effects, especially liver injury and fetal malformation.

Bosentan

Actions and Use. Bosentan [Tracleer], approved in 2001, is a nonspecific ERA that blocks ET_A receptors and ET_B receptors. In patients with PAH, the drug improves exercise tolerance and slows symptom progression. Presumably, benefits derive from blocking ET_A receptors rather than ET_B receptors. As noted, ET_A receptors promote vasoconstriction and cell proliferation, and hence blocking these receptors

should reduce pulmonary vascular resistance and may have a favorable impact on vascular remodeling. Blockade of ET_B receptors may be counterproductive, in that the result could be an *increase* in vascular resistance.

Pharmacokinetics. Bosentan is an oral drug with 50% bioavailability, both in the presence and absence of food. Plasma levels peak 3 to 4 hours after dosing. Protein binding in blood is high (over 98%). Bosentan undergoes metabolism in the liver, primarily by the cytochrome P450 isozymes CYP2C9 and CYP3A4, followed by excretion in the bile. The half-life is approximately 5 hours.

Adverse Effects. The most serious adverse effects are liver injury and teratogenesis. Bosentan can also cause headache, flushing, peripheral edema, nasal congestion, anemia, and reduced sperm production.

Hepatotoxicity. Liver injury is common. In 11% of patients, serum levels of liver aminotransferases exceed 3 times the upper limit of normal (ULN). Liver enzymes should be measured at baseline and monthly thereafter. If levels exceed 3 times the ULN at baseline, bosentan should not be used. If levels rise during treatment, and are accompanied by clinical symptoms (eg, nausea, vomiting, fever, jaundice, fatigue), bosentan should be discontinued. Fortunately, all cases of liver injury to date have been reversible; there have been no reports of permanent liver injury or liver failure.

Fetal Injury. Bosentan is classified in *Food and Drug Administration (FDA) Pregnancy Risk Category X*, and hence must not be used during pregnancy. In rats, the drug caused dose-dependent malformations of the head, mouth, face, and major blood vessels. Accordingly, pregnancy must be ruled out before initiating treatment, and sexually active women must use reliable contraception. Hormonal contraception may be unreliable, and hence should not be the sole form of contraception employed.

Anemia. Bosentan can reduce hemoglobin levels and the hematocrit. These hematologic changes usually develop during the first weeks of treatment and then stabilize by weeks 4 to 12. Blood tests should be done 1 month and 3 months after starting bosentan, and every 3 months thereafter.

Drug Interactions. Bosentan is subject to significant drug interactions. *Inhibitors of CYP2C9 and CYP3A4* have the potential to raise bosentan levels, thereby increasing the risk of toxicity.

Bosentan itself is an inducer of CYP2D6, and hence can accelerate the metabolism of certain other drugs. Important among these are *warfarin* (an anticoagulant that many people with PAH use) and *oral contraceptives*.

Two drugs—*cyclosporine* and *glyburide*—must not be taken with bosentan. Cyclosporine (an immunosuppressant) can greatly increase bosentan levels, and glyburide (a drug for type 2 diabetes) increases the risk of liver injury.

Preparations, Dosage, and Administration. Bosentan [Tracleer] is supplied in tablets (62.5 and 125 mg). For patients who weigh 40 kg or more, the dosage is 62.5 mg twice daily for 4 weeks, and then 125 mg twice daily thereafter for maintenance. For patients who weigh less than 40 kg, the dosage is 62.5 mg twice daily initially, and remains at 62.5 mg twice daily for maintenance. In patients with elevated transaminase levels, dosage should be adjusted as follows:

- Above 3 times the ULN but below 5 times the ULN—decrease dosage or interrupt dosing.
- Above 5 times the ULN—stop dosing, and don't resume until the level has returned to the baseline value.
- Above 8 times the ULN—stop dosing and don't resume.

To reduce the risk of liver injury and possible fetal exposure, bosentan must be prescribed through the Tracleer Access Program.

Ambrisentan

Ambrisentan [Letairis, Volibris⁺], approved in 2007, is much like bosentan with regard to actions, indications, and adverse effects. Both drugs block receptors for $ET-1$; both are taken to improve exercise tolerance and delay symptom progression in PAH; and both can cause severe birth defects. The drugs differ primarily in two respects. First, in contrast to bosentan, ambrisentan does *not* injure the liver. And second, whereas bosentan blocks ET_A and ET_B receptors, ambrisentan is selective for ET_A receptors. However, we don't know if this selectivity improves clinical outcome. As with bosentan, pregnancy must be ruled out before starting ambrisentan, and sexually active women must use two reliable forms of contraception. Like bosentan, ambrisentan can cause peripheral edema, headache, flushing, and anemia. In contrast to bosentan, ambrisentan does not reduce levels of warfarin. Ambrisentan is supplied in 5- and 10-mg film-coated tablets, which may be taken with or without food. Dosing begins at 5 mg once a day and, if this dosage is tolerated, may be increased to 10 mg once a day. Ambrisentan is not recommended for patients with moderate or severe hepatic impairment (because blood levels of the drug may become excessive). Owing to the risk of birth defects, ambrisentan is available only through a restricted distribution program, known as the Letairis Education and Access Program (LEAP).

Phosphodiesterase Type 5 Inhibitors

The phosphodiesterase type 5 (PDE5) inhibitors reduce pulmonary arterial pressure by causing dilation of pulmonary blood vessels. Two PDE5 inhibitors—sildenafil and tadalafil—are approved for PAH. Both drugs were originally developed for erectile dysfunction (ED). The basic pharmacology of these drugs and their use for ED are discussed in Chapter 66 (Drugs for Erectile Dysfunction and Benign Prostatic Hyperplasia). Consideration here is limited to their use in PAH.

Sildenafil

Sildenafil, sold as *Revatio*, was approved for oral therapy of PAH in 2005, and then for IV therapy in 2009. The same drug, sold as *Viagra*, has been available since 1998 for oral therapy of men with erectile dysfunction (ED).

How does sildenafil work? It causes selective inhibition of PDE5, the enzyme that inactivates cyclic GMP (cGMP). In arterioles of the lung and other tissues, endogenous nitric oxide triggers synthesis of cGMP, which in turn promotes vasodilation. Hence, by inhibiting PDE5, sildenafil can preserve cGMP, and can thereby enhance vasodilation mediated by nitric oxide. In patients with PAH, sildenafil reduces pulmonary arterial pressure and pulmonary vascular resistance. The drug may also suppress proliferation of pulmonary vascular smooth muscle cells.

Sildenafil is generally well tolerated. The most common adverse effects are headache, flushing, and dyspepsia. Transient visual disturbances and priapism (prolonged painful erection) occur infrequently. Very rarely, men have experienced sudden hearing loss or sight-threatening nonarteritic ischemic optic neuropathy. However, in both cases, a causal relationship has not been established.

Sildenafil can cause mild hypotension when used alone, and significant hypotension when combined with certain drugs. Combined use with alpha-adrenergic blockers can cause symptomatic postural hypotension. Of much greater concern, combined use with nitrates (eg, nitroglycerin, isosorbide dinitrate) can drop blood pressure enough to threaten life. Accordingly, concurrent use of sildenafil and nitrates is contraindicated.

Sildenafil is metabolized by CYP3A4 (the 3A4 isozyme of cytochrome P450). As a result, CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, ritonavir) can raise sildenafil levels, and CYP3A4 inducers (eg, rifampin, phenytoin) can lower its level.

For treatment of PAH, sildenafil is available in two formulations: 20-mg tablets for oral therapy, and a solution (10 mg/12.5 mL) for IV therapy. Both formulations are sold as *Revatio*. The oral dosage is 20 mg 3 times a day, taken with or without food. The IV dosage is 10 mg 3 times a day, given by bolus injection.

Tadalafil

Tadalafil, sold as *Adcirca*, was approved for oral therapy of PAH in 2009. The same drug, sold as *Cialis*, has been used for ED since 2003. As with sildenafil, benefits derive from dilating pulmonary blood vessels. The most common adverse effects are headache, dyspepsia, back pain, and muscle pain. Like sildenafil, tadalafil should not be combined with nitroglycerin or other nitrates, owing to a risk of severe hypotension. As with sildenafil, drugs that inhibit or induce CYP3A4 can alter levels of tadalafil. For treatment of PAH, tadalafil is available in 20-mg tablets. The dosage is 40 mg once a day, taken with or without food.

DRUGS FOR NEONATAL RESPIRATORY DISTRESS SYNDROME

Respiratory distress syndrome (RDS) is the primary cause of morbidity and mortality in premature infants. The underlying cause is deficiency of lung surfactant, a complex mixture of phospholipids and apoproteins that lowers surface tension on the alveolar surface. Consequences of surfactant deficiency include alveolar collapse, pulmonary edema, reduced lung compliance, small airway epithelial damage, hypoxia, and ultimately respiratory failure.

Increased production of cortisol during weeks 30 to 32 of gestation initiates production of lung surfactant. However, surfactant production is not fully adequate until weeks 34 to 36. As a result, the earlier the premature infant is delivered, the greater the risk of RDS. Among infants born during weeks 26 to 28, the incidence of RDS is 60% to 80%; by weeks 30 to 32, the incidence drops to 20%.

Prenatal and Postnatal Glucocorticoids

When preterm delivery cannot be prevented, injecting the mother with glucocorticoids can accelerate fetal lung maturation, and can thereby decrease the incidence and severity of RDS. Glucocorticoids act by stimulating production of fibroblast pneumocyte factor, which in turn stimulates production of surfactant by fetal pneumocytes. Glucocorticoids are effective when used during weeks 24 to 34 of gestation. Beyond week 34, fetal lungs are sufficiently mature that no benefit is gained by giving these drugs. Two drugs are recommended: *dexamethasone* and *betamethasone*. A *single course* consists of either (1) *dexamethasone*, 6 mg IM every 12 hours for four doses, or (2) *betamethasone*, two 12-mg IM doses, injected 24 hours apart. To be effective, the last glucocorticoid dose should be administered at least 24 hours before delivery, but no more than 7 days before. The basic pharmacology of the glucocorticoids is discussed in Chapters 60 and 72.

If pregnancy is successfully extended (eg, by giving a uterine relaxant), can repeat courses of glucocorticoids be of

benefit? Possibly. Giving a repeat course every week until delivery yields better short-term outcomes than giving a single course: With repeat courses, there is a lower incidence of RDS, less need for mechanical respiratory support, and a reduction in serious neonatal morbidity. Furthermore, long-term follow-up studies done to date suggest that repeat courses are safe: Compared with children who received a single prenatal course, those who received repeat prenatal courses showed no deficit in growth, blood pressure, neurocognitive function, or developmental scores, and no increase in neurodevelopmental complications. However, although repeat courses may not cause long-term harm, there is no proof that repeat courses offer any long-term benefits. Accordingly, until more conclusive data on long-term outcomes become available, it may be prudent to avoid routine use of repeat courses.

Although the risk/benefit ratio for *prenatal* glucocorticoids appears favorable, the risk/benefit ratio for *postnatal* glucocorticoids is not. Yes, postnatal glucocorticoids are effective for prevention and treatment of chronic lung disease in infants. However, there is a high price to pay: Treatment impairs growth, neuromotor development, and cognitive function. In one study, researchers evaluated 8-year-old children who had received dexamethasone when they were infants. Compared with children who had not received dexamethasone, the treated children were 1.5 inches shorter, had smaller heads, and did less well on tests of motor skills, visual-motor integration, and intelligence. In 2002, both the American Academy of Pediatrics and the Canadian Paediatric Society recommended against routine use of systemic postnatal dexamethasone for prevention and treatment of chronic lung disease in infants.

Lung Surfactant

Lung surfactant, administered by direct intratracheal instillation, is indicated for prevention and treatment (rescue therapy) of RDS. Surfactant therapy lowers the surface tension forces that cause alveolar collapse, and thereby rapidly improves oxygenation and lung compliance and reduces the need for supplemental oxygen and mechanical ventilation. Treatment decreases neonatal mortality by 33%.

In the United States, three preparations of lung surfactant are available: *poractant alfa*, *calfactant*, and *beractant*. Current data are insufficient to recommend any one drug over the others. *Initial* doses for prevention or treatment of RDS are as follows:

- *Poractant alfa* [Curosurf]—2.5 mL/kg
- *Calfactant* [Infasurf]—3 mL/kg
- *Beractant* [Survanta]—4 mL/kg

Because the effects of a single dose are often transient, repeated dosing may be needed. For *poractant alfa*, repeat doses should be 1.25 mL/kg—half the initial dose. For *calfactant* and *beractant*, repeat doses are the same as the initial dose.

Adverse effects result primarily from the administration process. Bradycardia and oxygen desaturation, which occur secondary to vagal stimulation and airway obstruction, are most common. If these occur, it may be necessary to temporarily suspend administration. Other adverse effects include pulmonary hemorrhage, mucus plugging, and endotracheal tube reflux.

Is there an effective alternative to using lung surfactant combined with mechanical ventilation in preterm infants? The answer is "Yes," as shown in the *Surfactant, Positive Pressure, and Oxygenation Randomized Trial* (SUPPORT). In this trial, preterm infants were treated with either continuous positive airway pressure (CPAP) or with surfactant plus mechanical ventilation. The result? The incidence of death, bronchopulmonary dysplasia, and other major outcomes were the same in both groups.

DRUGS FOR CYSTIC FIBROSIS

Cystic fibrosis (CF) is an inherited disorder that primarily damages the lungs, pancreas, and sweat glands. Some patients also develop liver disease. About 30,000 U.S. citizens have the disease. Fifty years ago, most children diagnosed with CF died before the age of 5. Today, the survival time is 37 years, with some living into their 40s and beyond. Drugs cannot cure CF, but they can reduce symptoms and retard progression of injury.

Pathophysiology of Cystic Fibrosis

The underlying cause of CF is mutation of the gene that codes for a particular type of chloride channel, referred to as the *cystic fibrosis transmembrane regulator* (CFTR). In cells that have defective CFTRs, the normal transmembrane flow of chloride ions, sodium ions, and water is disrupted. In the lungs, exocrine glands (eg, pancreas), and other structures, disruption of ion and water flux alters secretions.

Pancreas. Disruption of chloride transport in the pancreas impairs secretion of bicarbonate and digestive enzymes into the small intestine. The immediate result is maldigestion and malabsorption of fats and other nutrients. Absorption of fat-soluble vitamins, especially vitamins A and E, is reduced secondary to malabsorption of fats. Over time, accumulation of digestive enzymes within pancreatic cells leads to cell destruction. At autopsy, the pancreas appears scarred and fibrotic, which led pathologists to name this illness *fibrocystic disease of the pancreas*—later shortened to cystic fibrosis. Until replacement therapy with pancreatic enzymes became possible, malabsorption of nutrients was the major cause of CF death.

Lungs. Today, destruction of lung tissue is the major cause of morbidity and mortality among patients with CF. In the cells that line the airway, defective CFTRs impair secretion of chloride and enhance reabsorption of water and sodium. As a result, mucus becomes thick and viscous, causing plugging of the airway and promoting chronic bacterial colonization. All patients eventually develop active pulmonary infection; the most common pathogens are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Infection elicits an inflammatory response that is mediated primarily by neutrophils. Accumulation of DNA from dead neutrophils further increases the viscosity of sputum. Over time, chronic bronchitis and associated inflammation cause progressive destruction of lung tissue. In 95% of patients, death from cardiorespiratory failure ultimately ensues.

Reproductive Organs. Among patients with CF, 98% of males and 70% to 80% of females are infertile. In males, the usual cause is obstruction of the vas deferens. In females, the

cause appears to be production of thick, sticky cervical mucus, which impedes penetration of sperm.

Drug Therapy

Drugs are used to alleviate symptoms of CF and delay progression of injury to the lungs. Agents employed include pancreatic enzymes, fat-soluble vitamins, antibiotics, dornase alfa, and ibuprofen. Gene therapy is under investigation.

Nutritional Drugs

Pancreatic Enzymes. These enzymes are given as replacement therapy. All preparations contain lipase, protease, and amylase. The most effective formulations deliver the enzymes in enteric-coated microspheres, which are designed to protect the enzymes from stomach acid and ensure dissolution in the duodenum, the site where the enzymes act. Pancreatic enzymes are discussed in Chapter 80.

Fat-Soluble Vitamins. There are four fat-soluble vitamins: A, D, E, and K. Among patients with CF, deficiencies in vitamins A and E are relatively common, whereas deficiency in vitamin K is uncommon and deficiency in vitamin D is rare. Because vitamins are safe and relatively inexpensive, supplementation with all four is done routinely.

Pulmonary Drugs

Inhaled Antibiotics for Chronic Suppressive Therapy. Antibiotics are used long-term to suppress chronic infection with *P. aeruginosa*. The preferred route is *inhalation*. Why? Because this route achieves high concentrations in the airway while minimizing the risk of systemic toxicity. However, because treatment is prolonged, resistance is a concern. Two antibiotics—tobramycin and aztreonam—are approved for chronic inhalation therapy of *P. aeruginosa* infection. Both drugs improve pulmonary function, reduce the density of *P. aeruginosa* in sputum, and decrease the risk of hospitalization. In a trial that compared these drugs directly, aztreonam was more effective. Both drugs cost about \$5000 for a 28-day supply.

With *tobramycin* [TOBI], the dosage is 300 mg every 12 hours in repeating cycles of 28 days on and 28 days off. Each dose takes 10 to 15 minutes to administer. Common adverse effects include cough, wheezing, and hoarseness. In contrast to IV aminoglycosides, inhaled tobramycin is unlikely to cause hearing loss, although it can cause tinnitus (ringing in the ears). The basic pharmacology of tobramycin and other aminoglycosides is discussed in Chapter 87.

With *aztreonam* [Cayston], the dosage is 75 mg 3 times a day in repeating cycles of 28 days on and 28 days off. Each dose takes 2 to 3 minutes to administer, making aztreonam more convenient than tobramycin. Principal adverse effects are cough, nasal congestion, and wheezing. The basic pharmacology of aztreonam is presented in Chapter 85.

Oral and Intravenous Antibiotics for Acute Therapy. Acute exacerbations of pulmonary infection can be treated with oral or IV antibiotics. For mild infection, oral agents may suffice. For severe exacerbations, IV antibiotics are required. Options include aminoglycosides (eg, tobramycin, gentamicin), piperacillin/tazobactam, ticarcillin/clavulanate, and imipenem/cilastatin.

Inhaled Dornase Alfa. Dornase alfa [Pulmozyme], a purified preparation of recombinant human deoxyribonucle-

use, decreases the viscosity of sputum in patients with CF. The drug is administered by inhalation, using an approved nebulizer. Benefits derive from breaking down extracellular DNA that has accumulated in the lungs secondary to death of neutrophils. With daily use, dornase alfa can improve pulmonary function and decrease infection in some patients. The drug is generally well tolerated. Adverse effects include hoarseness, pharyngitis, laryngitis, rash, chest pain, and conjunctivitis. Dosing is begun at 2.5 mg once daily and may be increased to 2.5 mg twice daily if needed. To remain effective, dornase alfa must be administered every day for life. Unfortunately, treatment is expensive. A year's supply of dornase alfa costs over \$12,000. The nebulizer costs another \$2000.

Oral Ibuprofen. High-dose ibuprofen can slow progression of pulmonary damage in patients with mild lung disease caused by CF. Benefits derive from suppressing the inflammatory response that underlies destruction of lung tissue. Ibuprofen dosage should be sufficient to produce peak plasma drug levels of 50 to 100 mg/mL. Side effects attributable to ibuprofen include conjunctivitis and epistaxis (nosebleed).

Inhaled Beta₂-Adrenergic Agonists. Salmeterol [Servent Diskus] and other inhaled beta₂ agonists can be used long term to improve lung function. Benefits derive from causing bronchodilation and improving ciliary function.

DRUGS FOR SICKLE CELL ANEMIA

Sickle cell anemia (SCA) is an inherited blood disorder characterized by abnormal hemoglobin, chronic anemia, periodic painful episodes, and reduced life expectancy. The underlying cause is a mutation in the gene that codes for hemoglobin (Hb). People who inherit two copies of the gene (one from each parent) produce an altered form of Hb, known as HbS. (People with just one copy are carriers, but do not make HbS.) When HbS is fully oxygenated, there is no problem. However, when HbS gives up its oxygen, molecules of HbS can polymerize, forming long, rigid, rod-like chains. As a result, red blood cells (RBCs) assume a sickle (crescent) shape, and hence cannot pass through tiny blood vessels. As more RBCs get stuck, blood flow stops, thereby depriving tissues of required nutrients and oxygen. The result is severe pain, referred to as a vaso-occlusive crisis. Pain location depends on where vessel blockage occurs (eg, hands and feet, joints and extremities, abdomen). The crisis may last a few hours to a few weeks. Some patients have 15 or more painful episodes a year, whereas others may have 1 a year or less. Over time, vaso-occlusive events produce progressive organ damage and premature death. The median age at death is 42 for men and 48 for women. In many cases, death results from pulmonary arterial hypertension. Management of this condition is discussed above.

In addition to vaso-occlusive events, people with SCA experience chronic anemia (shortage of RBCs). Why? Unlike normal RBCs, which persist about 120 days, sickled RBCs die in 10 to 20 days. Because RBC loss is unusually rapid, replacements cannot be made fast enough, and hence a chronic shortage results.

Who is vulnerable to SCA? Worldwide, millions of people have the disease. In the United States, about 72,000 people have SCA. Most are African Americans (about 1 in 700 carry two copies of the sickle cell gene, and 1 in 14 carry one copy).

In addition, SCA afflicts between 1 in 1000 to 1400 Hispanic Americans. The disease is not found among white Americans.

Researchers believe that the sickle cell mutation arose in a region where malaria is endemic. There is evidence that, in people with *one* copy of the gene, malaria is less deadly than in people who do not have the gene. As a result, those who carried the gene were more likely to survive, and hence could pass the advantage on to their children. Of course, in areas like the United States, where malaria rarely occurs, the gene offers no survival advantage—and, when two copies are inherited, the gene becomes a threat to survival.

Treatment consists of transfusions, analgesics, glucocorticoids, and hydroxyurea. Blood transfusions help correct anemia and reduce painful episodes. Analgesics and glucocorticoids can alleviate pain. Hydroxyurea can reduce the incidence and severity of painful episodes and, perhaps more importantly, it can prolong life.

Analgesics and Glucocorticoids

For patients undergoing an acute crisis, analgesics and hydration are the cornerstone of treatment. Unfortunately, most patients generally fail to receive adequate pain relief. If the pain is moderate, a nonopioid analgesic (acetaminophen or a nonsteroidal anti-inflammatory agent) may be sufficient. However, if pain is severe, intensive therapy with an opioid is required. Parenteral (IV or IM) morphine and meperidine have been employed. Patient-controlled analgesia may be especially effective. The basic pharmacology of the opioids is discussed in Chapter 28.

High doses of intravenous methylprednisolone (a glucocorticoid) can shorten the duration of a sickle cell crisis. The drug should be used together with, not instead of, an opioid. Unfortunately, when glucocorticoids are discontinued, rebound pain may occur. The basic pharmacology of the glucocorticoids is discussed in Chapters 60 and 72.

Hydroxyurea

Hydroxyurea was originally developed to treat cancer (see Chapter 102), and is now used for SCA as well. Treatment can reduce the number of painful events as well as the need for hospitalization and transfusions. Furthermore, it can reduce mortality. Currently, hydroxyurea is approved only for adults. Formulations for SCA are marketed as *Droxia*, and formulations for cancer are marketed as *Hydrea*.

Mechanism of Action. Hydroxyurea increases production of fetal hemoglobin (HbF), a form of Hb present in infants but not normally present after the sixth month of postnatal life. In patients with SCA, elevation of HbF decreases hemoglobin polymerization, and thereby decreases RBC sickling and prolongs RBC life. Hydroxyurea also reduces adhesion of RBCs to the vascular endothelium. Precisely how the drug elevates HbF has not been established.

Clinical Trials. The first major study with hydroxyurea—the Multicenter Study of Hydroxyurea (MSH) in Sickle Cell Anemia trial—was conducted between 1992 and 1995. In this double-blind, randomized, placebo-controlled trial, hydroxyurea produced a 44% reduction in the incidence of painful episodes, a 58% reduction in hospitalizations, and a 34% reduction in transfusions. On the basis of these results, the FDA approved hydroxyurea for reducing

painful episodes in adults with SCA. In 2003, results of the MSH Patients' Follow-up trial were published. This trial, which followed patients from the original MSH trial, evaluated the impact of prolonged therapy (up to 9 years) on mortality. The result? Mortality among patients taking hydroxyurea was 40% lower than among those not taking the drug. Furthermore, reductions in mortality were proportional to the extent of HbF elevation and to reductions in painful episodes. It is important to note that hydroxyurea is more likely to benefit patients with severe SCA than patients with moderate or mild SCA. Accordingly, treatment is strongly recommended for the 30% of patients with severe SCA, and is not recommended for the 20% of patients with mild SCA. Whether the drug should be used by the 50% of patients with moderate SCA is unclear.

Adverse Effects. Hydroxyurea can cause severe *myelosuppression*. Life-threatening reductions in blood-cell counts can result. Accordingly, frequent monitoring of hematologic status is required. Hydroxyurea should not be used if bone marrow function is already significantly depressed.

Hydroxyurea can cause *fetal harm*, and hence should be avoided during pregnancy. The drug is classified in FDA Pregnancy Risk Category D.

Hydroxyurea is *carcinogenic* in animals, and probably in humans too. Among patients receiving hydroxyurea for cancer, a few have developed leukemia. However, it is not clear that hydroxyurea was the cause.

At this time, possible long-term adverse effects in patients with SCA are unknown.

Hematologic Monitoring. Hematologic status should be determined every 2 weeks. Acceptable values and values indicating toxicity are as follows:

- *Neutrophils*—acceptable, 2500 cells/mm³; toxic, below 2000 cells/mm³
- *Platelets*—acceptable, 95,000/mm³; toxic, below 80,000/mm³
- *Hemoglobin*—acceptable, 5.3 gm/dL; toxic, below 4.5 gm/dL
- *Reticulocytes*—acceptable, 95,000/mm³ (if Hb is below 9 gm/dL); toxic, below 80,000/mm³ (if Hb is below 9 gm/dL)

Preparations, Dosage, and Administration. For treatment of SCA, hydroxyurea [Droxia] is available in capsules (200, 300, and 400 mg) for oral dosing. The initial dosage is 15 mg/kg once a day. If blood counts remain acceptable, dosage may be increased by 5 mg/kg/day every 12 weeks—up to a maximum of 35 mg/kg/day. If blood counts indicate toxicity, treatment should be temporarily interrupted. Recovery usually occurs in 2 weeks, after which treatment can be resumed, but at a reduced dosage.

DRUGS FOR HYPERURICEMIA CAUSED BY CANCER CHEMOTHERAPY

Hyperuricemia (elevation of uric acid levels) is a common consequence of cancer chemotherapy. The cause is breakdown of DNA following massive cell death. Two drugs are available for management: rasburicase and allopurinol. Rasburicase accelerates uric acid removal; allopurinol blocks uric acid production.

Rasburicase

Action and Use. Rasburicase [Elitek, Fasturtec[◆]], produced by recombinant DNA technology, is a form of urate oxidase, an enzyme that converts uric acid into a soluble, inactive product (allantoin). The drug is indicated for management of hyperuricemia in adult and pediatric patients undergoing treatment for leukemias, lymphomas, and solid tumors—diseases in which cell lysis caused by chemotherapy is expected to produce a significant increase in plasma uric acid.

Adverse Effects. In clinical trials, the most common reactions were vomiting (50%), fever (46%), nausea (27%), abdominal pain (20%), constipation (20%), diarrhea (20%), and rash (13%). More serious reactions included neutropenia and fever (4%), respiratory distress (3%), sepsis (3%), and mucositis (2%). The most severe reactions, which occurred in 1% of patients or less, were hemolysis, methemoglobinemia, and severe allergic reactions, including anaphylaxis; if any of these reactions occurs, rasburicase should be discontinued immediately and never used again.

Preparations, Dosage, and Administration. Rasburicase [Elitek, Fasturtec[◆]] is supplied as a powder (1.5 and 7.5 mg/vial) for reconstitution in the diluent provided. Vigorous agitation should be avoided. The recommended dosage is 0.2 mg/kg, infused over 30 minutes, on 5 consecutive days. Start the first infusion 4 to 24 hours prior to the first dose of chemotherapy.

Allopurinol

Allopurinol [Zyloprim] is used to manage hyperuricemia associated with gout and with cancer chemotherapy. Benefits derive from inhibiting xanthine oxidase, the enzyme needed to convert DNA breakdown products (xanthine and hypoxanthine) into uric acid. Allopurinol is discussed at length in Chapter 74 (Drug Therapy of Gout).

PHOSPHATE BINDERS FOR PATIENTS ON DIALYSIS

Phosphate binders are used to treat hyperphosphatemia, a common complication of end-stage renal disease. Blood phosphate is high during renal failure because glomerular filtration of phosphate is reduced and tubular reabsorption of phosphate is increased. Hyperphosphatemia is a concern because it promotes hyperparathyroidism, which in turn promotes *hypercalcemia*, a risk factor for cardiovascular (CV) calcification and CV morbidity and mortality.

Treatment of hyperphosphatemia consists of three measures: (1) reducing phosphate intake, (2) removing phosphate with hemodialysis, and (3) reducing intestinal absorption of phosphate with a phosphate-binding drug. Reducing phosphate in the diet is problematic in that most dietary phosphate comes from proteins (eg, meats, fish, dairy products, peas, and lentils). Hence, reducing dietary phosphate may result in malnutrition. Accordingly, the ability to manage hyperphosphatemia by reducing phosphate intake is limited.

As indicated in Table 107-2, phosphate-binding drugs fall into two major groups: *calcium-based phosphate binders* (eg, calcium carbonate) and *calcium-free phosphate binders* (eg, sevelamer carbonate). All of these drugs are equally effective at reducing phosphate absorption. And they all pose a risk of adverse GI effects. The principal differences among them relate to (1) *price* (the calcium-based drugs cost much less than the calcium-free drugs) and (2) the risk of exacerbating *hypercalcemia* (the calcium-based drugs increase hypercalcemia risk, whereas the calcium-free drugs do not). Because of these

TABLE 107-2 ■ Phosphate Binders for Patients on Renal Dialysis

Drug	Trade Name	Formulation (Including Calcium Content)	Usual Single Dose (Taken 3 Times a Day with Meals)	Calcium Load (mg/day)	Annual Cost	Comments
Calcium-Based Phosphate Binders						
Calcium carbonate	Os-Cal 500	Tablets, 1250 mg (500 mg Ca)	1250 mg	1500	\$100–\$200	Cheap, but can promote hypercalcemia
	Caltrate-600	Tablets, 1500 mg (600 mg Ca)	1500 mg	1800		
Calcium acetate	PhosLo	Tablets, 667 mg (169 mg Ca)	2001–2668 mg	507–676	\$1000–\$2000	Relatively cheap, but can promote hypercalcemia
		Gelcaps, 667 mg (169 mg Ca)	2001–2668 mg	507–676		
Calcium-Free Phosphate Binders						
Sevelamer hydrochloride	Renagel	Tablets, 400 mg (0 mg Ca)	800–1600 mg	0	\$4400–\$8800	Expensive; lowers cholesterol; does not promote hypercalcemia, but does promote metabolic acidosis
		Tablets, 800 mg (0 mg Ca)	800–1600 mg			
Sevelamer carbonate	Renvela	Tablets, 800 mg (0 mg Ca)	800–1600 mg	0	\$5500–\$11,000	Same as sevelamer hydrochloride, but may cause less metabolic acidosis
Lanthanum carbonate	Fosrenol	Chewable tablets, 500, 750, and 1000 mg (0 mg Ca)	1500–3000 mg	0	\$7000–\$14,000	Expensive; does not lower cholesterol; does not promote hypercalcemia or metabolic acidosis

differences, the prescriber is faced with a dilemma: Do I save the patient money (with a calcium-based binder), but increase the risk of hypercalcemia and associated CV calcification? Or do I reduce the risk of hypercalcemia (with a calcium-free binder), but greatly increase the cost? A reasonable solution to the dilemma might be this: Reserve the expensive, calcium-free binders for patients who already have hypercalcemia and evidence of coronary artery calcification, and prescribe the cheaper, calcium-free binders for patients with normal calcium levels and no coronary calcification.

Of the calcium-free phosphate binders in current use, one drug—sevelamer—deserves comment. Sevelamer is available as two salts: *sevelamer hydrochloride* [Renagel] and *sevelamer carbonate* [Renvela]. Both salts are equally good at reducing absorption of dietary phosphate, and they both share an additional asset: they can bind with bile salts in the intestine, and can thereby decrease the synthesis of cholesterol, a major risk factor for CV morbidity and mortality. Although these salts are very similar, they differ in one important way: Sevelamer hydrochloride can cause *metabolic acidosis*, whereas sevelamer carbonate may not. Metabolic acidosis is a concern because it increases the risk of hyperkalemia, breakdown of proteins, bone dissolution, osteodystrophy, and even death. Since the carbonate component of sevelamer carbonate can act as a buffer, the risk of acidosis with this salt is likely to be lower than with sevelamer hydrochloride. However, there are no data to show that patients fare better with the carbonate salt.

GAMMA-HYDROXYBUTYRATE FOR CATAPLEXY IN PATIENTS WITH NARCOLEPSY

History. Gamma-hydroxybutyrate (GHB) [Xyrem], also known as *sodium oxybate*, is a central nervous system (CNS) depressant with a rapid onset and short duration. The drug was originally developed as a surgical anesthetic, but was discontinued owing to serious side effects: profound respiratory depression, coma, and death. In the 1990s, GHB gained notoriety as a drug of abuse: It was used at parties to produce euphoria and disinhibition, and it was administered clandestinely to facilitate rape (see Box 40–1). As a result, GHB was declared illegal.

Therapeutic Use. In 2002, GHB became the first and only drug approved by the FDA for treating *cataplexy* in patients with narcolepsy. Narcolepsy itself, which afflicts about 120,000 Americans, is characterized by fragmented sleep, daytime somnolence, and uncontrollable attacks of sleep during waking hours. In addition, about 60% to 70% of patients experience cataplexy (sudden loss of muscle tone), typically triggered by intense emotion, such as anger, fear, grief, or even amusement. A cataplectic attack may last a few seconds to many minutes, and can range in severity from dropping of the jaw or slumping of the head to buckling of the legs or collapse of the entire body. As discussed in Chapter 36, patients take CNS stimulants (eg, methylphenidate [Ritalin], dextroamphetamine [Dexedrine]) to promote daytime wakefulness

and reduce sudden sleep attacks. GHB is indicated specifically to reduce attacks of cataplexy. Benefits appear to derive from rebound CNS excitement that occurs when the drug's depressant effects wear off. In addition to reducing cataplexy, GHB can improve the quality of nighttime sleep, and can thereby help reduce daytime sleepiness.

Adverse Effects and Abuse. In clinical trials, GHB produced confusion, depression, headache, dizziness, sleepwalking, bedwetting, nausea, and vomiting. In two patients, respiratory depression occurred. The risk of respiratory depression is increased by combining GHB with alcohol and other CNS depressants. Because of its sodium content (a 9-gm dose contains 1.6 gm of sodium), GHB may pose a risk to patients with heart failure. Abuse of the drug could cause physical dependence. Because of its abuse history, GHB is regulated as a Schedule III substance.

Availability. Owing to concerns about adverse effects and abuse, availability of GHB is regulated under a strict and comprehensive risk management program. Provisions include limited distribution, prescriber and patient education, prescriber and patient registries, and detailed patient surveillance. Under the program, GHB can be obtained only through a single centralized pharmacy. Before the pharmacy can dispense GHB, the prescriber must verify that the patient has received instruction on its safe use.

Preparations, Dosage, and Administration. Gamma-hydroxybutyrate [Xyrem] is available in oral solution (500 mg/mL in 180-mL bottles). Patients take two doses each night, one at bedtime and one 2.5 to 4 hours later. At treatment onset, each dose is 2.25 gm (4.5 gm total per night). Dosage can be gradually increased to a maximum of 9 gm total per night. In patients with impaired liver function, the dosage should be halved. Treatment is expensive: At 9 gm per night, the cost is about \$740 per month (\$8880 per year).

RILUZOLE FOR AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) is a neuromuscular disorder characterized by progressive muscle wasting and loss of strength. The underlying cause is degeneration of motor neurons in the spinal cord, brainstem, and motor cortex. Why motor neurons degenerate is largely unknown. Initial symptoms typically include weakness in the hands and legs, muscle cramps, stiffness, and twitching. Over time, the patient becomes weaker and weaker. Eventually, all skeletal muscles, including the muscles of respiration, become paralyzed. Intellectual function, eye movement, bladder function, and sensation are not affected. Most patients die within 3 to 5 years, although some survive for a decade or longer. In the United States, about 30,000 people have ALS, and 5000 new cases are diagnosed each year. At this time, ALS has no cure.

In 2009, the American Academy of Neurology issued two new guidelines for optimizing treatment of ALS. These guidelines—*Practice Parameter Update: The Care of the Patient with Amyotrophic Lateral Sclerosis: Drug, Nutritional, and Respiratory Therapies (an Evidence-Based Review)* and *Practice Parameter Update: The Care of the Patient with Amyotrophic Lateral Sclerosis: Multidisciplinary Care, Symptom Management, and Cognitive/Behavioral Impairment (an Evidence-Based Review)*—are available online at www.aan.com/globals/axon/assets/6409.pdf and www.aan.com/globals/axon/assets/6410.pdf.

Riluzole. Riluzole [Rilutek], a glutamate antagonist, is the only drug approved for ALS. In clinical trials, riluzole prolonged life or delayed the need for a tracheostomy by 3 to 6 months. However, not only were benefits modest, they were limited to patients whose nerve degeneration began in the *medulla*; riluzole did not help patients whose nerve degeneration began in the *spinal cord*. The reason for this difference is unknown.

Riluzole is generally well tolerated. The most common adverse effects are asthenia (decreased strength), GI reactions (nausea, vomiting, diarrhea, abdominal pain), CNS effects (dizziness, vertigo, somnolence), and decreased lung function. Neutropenia develops rarely.

Riluzole can injure the liver, as indicated by an increase in circulating aminotransferase levels. Risk is higher in patients with pre-existing liver disease. To monitor for liver injury, measure aminotransferase levels at baseline, then monthly for 3 months, then every 3 months for the first year, and periodically thereafter. Riluzole should be discontinued if aminotransferase levels exceed 5 times the upper limit of normal, or if clinical jaundice is diagnosed.

Riluzole is available in 50-mg oral tablets. The recommended dosage is 50 mg every 12 hours. Increasing the dosage does not increase benefits, but does increase adverse effects. Riluzole should be taken 1 hour before meals or 2 hours after to increase bioavailability.

TETRABENAZINE FOR CHOREA OF HUNTINGTON'S DISEASE

Huntington's Disease

Huntington's disease (HD) is an inherited neurodegenerative disorder characterized by cognitive dysfunction, psychiatric changes, and movement disorders. The underlying cause is genetically based death of CNS neurons. Symptoms typically begin between the ages of 30 and 55 years, and then slowly progress. Death occurs 10 to 30 years after symptom onset. Huntington's disease is a rare disorder with a prevalence of 1 in 10,000.

Psychiatric symptoms, which may precede movement disorders, include anxiety, paranoid psychosis, personality changes, and depression and suicidality. Management includes standard medications for these conditions. Keep in mind, however, that antipsychotic drugs can confound the diagnosis and management of HD movement disorders. Why? Because antipsychotic agents can cause extrapyramidal movement disorders. Hence, if a patient develops a movement disorder, it may be hard to tell if the disorder is drug induced or caused by HD.

Motor symptoms are mild at first, and become more pronounced as additional neurons die. Initial symptoms may be limited to clumsiness, balance difficulties, and facial tics. Later on, patients develop *chorea*, manifesting as involuntary, irregular, flowing movements that may shift from one area of the body to another. Severe chorea manifests as pronounced continuous movements of the whole body. Other late symptoms include rigidity, difficulty swallowing, hesitant or slurred speech, rapid jerky eye movements, and severe coordination and balance problems. What causes these motor symptoms? *Excessive activity of dopamine (DA)*, possibly secondary to the death of neurons that produce acetylcholine and gamma-aminobutyric acid (GABA).

TABLE 107-3 ■ Drugs for Chorea of Huntington's Disease

Drugs	Approved for HD	Major Side Effects
Drugs That Reduce Dopamine Stores		
Tetrabenazine [Xenazine, Nitoman [◆]]	Yes	Depression, suicidal thoughts and actions
Reserpine (generic only)	No	Depression, hypotension
Drugs That Block Dopamine Receptors		
First-Generation Antipsychotics		
Haloperidol [Haldol]	No	Extrapyramidal effects
Pimozide [Orap]	No	Extrapyramidal effects, sedation
Second-Generation Antipsychotics		
Risperidone [Risperdal]	No	Extrapyramidal effects, but less likely than
Ziprasidone [Geodon]	No	with first-generation antipsychotics
Quetiapine [Seroquel]	No	

HD = Huntington's disease.

Huntington's chorea often responds to drugs that decrease the activity of DA (Table 107-3). Two mechanisms are involved: reduction of DA stores and blockade of DA receptors. We can reduce DA stores with tetrabenazine or reserpine. Unfortunately, both drugs can cause depression, a disorder often associated with HD. In addition, reserpine can cause hypotension. We can block DA receptors with antipsychotic drugs. Unfortunately, these agents can cause extrapyramidal side effects. Hence their use may substitute one movement disorder for another. With the exception of tetrabenazine, all of these drugs are discussed in previous chapters. Accordingly, discussion here is limited to tetrabenazine. The basic pharmacology of reserpine is presented in Chapter 19 (Indirect-Acting Antiadrenergic Agents), and the basic pharmacology of the antipsychotic drugs is presented in Chapter 31 (Antipsychotic Agents and Their Use in Schizophrenia).

Tetrabenazine

In 2008, the FDA approved tetrabenazine [Xenazine, Nitoman[◆]] for treatment of chorea associated with HD, making tetrabenazine the first and only drug approved for HD in the United States. However, although tetrabenazine is the only drug approved for HD, other drugs have been used to treat HD for years. Moreover, tetrabenazine is not a new compound. It was developed 50 years ago as a treatment for schizophrenia, and has been used in Europe for decades.

In clinical trials for Huntington's chorea, daily treatment with tetrabenazine produced a 23.5% improvement in symptom severity. For some patients, benefits persisted over 5 years of continuous drug use. How does tetrabenazine work? It reduces the availability of DA and other monoamine neurotransmitters (ie, serotonin, norepinephrine). Specifically, tetrabenazine inhibits a transporter—the *type 2 vesicular monoamine transporter* (VMAT-2)—that moves monoamine neurotransmitters into vesicles within nerve terminals. As a result of VMAT-2 inhibition, (1) transmitter molecules that remain outside the vesicles undergo destruction by monoamine oxidase and (2) the transmitter content of the vesicles themselves

is reduced. Hence, when an action potential reaches the nerve ending, the vesicles have less transmitter to release into the synaptic cleft.

Tetrabenazine is well absorbed following oral dosing, and then undergoes extensive hepatic metabolism by CYP2D6 (the 2D6 isozyme of cytochrome P450). Parent drug and metabolites are eliminated in the urine. Their half-lives range from 4 to 8 hours. In patients with hepatic impairment, and in those with low CYP2D6 activity, the half-life of tetrabenazine is prolonged, and plasma drug levels are elevated.

Many patients experience adverse effects. The most common are extrapyramidal reactions (33%), including parkinsonism, akathisia (profound restlessness), and dystonia (a reaction characterized by severe spasm of the muscles of the tongue, face, neck, or back). Other common reactions include drowsiness (31%), insomnia (22%), fatigue (22%), anxiety (15%), and nausea (13%). However, the side effects of greatest concern are *depression* (19%) and *suicidality*. Recall that both depression and suicidality are common in HD. Tetrabenazine increases the risk of both. Accordingly, all patients using the drug should be watched closely for new or worsening depression, and for expression of suicidal thoughts or behavior. If these occur, the dosage of tetrabenazine should be reduced. Patients may also benefit from starting or intensifying treatment with an antidepressant. Tetrabenazine is contraindicated for patients who are actively suicidal, and for those with depression that is not adequately treated.

Tetrabenazine [Xenazine, Nitoman[◆]] is supplied in 12.5- and 25-mg tablets. Dosage must be individually titrated over several weeks. The goal is to control symptoms without causing intolerable side effects. Dosing starts at 12.5 mg once daily in the morning. After 1 week, dosage is increased to 12.5 mg twice daily. Further increases of 12.5 mg/day are made at weekly intervals. Daily totals of 37.5 mg to 50 mg should be given as three divided doses. The maximum single dose is 25 mg, and the maximum daily dose is 100 mg. Dosage should be reduced in patients with low CYP2D6 activity. Patients with hepatic impairment should not use this drug.

DRUGS FOR FIBROMYALGIA SYNDROME

Fibromyalgia syndrome (FMS) is a chronic disorder characterized by widespread musculoskeletal pain, profound fatigue, nonrestorative sleep, and cognitive dysfunction (eg, impaired memory and concentration). The condition affects about 2% of the population, making it one of the most common of chronic pain syndromes. The incidence is 7 times greater in women than in men.

What causes the pain of FMS? We don't know completely. However, we do know that the pain is *not* the result of pathologic changes in muscles, bones, or joints. Rather, the pain results from abnormal central processing of pain signals, such that patients have a reduced threshold to mechanical and thermal pain stimuli. The neurotransmitters involved in pain perception—serotonin, dopamine, norepinephrine, and substance P, among others—are also involved in regulation of sleep, mood, and cognition, which may explain why the symptoms of FMS are so diverse.

Diagnostic criteria for FMS were published by the American College of Rheumatology in 1990. For a diagnosis, three conditions must be met. First, there must be widespread, ach-

TABLE 107-4 ■ Drugs for Fibromyalgia Syndrome

Drugs	Approved for FMS	Comments
DRUGS FOR PAIN RELIEF		
Antidepressants: TCAs and Related Compounds		
Amitriptyline [Elavil]	No	Highly effective; recommended as first-line therapy for FMS
Cyclobenzaprine [Flexeril]*	No	Moderately effective
Antidepressants: SSRIs		
Fluoxetine [Prozac]	No	Moderately effective
Paroxetine [Paxil]	No	Moderately effective
Antidepressants: SNRIs		
Milnacipran [Savella] [†]	Yes	Moderately effective
Duloxetine [Cymbalta]	Yes	Moderately effective
Anticonvulsants		
Gabapentin [Neurontin]	No	Moderately effective
Pregabalin [Lyrica]	Yes	Moderately effective
Analgesics		
Tramadol [Ultram]	No	Moderately effective
Opioids	No	Probably effective, but, owing to side effects and abuse potential, should not be used unless safer treatments have failed
NSAIDs	No	Ineffective when used alone, but may add to analgesic benefits of other drugs
DRUGS FOR SLEEP DISTURBANCES		
TCAs and Related Compounds		
Amitriptyline [Elavil]	No	A foundation of therapy for sleep disturbances
Cyclobenzaprine [Flexeril]*	No	A foundation of therapy for sleep disturbances
Benzodiazepine-like Drugs		
Zolpidem [Ambien]	No	Benzodiazepine-like drugs are used for patients intolerant of or unresponsive to amitriptyline or cyclobenzaprine
Zaleplon [Sonata]	No	
Eszopiclone [Lunesta]	No	
Dopaminergic Drugs for RLS		
Levodopa/carbidopa [Sinemet]	No	RLS is a major cause of unrestorative sleep in FMS. Dopaminergic drugs can help.
Pramipexole [Mirapex]	No	
Ropinirole [Requip]	No	

FMS = fibromyalgia syndrome, NSAIDs = nonsteroidal anti-inflammatory drugs, RLS = restless legs syndrome, SNRIs = serotonin/norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

*Cyclobenzaprine is nearly identical in structure to amitriptyline, but is not used as an antidepressant.

[†]In the United States, milnacipran is approved only for FMS. In Europe, the drug is approved for FMS and depression.

ing pain for at least 3 months. Second, the pain must be on both sides of the body, both above and below the waist. Third, the patient must experience pain when pressure is applied to at least 11 of 18 well-defined "tender points" (eg, in the neck at the suboccipital muscle insertions, in the knees at the medial fat pad proximal to the joint line).

Drugs for FMS can be placed into two basic groups: drugs for pain management and drugs for sleep disturbances (Table 107-4). For pain management, we can use antidepressants, anticonvulsants, or analgesics. For sleep disturbances, we can use certain antidepressants, benzodiazepine-like drugs, or dopaminergic agents.

Management of FMS pain has been described in an evidence-based guideline—*Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children*—commissioned by the American Pain Society. This guideline stresses the importance of a multidisciplinary approach that uses drug therapy combined with nondrug interventions (eg, physical therapy, aerobic exercise, biofeedback, relaxation techniques, cognitive behavioral therapy). Drugs for pain relief are summarized in Table 107-4. For the most part, these drugs work in the CNS to alter signaling in pain pathways. With the exception of milnacipran, all of these drugs have been discussed in previous chapters. Of note, only three

drugs—duloxetine, milnacipran, and pregabalin—have been specifically approved for treating FMS. Keep in mind, however, that approval does not mean that these three drugs are more effective than the rest. But it does mean that at least some efficacy has been documented in clinical trials, and that the manufacturer has used these data to obtain FDA approval to market these drugs for FMS.

Antidepressants and Related Drugs

Antidepressants are a mainstay of FMS pain therapy. In clinical trials, these drugs have reduced pain and fatigue, and have improved sleep and sense of well-being. Tricyclic antidepressants (TCAs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) appear most effective. With all antidepressants, benefits in FMS are largely independent of antidepressant effects. Put another way, pain relief is about equal in patients who are depressed and in those who are not. Although these drugs can be helpful, keep in mind that all antidepressants may increase the risk of suicidal thoughts and behavior in children, adolescents, and young adults. Appropriate caution must be exercised. The basic pharmacology of the antidepressants is discussed in Chapter 32.

Tricyclic Antidepressants and Cyclobenzaprine

Tricyclic antidepressants are the most effective agents we have for reducing pain and other symptoms of FMS. However, despite their benefits, none of the TCAs is approved for FMS. There is strong evidence that one agent—*amitriptyline* [Elavil]—can reduce both pain and fatigue, and can also improve sleep. How do TCAs work? As discussed in Chapter 32 (Antidepressants), TCAs block neuronal reuptake of norepinephrine and serotonin, and they block receptors for acetylcholine (ACh). In patients with FMS, benefits are believed to result from blockade of norepinephrine and serotonin reuptake, which increases the availability of these transmitters at central synapses, which in turn activates spinal inhibition of pain signaling. Major side effects (eg, dry mouth, blurred vision, urinary retention, constipation) result from blockade of receptors for ACh.

Cyclobenzaprine [Flexeril] is a tricyclic compound nearly identical in structure to amitriptyline. However, despite this similarity, the drug is used mainly as a muscle relaxant (see Chapter 25), not as an antidepressant. In patients with FMS, cyclobenzaprine can improve sleep quality, and can produce modest improvements in pain, stiffness, and fatigue.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Two SSRIs—*fluoxetine* [Prozac] and *paroxetine* [Paxil]—are beneficial in FMS, even though neither drug is approved for the disorder. In one randomized controlled trial, fluoxetine reduced pain and other symptoms of FMS. In another trial, paroxetine improved patient scores on the Fibromyalgia Impact Questionnaire.

Serotonin/Norepinephrine Reuptake Inhibitors

As discussed in Chapter 32, the SNRIs block neuronal reuptake of serotonin and norepinephrine, in contrast to the SSRIs, which block reuptake of serotonin only. Presumably, benefits of the SNRIs are the result of increased availability of serotonin and norepinephrine at CNS synapses.

Duloxetine. In 2008, the FDA approved duloxetine [Cymbalta] for treatment of FMS, making it the second drug ap-

proved for this disorder. (Pregabalin [Lyrica], approved in 2007, was the first.) As noted in Chapter 32, duloxetine is also approved for depression, generalized anxiety disorder, chronic musculoskeletal pain, and pain of diabetic neuropathy. In patients with FMS, duloxetine can reduce pain, fatigue, and stiffness, and can improve overall quality of life. If the patient also suffers from depression, duloxetine can help with that too. Unfortunately, duloxetine can cause a variety of adverse effects (eg, nausea, dry mouth, constipation, insomnia, dizziness, loss of appetite), and is subject to multiple drug interactions.

Milnacipran. Milnacipran [Savella] was approved for FMS in 2009, making it the third drug approved for FMS in the United States. Unlike duloxetine, milnacipran is not approved here for depression. However, the drug has been used to treat depression in Europe and Asia since 1997. In clinical trials, milnacipran reduced pain and fatigue of FMS, and improved sleep and cognitive function. Furthermore, benefits were maintained for up to 1 year with daily dosing. As with duloxetine, benefits are presumed to derive from elevation of synaptic serotonin and norepinephrine concentrations secondary to blockade of transmitter reuptake.

Milnacipran has good oral bioavailability, both in the presence and absence of food. Plasma levels peak 2 to 4 hours after dosing. Milnacipran is eliminated in the urine, primarily as unchanged drug (55%). In patients with normal kidney function, the half-life is 6 to 8 hours. In patients with significant renal impairment, both the half-life and peak blood levels are increased.

Milnacipran can cause multiple adverse effects. In clinical trials, the most common were nausea (35%), headache (19%), constipation (16%), insomnia (12%), dizziness (11%), hot flushes (11%), excessive sweating (8%), vomiting (6%), dry mouth (5%), and cardiovascular effects: palpitations (8%), increased heart rate (5%), and hypertension (7%). To reduce the risk of adverse cardiovascular events, heart rate and blood pressure should be measured at baseline and periodically during treatment. Pre-existing hypertension and tachycardia should be controlled before using the drug. Milnacipran can cause mydriasis (pupil dilation), and hence is contraindicated in patients with uncontrolled narrow-angle glaucoma. There is some risk of liver injury, as indicated by elevations of alanine and aspartate aminotransferases. Like other serotonin reuptake inhibitors, milnacipran can increase the risk of bleeding. And like all other antidepressants, milnacipran may increase the risk of suicidal thoughts and behavior.

Combining milnacipran with other serotonergic drugs increases the risk of serotonin syndrome. Accordingly, milnacipran should not be combined with SSRIs, other SNRIs, or monoamine oxidase inhibitors (MAOIs). Furthermore, MAOIs should be discontinued at least 14 days before starting milnacipran, and milnacipran should be discontinued at least 5 days before starting an MAOI. Because of milnacipran's cardiovascular effects, the drug should not be combined with other drugs that increase blood pressure or heart rate. Because milnacipran can promote bleeding, it should not be combined with aspirin, warfarin, or any other drug that can suppress coagulation.

Milnacipran [Savella] is available in tablets (12.5, 25, 50, and 100 mg) for dosing with or without food. Dosage should be titrated as follows: 12.5 mg once on day 1, 12.5 mg twice on days 2 and 3, 25 mg twice on days 4 through 7, and 50 mg twice daily thereafter. In patients with severe renal impairment, the maintenance dosage should be cut in half, to 25 mg

twice daily. Patients with end-stage renal disease should not use this drug. When milnacipran is discontinued, dosage should be tapered gradually.

Anticonvulsants

Two anticonvulsants—*pregabalin* [Lyrica] and *gabapentin* [Neurontin]—are moderately effective in reducing pain of FMS. Pregabalin is approved for FMS; gabapentin is not. Benefits of pregabalin may derive from suppressing release of glutamate (an excitatory neurotransmitter), whereas benefits of gabapentin may derive from increasing release of GABA (an inhibitory neurotransmitter). Side effects of these drugs include fatigue, sedation, nausea, drowsiness, dizziness, and weight gain. The basic pharmacology of pregabalin and gabapentin is presented in Chapter 24.

Analgesics

Tramadol. Tramadol [Ultram] is a centrally acting non-opioid analgesic. In patients with FMS, the drug can produce a moderate reduction in discomfort. How does tramadol work? Like the TCAs, it blocks neuronal reuptake of 5-hydroxytryptamine and norepinephrine, and thereby enhances spinal inhibition of pain signaling. Additional pain relief may come from weak agonist activity at mu opioid receptors. The basic pharmacology of tramadol is presented in Chapter 28.

Opioid Analgesics. Opioids are strong analgesics that may help control the pain of FMS. Unfortunately, these drugs can cause significant adverse effects (eg, sedation, respiratory depression, constipation, impaired cognition) and they pose a risk of dependence and abuse. Accordingly, opioids should not be used as first-line agents. Rather, they should be reserved for patients who have not responded adequately to preferred pharmacologic and nonpharmacologic treatments. The basic pharmacology of the opioids is presented in Chapter 28.

Nonsteroidal Anti-inflammatory Agents (NSAIDs). When used alone, aspirin, ibuprofen, and other NSAIDs offer little or no benefit in FMS—probably because FMS is not an inflammatory disorder. Accordingly, monotherapy with NSAIDs is not recommended. However, NSAIDs may provide some additional analgesia when combined with other agents.

Drugs for Sleep Disturbances

For many patients, disturbed sleep is the most troubling symptom of FMS. As with management of FMS pain, the drugs of first choice are TCAs and cyclobenzaprine. If these agents are ineffective or intolerable, a benzodiazepine-like sedative may be tried. Options include zolpidem [Ambien], zaleplon [Sonata], and eszopiclone [Lunesta]. The most common cause of disturbed sleep in FMS is restless legs syndrome, which can be managed with gabapentin [Horizant], or a dopaminergic agent, such as levodopa/carbidopa [Sinemet] or a direct-acting dopamine agonist (eg, pramipexole [Mirapex], ropinirole [Requip]).

DRUGS FOR HEREDITARY ANGIOEDEMA

Hereditary angioedema (HAE) is a genetic disorder characterized by localized, self-limiting episodes of edema (tissue swelling) that occur mainly in the larynx, subcutaneous tissue,

and submucosa of the intestinal wall. Edema of the larynx and facial area can cause fatal obstruction of the airway. Abdominal attacks (from intestinal edema) can cause severe abdominal pain, cramping, nausea, and vomiting. On average, attacks occur every 10 to 14 days, and last for 3 to 5 days. The underlying cause of HAE is a *deficiency in C1-esterase inhibitor*—or simply *C1-inhibitor* (C1-INH)—owing to a mutation in the C1-INH gene. HAE is a rare disorder that affects just 1 in 10,000 to 50,000 Americans.

Why does edema occur? The major pathway is depicted in Figure 107-1. As indicated, there are two important mediators: *kallikrein* and *bradykinin*. Kallikrein catalyzes the formation of bradykinin. And then bradykinin, acting through bradykinin type 2 receptors (B2 receptors), increases vascular permeability, allowing fluid to leak out of capillaries and infiltrate the surrounding tissue. In people *without* HAE, endogenous C1-INH suppresses conversion of prekallikrein into kallikrein, and thereby prevents excessive production of bradykinin. By contrast, in people *with* HAE, there is insufficient C1-INH to keep kallikrein synthesis in check, and hence overproduction of bradykinin results.

The principal drugs for HAE work in one of four ways. Specifically, they:

- Stimulate production of C1-INH
- Replace deficient C1-INH
- Mimic C1-INH
- Block bradykinin B2 receptors

Drugs that stimulate production of C1-INH are used for prophylaxis only. Preparations that replace deficient C1-INH can be used for prophylaxis or treatment. And drugs that mimic C1-INH or block B2 receptors are used for treatment only.

Old Drugs for HAE

For many years, patients have used *androgens* (eg, danazol [Danocrine], stanozolol [Winstrol]) for *prophylaxis*. With regular use, these drugs can reduce both the frequency and intensity of attacks. How? By promoting synthesis of C1-INH by the liver. Unfortunately, androgens can cause significant side effects, including liver damage, virilization, acne, weight gain, lipid abnormalities, and menstrual irregularities. Furthermore, although androgens can help *prevent* attacks, they cannot treat an attack once it has begun.

New Drugs for HAE

Prior to 2008, we had no drugs approved specifically for HAE. Now we have four: ecallantide, icatibant, and two preparations of C1-INH. Properties of these drugs are summarized in Table 107-5.

C1-Inhibitor

We have two preparations of C1-INH, marketed as *Cinryze* and *Beriner*. Both are prepared by extraction of C1-INH from human plasma. Cinryze is approved only for prophylaxis of HAE. Beriner is approved only for treatment of HAE, and then only for acute abdominal attacks and facial swelling. Both drugs are administered IV, and hence are not suited for use at home. How do these drugs reduce edema? As shown in Figure 107-1, they block the conversion of prekallikrein to kallikrein, and thereby suppress production of bradykinin, a

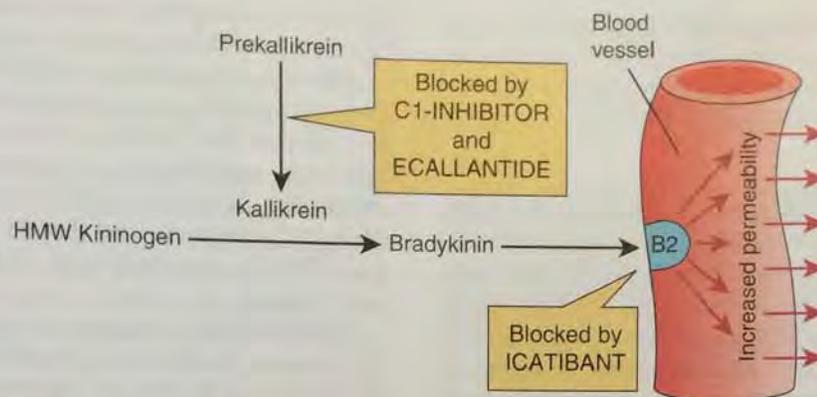


Figure 107-1 ■ Drug actions in hereditary angioedema.

Two drugs—C1-inhibitor and ecallantide—suppress production of kallikrein, and thereby suppress production of bradykinin. Icatibant blocks bradykinin B2 receptors, and thereby prevents bradykinin-mediated increases in vessel permeability, the immediate cause of edema. (B2 = bradykinin type 2 receptor, HMW = high-molecular-weight.)

TABLE 107-5 ■ Drugs for Hereditary Angioedema

Drug	Mechanism	Source	FDA-Approved Use	Year Approved	Route	Formulation	Dosage
C1-inhibitor [Cinryze]	Inhibits kallikrein, and thereby suppresses formation of bradykinin	Purified from human plasma	Prophylaxis only	2008	IV	Powder (500 units) in single-use vials	1000 units every 3–4 days
C1-inhibitor [Berinert]	Same as Cinryze	Purified from human plasma	Treatment of acute attacks affecting the face and/or abdomen	2009	IV	Powder (500 units) in single-use vials	20 units/kg once during the attack
Ecallantide [Kalbitor]	Same as Cinryze	Recombinant DNA technology	Treatment of any acute attack	2009	SubQ	Solution (10 mg) in single-use vials	30 mg (10 mg injected at three different sites); can be repeated within 24 hr if the attack persists
Icatibant [Firazyr]	Blocks bradykinin B2 receptors	Chemical synthesis	Treatment of any acute attack	2011	subQ	Solution (30 mg) in single-use, pre-filled syringes	30 mg as one injection into the abdomen; can be repeated twice at intervals of 6 hr or longer

B2 = bradykinin type 2.

compound that causes edema by increasing vascular permeability. Common side effects are headache, muscle spasms, abdominal pain, nausea, vomiting, and diarrhea. The most serious side effect is an increase in HAE pain. Because these preparations are foreign proteins, they pose a risk of hypersensitivity reactions, including severe anaphylaxis. Accordingly, epinephrine should be immediately available. Because these preparations are made from human plasma, they pose a theoretical risk of transmitting viruses and Creutzfeldt-Jakob disease. However, no cases of transmission have ever been reported. Dosages for both preparations are shown in Table 107-5.

Ecallantide

Ecallantide [Kalbitor], prepared by recombinant DNA technology, is approved for subQ treatment of all HAE attacks, regardless of the site. Like the C1-INH inhibitors, ecallantide reduces edema by suppressing conversion of prekallikrein to kallikrein (see Fig. 107-1). Side effects include headache, fatigue, fever, nausea, diarrhea, injection-site reactions, and mild hypersensitivity reactions. Of much greater concern, anaphylaxis develops in nearly 4% of patients. Accordingly, ecallantide should be administered only by clinicians with appropriate support to manage anaphylaxis and HAE itself. A single dose consists of 30 mg administered as three 10-mg

subQ injections, made at least 2 inches apart into the abdomen, thigh, or upper arm. The injections may be made into the same anatomic region or different regions. One additional 30-mg dose can be administered within 24 hours.

Icatibant

Like ecallantide, icatibant [Firazyr] is approved for subQ treatment of all HAE attacks, regardless of the site. In contrast to the other new drugs for HAE, which work by preventing the conversion of prekallikrein to kallikrein, icatibant works by blocking bradykinin B2 receptors on blood vessels. By doing so, icatibant prevents bradykinin-mediated increases in vessel permeability, the immediate cause of edema. The most common side effects are injection-site reactions (eg, bruising, burning, redness, irritation, edema, pain), which occur in nearly all patients. Other side effects are fever (4%), dizziness (3%), and elevation of liver enzymes (4%). The recommended dosage is 30 mg injected subQ into the abdomen. If needed, two additional 30-mg doses can be given at intervals of 6 hours or longer. Icatibant, supplied in single-dose, pre-filled syringes, is the only new drug for HAE approved for dosing at home.

BELIMUMAB FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic, potentially fatal autoimmune disease that can attack multiple sites. Among these are the joints, skin, lungs, and heart, as well as two other sites—the kidneys and central nervous system (CNS)—which are often severely affected. Common symptoms are joint pain, swollen joints, fever, chest pain, hair loss, and fatigue. All patients have antinuclear antibodies (ANAs), that is, antibodies directed against the patient's own DNA. Disease onset is between age 15 and 44 years. The Centers for Disease Control and Prevention estimate that between 300,000 and 4 million Americans have SLE. The incidence in women is 9 times the incidence in men, and the incidence in black women is 3 times the incidence in white women.

We cannot cure SLE, but we can reduce symptoms and complications with drugs. Standard treatments include non-steroidal anti-inflammatory drugs (for arthritis and fever), hydroxychloroquine (for arthritis and rash), and glucocorticoids (for kidney and CNS attacks). Hydroxychloroquine and glucocorticoids can also help prevent symptom flares. Powerful immunosuppressants—cyclophosphamide [Cytotoxan, Procytox \star], azathioprine [Imuran], mycophenolate mofetil [CellCept], and methotrexate—are generally reserved for severe disease that has not responded to oral glucocorticoids.

Belimumab

Belimumab [Benlysta], approved in 2011, is the first drug approved for SLE since 1955. Unfortunately, belimumab is expensive, benefits are modest, and there is no proof of efficacy in African Americans or in patients with kidney or CNS involvement. Furthermore, the drug may actually increase mortality. Accordingly, belimumab is indicated only as add-on therapy for adults with ANA-positive SLE that has not re-

sponded to traditional drugs. Belimumab should not be used in patients with lupus nephritis or in those with CNS lupus.

Mechanism of Action. Belimumab is a monoclonal antibody that inhibits B-lymphocyte stimulator (BLyS), a regulatory protein that prolongs the survival of B lymphocytes—cells that contribute to the production of autoantibodies. Presumably, by inhibiting BLyS, belimumab suppresses autoantibody production, and thereby helps alleviate SLE symptoms. Of note, in patients with SLE, levels of BLyS are abnormally high.

Clinical Trials. Belimumab was evaluated in two large, randomized, double-blind, placebo-controlled trials, known as BLISS-52 and BLISS-76. Patients received standard therapy (eg, prednisone, azathioprine, hydroxychloroquine) plus either belimumab or placebo. The result? Symptomatic improvement was greater in the belimumab group than in the placebo group, and patients on belimumab experienced fewer disease flares and more were able to decrease their dosage of prednisone. Unfortunately, benefits were limited to just a few people: only 1 of every 8 patients improved. Furthermore, although the trials showed a modest benefit for some patients, important clinical issues were not addressed. As a result:

- We don't know if belimumab will benefit patients with active lupus involving the kidneys or CNS. Why? Because these patients were excluded from the trials.
- We don't know if belimumab benefits African Americans. Why? Because only a few black patients were enrolled—and none of them responded. Studies with more black patients are planned to verify if these negative results are valid.
- We cannot recommend combined use of belimumab with other biologics for SLE or with IV cyclophosphamide. Why? Because these combinations were not studied.

Adverse Effects. The most common reactions are nausea (15%), diarrhea (12%), fever (10%), bronchitis (9%), nasopharyngitis (9%), insomnia (7%), arm or leg pain (6%), migraine (5%), depression (5%), urinary tract infection (4%), and leukopenia (4%).

Infusion/Hypersensitivity Reactions. Infusion/hypersensitivity reactions range from mild (myalgia, headache, rash, urticaria) to severe: anaphylaxis, manifesting as angioedema, hypotension, and dyspnea. Patients should be monitored during the infusion and after. If anaphylaxis develops, the infusion should be stopped immediately. Owing to the risk of anaphylaxis, belimumab should be administered only by a provider prepared to manage a severe reaction.

Depression. In clinical trials, serious depression developed in 0.4% of patients receiving belimumab versus 0.1% of those receiving placebo. Two belimumab recipients committed suicide. Most patients who reported depression or suicidal behavior had a history of depression or other serious psychiatric disorders, and most were receiving psychotherapeutic drugs. Although belimumab is associated with an increased risk of depression, a causal relationship has not been established.

Infection. Like other immunosuppressants, belimumab is associated with an increased risk of infection. Belimumab should not be started in patients with a chronic infection. If an infection develops during treatment, interruption of belimumab should be considered.

Mortality. Belimumab may pose an increased risk of death. In clinical trials, 0.9% of patients receiving belimumab died, compared with 0.4% of patients receiving placebo. Causes of death included infection, cardiovascular disease, and suicide.

Drug Interactions. Formal studies have not been conducted.

Vaccine Interactions. Because of its immunosuppressant actions, belimumab may pose a risk of infection from live virus vaccines. Accordingly, belimumab should not be administered within 30 days of receiving a live virus vac-

cine, and these vaccines should not be administered to patients receiving belimumab. By suppressing immune responses, belimumab may interfere with responses to all vaccines.

Preparations, Dosage, and Administration. Belimumab [Benlysta] is supplied as a powder (120 and 400 mg) to be reconstituted for IV infusion. The dosage is 10 mg/kg—infused over 1 hour—every 2 weeks for three doses, and every 4 weeks thereafter. Premedication may reduce the risk of an infusion/hypersensitivity reaction. As noted above, infusions must be done by a healthcare provider with expertise in managing anaphylaxis. Treatment costs about \$35,000 a year.

KEY POINTS

- Pulmonary arterial hypertension (PAH) is a potentially fatal disease of the small pulmonary arteries.
- The primary vascular changes in PAH are vasoconstriction, proliferation of smooth muscle cells and endothelial cells, and pulmonary thrombosis.
- Prostacyclin analogs (eg, epoprostenol, iloprost) reduce symptoms of PAH by promoting vasodilation, suppressing proliferation of smooth muscle cells, and inhibiting platelet aggregation.
- Epoprostenol is administered by continuous IV infusion through a central venous catheter, and hence is inconvenient as well as dangerous (owing to a risk of catheter-related sepsis).
- Iloprost is administered by oral inhalation, and hence is much more convenient than epoprostenol. However, iloprost can cause significant hypotension.
- Bosentan is an endothelin-1 receptor antagonist indicated for oral therapy of PAH. Benefits derive from reducing pulmonary vascular resistance and altering vascular remodeling.
- Bosentan is hepatotoxic and highly teratogenic.
- Sildenafil is a PDE5 inhibitor used for oral and IV therapy of PAH. Inhibition of PDE5 preserves cGMP in pulmonary arteries, and thereby enhances vasodilation mediated by nitric oxide.
- Sepsis is a life-threatening condition in which systemic infection triggers a generalized inflammatory response and activation of the coagulation system. The end result is diffuse endovascular injury and multiorgan dysfunction, often leading to death.
- Respiratory distress syndrome (RDS), the primary cause of morbidity and mortality in premature infants, results from a deficiency in lung surfactant.
- When preterm birth is unavoidable, injecting the mother with glucocorticoids can accelerate fetal lung maturation, and can thereby decrease the risk of RDS.
- Lung surfactant—poractant alfa, calfactant, or beractant—is given to preterm infants to prevent or treat RDS.
- Cystic fibrosis (CF) is an inherited disorder that results in damage to the lungs, pancreas, and other organs.
- Inhaled dornase alfa [Pulmozyme] can improve pulmonary function and decrease infection in some patients with CF. The drug decreases the viscosity of sputum by breaking down extracellular DNA that has accumulated secondary to death of neutrophils.
- Inhaled tobramycin [TOBI] is the drug of choice for treating chronic *P. aeruginosa* pulmonary infection in patients with CF.
- High-dose ibuprofen can slow progression of pulmonary damage in CF. Benefits derive from suppressing the inflammatory response that underlies destruction of lung tissue.
- In patients with CF, supplemental pancreatic enzymes promote digestion and absorption of nutrients. All preparations contain lipase, protease, and amylase.
- In patients with sickle cell anemia (SCA), hydroxyurea can reduce the number of painful episodes, hospitalizations, and transfusions, and can prolong life. Benefits derive from increasing production of fetal hemoglobin.
- At high doses, hydroxyurea can cause severe myelosuppression. However, at the doses employed for SCA, myelosuppression is transient and mild.
- Hyperuricemia secondary to cancer chemotherapy can be managed with two drugs: rasburicase (which accelerates uric acid removal) and allopurinol (which blocks uric acid production).
- Phosphate binders are used to treat hyperphosphatemia, a common complication of end-stage renal disease.
- Calcium-based phosphate binders (eg, calcium carbonate) are cheap, but pose a risk of hypercalcemia.
- Calcium-free phosphate binders (eg, sevelamer carbonate) do not promote hypercalcemia, but cost much more than the calcium-based drugs.
- Gamma-hydroxybutyrate can decrease attacks of cataplexy in patients with narcolepsy, and can also decrease daytime drowsiness (by helping to promote sleep).
- Gamma-hydroxybutyrate has significant abuse potential and can cause serious adverse effects (respiratory depression, coma, death). Accordingly, distribution of the drug is strictly controlled.
- In patients with amyotrophic lateral sclerosis (Lou Gehrig's disease), riluzole [Rilutek] can prolong life or delay the need for a tracheostomy by a few months.
- Huntington's disease is an inherited neurodegenerative disorder characterized by psychiatric problems, cognitive changes, and movement disorders, especially Huntington's chorea.

- We can treat Huntington's chorea with drugs that reduce neuronal stores of dopamine (eg, tetrabenazine, reserpine) or with drugs that block neuronal dopamine receptors (eg, haloperidol, quetiapine, and other antipsychotic agents).
- Tetrabenazine is the first and only drug approved for treating chorea of Huntington's disease.
- Fibromyalgia syndrome (FMS) is a chronic disorder characterized by widespread musculoskeletal pain, profound fatigue, nonrestorative sleep, and cognitive dysfunction.
- Drugs of first choice for FMS are amitriptyline (a TCA) and cyclobenzaprine, a drug nearly identical in structure to amitriptyline.
- Milnacipran is a serotonin/norepinephrine reuptake inhibitor that produces moderate pain reduction in FMS.
- Hereditary angioedema (HAE) is a genetic disorder characterized by localized, self-limiting episodes of edema that occur mainly in the larynx, subcutaneous tissue, and submucosa of the intestinal wall.
- The underlying cause of HAE is a deficiency in C1-esterase inhibitor, also known as C1-inhibitor (C1-INH).
- Three new drugs for HAE—ecallantide and two preparations of C1-INH—work by suppressing the conversion of prekallikrein into kallikrein. All three must be administered by a healthcare provider.
- One new drug for HAE—icatibant—blocks bradykinin type 2 receptors, and thereby prevents bradykinin-mediated increases in vascular permeability, the immediate cause of edema. Icatibant, administered subQ, is the only new drug for HAE approved for dosing at home.
- Systemic lupus erythematosus (SLE) is a chronic, potentially fatal autoimmune disorder that can affect multiple organ systems.
- Belimumab, a drug for SLE, is a monoclonal antibody that inhibits B-lymphocyte stimulator, and thereby shortens the life of B lymphocytes—cells that contribute to autoantibody production.
- Belimumab is only moderately effective, and there is no evidence that it can help African Americans or patients with active lupus of the kidneys or CNS.

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Dietary Supplements

Regulation of Dietary Supplements

Dietary Supplement Health and Education Act of 1994

Current Good Manufacturing Practices Ruling Dietary Supplement and Nonprescription Drug Consumer Protection Act

A Comment on the Regulatory Status of Dietary Supplements

Private Quality Certification Programs

Standardization of Herbal Products

Adverse Interactions with Conventional Drugs

Some Commonly Used Dietary Supplements

Black Cohosh

Coenzyme Q-10

Cranberry Juice

Echinacea

Feverfew

Flaxseed

Garlic

Ginger Root

Ginkgo biloba

Glucosamine

Green Tea

Probiotics

Resveratrol

Saw Palmetto

Soy

St. John's Wort

Valerian

Harmful Supplements to Avoid

Comfrey

Kava

Ma Huang (Ephedra)

The Food and Drug Administration (FDA) defines dietary supplements as “vitamins, minerals, herbs and other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites” intended to supplement the diet. Throughout history, preparations made from or containing these agents have been employed as remedies.

Dietary supplements are the most common form of *complementary and alternative medicine* (CAM), which can be defined as treatment practices that are not widely accepted or practiced by mainstream clinicians in a given culture. CAM encompasses a large and diverse group of theories and practices. Among these are prayer, homeopathy, massage, mind-

body techniques, therapeutic touch, acupuncture, and treatment with vitamins, minerals, nonvitamin/nonmineral products (eg, herbal products), and other natural remedies.

In the United States, use of CAM is widespread. According to the 2007 National Health Interview Survey (NHIS), conducted by the National Center for Health Statistics, 4 out of 10 Americans used some form of CAM in the previous year. The forms of CAM used most often were nonvitamin/nonmineral natural products (17.7%) and deep breathing exercises (12.7%). Usage was highest among American Indian and Alaskan Native adults (50.3%), lower among white adults (43.1%) and Asian adults (39.9%), and lowest among black adults (25.5%).

The popularity of supplements may be explained by several factors (Table 108-1). Some people like the sense of empowerment that comes from self-diagnosis and self-prescribing. Others may turn to supplements out of anger or frustration with their healthcare providers. Still others may distrust conventional medicine or may feel it has failed them. In addition, supplements may also be a way to save money: Since these products are available without prescription, they can be purchased without the cost of visiting a prescriber. In fact, according to the NHIS, there is a clear relationship between concern about the costs of conventional care and the likelihood of turning to CAM. However, perhaps the strongest force driving the demand for nutritional supplements is aggressive marketing.

Much of our information on *botanicals* has been amassed by the German Commission E, an expert panel composed of physicians, pharmacists, pharmacologists, and biostatisticians. The commission was established by the German Federal Health Agency (equivalent to our FDA) to review and analyze the world literature on plant-based products. Commission E monographs contain information on the chemistry, pharmacology, toxicology, and traditional uses of medicinal herbs, as well as data on clinical trials, epidemiologic studies, and patient case records.

A new subscription service—the *Natural Medicines Brand Evidence-based Rating* (NMBER™) system—offers evidence-based ratings for over 60,000 specific supplement products. Based on scientific evidence of safety and efficacy, each product is assigned a rating between 1 and 10. Products with a low rating are not recommended, whereas those with a high rating are. The NMBER system, created by the publishers of the *Natural Medicines Comprehensive Database*, can be accessed online at NMBER.therapeuticresearch.com. There is a fee.

Despite the NMBER system and the work of Commission E, our understanding of CAM is far from complete. To advance our knowledge, the National Institutes of Health created the National Center for Complementary and Alternative Medicine (NCCAM) in the late 1990s. The NCCAM is charged with promoting and funding basic research and clinical

TABLE 108-1 • Why People Use Dietary Supplements

- Perception that supplements are safer and “healthier” than conventional drugs
- Sense of control over one’s care
- Emotional comfort from taking action
- Cultural influence
- Limited access to professional care
- Lack of health insurance
- Convenience
- Media hype and aggressive marketing
- Recommendation from family and friends

cal trials designed to address open questions on the safety and efficacy of CAM.

REGULATION OF DIETARY SUPPLEMENTS

Dietary Supplement Health and Education Act of 1994

Core Provisions

Botanical products (medicinal herbs), vitamins, and minerals are regulated under the *Dietary Supplement Health and Education Act of 1994* (DSHEA)—a bill that exempts these products from meaningful FDA regulation. The DSHEA created a special category for nutritional supplements that exempts them from the scrutiny applied to other foods. The DSHEA also states that products not already sold as drugs can now be sold as *dietary supplements*. Put another way, if a manufacturer is willing to call its product by another name—“dietary supplement” rather than “drug”—the product can qualify for regulation under the DSHEA, thereby avoiding regulation under the more stringent Food, Drug, and Cosmetic Act. As discussed in Chapter 3, the Food, Drug, and Cosmetic Act requires that conventional drugs—both prescription and over-the-counter agents—undergo rigorous evaluation of safety and efficacy prior to receiving FDA approval for marketing. The DSHEA imposes no such requirements on “dietary supplements.” That is, dietary supplements can be manufactured and marketed without giving the FDA any proof they are safe or effective. All the manufacturer must do is notify the FDA of efficacy claims. If a product eventually proves harmful or makes false claims, the FDA does have the authority to intervene—but only *after* the product had been released for marketing. Furthermore, in order to challenge a claim of efficacy, the FDA must file suit in court; the challenge cannot be made through a simple administrative procedure. As you might guess, the DSHEA was created in response to intensive lobbying from the multibillion-dollar dietary supplement industry, which wanted to minimize government oversight.

Package Labeling

The DSHEA does impose some restrictions on labeling. All herbal products must be labeled as “dietary supplements.” In addition, the label must not claim that the product can be used to diagnose, prevent, treat, or cure a disease. In fact, it must state the opposite: *This product is not intended to diagnose, treat, cure, or prevent any disease.* However, the label is allowed to make claims about the product’s ability to favorably

influence *body structure or function*. Put another way, the label can insinuate specific benefits, but can’t make overt claims. By way of illustration, labels *can* bear statements like these:

- Helps promote urinary tract health
- Helps maintain cardiovascular function
- Energizes and rejuvenates
- Reduces stress and frustration
- Improves absentmindedness
- Supports the immune system

But labels *can’t* bear statements or terms like these:

- Protects against cancer
- Reduces pain and stiffness of arthritis
- Lowers cholesterol
- Supports the body’s antiviral capabilities
- Improves symptoms of Alzheimer’s disease
- Relieves menopausal hot flashes
- “Antibiotic,” “antiseptic,” “antidepressant,” “laxative,” or “diuretic”

If all of this sounds like semantic hair splitting—it largely is. Furthermore, regardless of what the label says, common sense says that people *will* take herbal products with the intent to prevent or treat disease.

Under the provisions of the DSHEA, there is no assurance that a product actually contains what the label proclaims: The package may contain ingredients that are *not* listed, or it may *lack* ingredients that *are* listed. These shortcomings and others have been addressed by the Current Good Manufacturing Practices ruling, issued by the FDA in 2007 (see below).

Adverse Effects

With dietary supplements, as with conventional drugs, the manufacturer is responsible for safety. However, the similarity ends there. Under the DSHEA, a product is presumed safe until proved hazardous. Furthermore, the burden for proving danger lies with the consumer and the FDA. With conventional drugs, opposite logic and regulations apply: Drugs are presumed dangerous until rigorous testing by the manufacturer reveals an absence of serious toxicity. Because of this system, the number of dangerous drugs that reach the market is kept to a minimum. Ask yourself, “Which product would I be more comfortable using—one that has been tested for adverse effects *before* I take it, or one that is evaluated for toxicity only *after* it caused me harm?”

Impurities, Adulterants, and Variability

The DSHEA does not address the issues of impurities, adulterants, or variability. As a result, dangerous products have been allowed to reach consumers. A few examples illustrate the problem:

- A combination product used to “cleanse the bowel” caused life-threatening heart block. Analysis revealed contamination with *Digitalis lanata*, a plant with powerful effects on the heart.
- Among 125 ephedra products analyzed by the FDA, ephedrine content per dose ranged from undetectable to 110 mg. Also, some products had 6 to 20 additional ingredients.
- Testing of 10 brands of ginseng products revealed a 20-fold variation in ginsenoside content.

- When the California Department of Health Sciences analyzed 243 Asian patent medicines, they found 24 containing lead, 35 containing mercury, and 36 containing arsenic—all in levels above those permitted in drugs. Seven percent of the products were adulterated with undeclared pharmaceuticals, including ephedrine, chlorpheniramine, methyltestosterone, and phenacetin.

As discussed below, the Current Good Manufacturing Practices ruling, issued by the FDA in 2007, should prevent the sale of such products in the future.

Other Provisions

DSHEA directed the Secretary of Health and Human Services to establish an office within the National Institutes of Health to focus on research regarding CAM. In response, the Secretary created the National Center for Complementary and Alternative Medicine mentioned above.

DSHEA allows retail stores to display promotional material to inform consumers about health-related benefits of products, as long as the material is not false or misleading, and is not displayed close to the product itself.

Current Good Manufacturing Practices Ruling

In June 2007, the FDA issued a set of standards to regulate manufacturing and labeling of dietary supplements. These standards, referred to as Current Good Manufacturing Practices (CGMPs), are designed to ensure that dietary supplements be devoid of adulterants, contaminants, and impurities, and that package labels accurately reflect the identity, purity, quality, and strength of what's inside. In addition, the label should indicate not only active ingredients but also inactive ingredients. The CGMPs also mandate that manufacturers establish quality-control procedures, with the objective of preventing mislabeled, underfilled, or overfilled formulations; variations in tablet size, color, or potency; and contamination with drugs, bacteria, pesticides, glass, lead, and other potential contaminants. Unfortunately, even with the new standards and rules, there is still no assurance that dietary supplements will be either safe or effective—but at least we will have improved confidence regarding package contents.

Dietary Supplement and Nonprescription Drug Consumer Protection Act

This act, passed in 2006, mandates reporting of serious adverse events for nonprescription drugs and dietary supplements. The following events should be reported: deaths, hospitalizations, life-threatening experiences, persistent or significant disabilities, and birth defects. Manufacturers and distributors must report these to the FDA within 15 days. Reports can be filed by telephone or by mail, or through the MEDWATCH program (see Chapter 7).

A Comment on the Regulatory Status of Dietary Supplements

Unlike conventional drugs, herbal products and other dietary supplements are not regulated for either safety or efficacy. Many of these products have constituents that can

produce profound pharmacologic effects, both beneficial and adverse. Nonetheless, reliable information on clinical effects is largely lacking. Congress does not allow conventional drugs to be dispensed in the absence of extensive testing, but has made an exception for the supplements. This is both irrational and dangerous. After all, whether you ingest ephedrine in the form of a pill or in the form of Ma huang, it's still ephedrine, and it's still going to have powerful effects. Clearly, herbal products should be evaluated and regulated in essentially the same manner as conventional drugs. An editorial in the *New England Journal of Medicine* (339:839–841, 1998) addressed this issue with eloquence. Here's the concluding paragraph:

It is time for the scientific community to stop giving alternative medicine a free ride. There cannot be two kinds of medicine—conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work. Once a treatment has been tested rigorously, it no longer matters whether it was considered alternative at the outset. If it is found to be reasonably safe and effective, it will be accepted. But assertions, speculation, and testimonials do not substitute for evidence. Alternative treatments should be subjected to scientific testing no less rigorous than that required for conventional treatments.

PRIVATE QUALITY CERTIFICATION PROGRAMS

Rather than wait for implementation of CGMPs, four private organizations—the U.S. Pharmacopeia (USP), ConsumerLab, the Natural Products Association, and NSF International (formerly known as the National Sanitation Foundation)—have already begun testing dietary supplements for quality. A “seal of approval” is given to products that meet their standards, which are very similar to the CGMPs described above. The USP standards are enforceable by the FDA. All four organizations require manufacturers to pay for the tests, and all four report on the following:

- Current Good Manufacturing Practices
- Purity
- Identity
- Potency
- Dissolution
- Accuracy of labeling

In addition, two organizations—the USP and ConsumerLab—report on postapproval surveillance.

STANDARDIZATION OF HERBAL PRODUCTS

With herbal products, there is often uncertainty about the amounts of active ingredients. The concentration of active ingredients in herbal crops can vary from year to year and from place to place. Reasons include differences in sunshine, rainfall, temperature, and soil nutrients. As a result, the potency of herbal products can vary widely.

TABLE 108-2 • Concentrations of Active Agents in Some Standardized Herbal Preparations

Herb	Amount of Active Agent
Black cohosh	2.5% Triterpene glycosides
Echinacea	4% Phenolic compounds
Feverfew	0.2% Parthenolide
<i>Ginkgo biloba</i>	24% Ginkgo flavenoids, 6% terpenoids
St. John's wort	0.3% Hypericin
Valerian root	1% Valerianic acid

Variability can be reduced through standardization, a three-step process in which the manufacturer (1) prepares an extract of plant parts, (2) analyzes the extract for one or two known active ingredients, and (3) dilutes or concentrates the extract such that the final product contains a predetermined amount of the active ingredient(s). The objective is to achieve therapeutic equivalence from batch to batch made by the same manufacturer, and among batches made by different manufacturers. Table 108-2 lists the concentrations of active ingredients in some standardized preparations.

Standardization has two important benefits. First, it permits accurate dosing. Second, it permits extrapolation of data obtained in clinical trials to the public in general.

Unfortunately, standardization also has drawbacks. The extraction process might destroy active compounds. Furthermore, the process may fail to extract as-yet unidentified active agents, and hence the extract may have a different spectrum of effects than the intact plant. To the extent this is true, historic data obtained with whole plants will lose some value as a basis for helping us understand clinical responses to the standardized extract.

ADVERSE INTERACTIONS WITH CONVENTIONAL DRUGS

Herbal products and other dietary supplements can interact with conventional drugs, sometimes with disastrous results. The principal concerns are increased toxicity and decreased therapeutic effects. Clinicians and consumers should be alert to these possibilities. Unfortunately, with many supplements, reliable information on adverse interactions is lacking—in large part because potential interactions have not been systematically studied. Hence, if a patient is taking a conventional medication and a dietary supplement, and therapeutic effects are lost or toxicity appears, it may be impossible to say for sure that the supplement was (or was not) responsible.

A few important interactions have been identified, including the following:

- St. John's wort can induce CYP3A4 (the 3A4 isozyme of cytochrome P450), and can thereby accelerate the metabolism of many drugs, causing a loss of therapeutic effects.
- Several herbal products, including *Ginkgo biloba*, feverfew, and garlic, suppress platelet aggregation, and hence can increase the risk of bleeding in patients receiving antiplatelet drugs (eg, aspirin) or anticoagulants (eg, warfarin, heparin).

- Ma huang (ephedra) contains ephedrine, a compound that can elevate blood pressure and stimulate the heart and central nervous system (CNS). Accordingly, ephedra can intensify the effects of pressor agents, cardiac stimulants, and CNS stimulants, and counteract the beneficial effects of antihypertensive drugs and CNS depressants.

These interactions, at least, can be avoided—provided the prescriber is aware of them, and provided the patient informs the prescriber about supplement use. Unfortunately, up to 70% of patients neglect to do so.

SOME COMMONLY USED DIETARY SUPPLEMENTS

Black Cohosh

Uses. Black cohosh (*Cimicifuga racemosa*) is used for treating symptoms of menopause, including hot flashes, vaginal dryness, palpitations, depression, irritability, and sleep disturbance. The preparation should *not* be used to reduce hot flashes caused by tamoxifen and other selective estrogen receptor modulators (SERMs).

Actions. How black cohosh works is unknown. At one time, we believed it suppressed release of luteinizing hormone (LH). However, clinical studies have failed to show an effect on female hormones, including LH, estradiol, prolactin, and follicle-stimulating hormone. In laboratory studies, black cohosh does not interact with estrogen receptors: It doesn't bind these receptors, up-regulate estrogen-dependent genes, or promote growth of estrogen-dependent tumors (at least in animals). In the laboratory, black cohosh inhibits the growth of prostate cancer cells.

Effectiveness. Black cohosh has been evaluated extensively in Germany, where most studies indicate it can effectively relieve menopausal symptoms. In fact, some studies have shown black cohosh to be as beneficial as hormone therapy (HT), the conventional treatment for menopausal symptoms. Unlike HT, black cohosh has not been evaluated for long-term use (ie, beyond 6 months). Many commercial black cohosh products include St. John's wort in their formulations to address the psychological symptoms associated with menopause. These products should be avoided due to the large number of drug interactions associated with St. John's wort (see below). The American College of Obstetricians and Gynecologists supports the short-term use of black cohosh for relieving menopausal symptoms.

Adverse Effects. The German Commission E states that black cohosh is safe for routine use. Gastrointestinal symptoms are most common. Other possible adverse effects include rash, headache, dizziness, weight gain, and cramps. Rarely, black cohosh has been associated with *liver toxicity*; but a direct causal link has not been established. Due to lack of scientific information on long-term effects in humans, the German Commission E recommends using black cohosh for no more than 6 months. Because of its estrogenic effects, black cohosh should not be taken during pregnancy, especially during the first and second trimesters.

Interactions with Conventional Drugs. Black cohosh may potentiate the hypotensive effects of antihypertensive drugs as well as the hypoglycemic effects of insulin and other drugs for diabetes. In women under anesthesia, the herb has caused hypotension that was difficult to manage. Owing to its

estrogenic actions, black cohosh may potentiate the effects of estrogens used for hormone replacement or contraception, and may reduce the effects of estrogen receptor antagonists. Black cohosh should be used with caution in patients taking other drugs that may harm the liver.

Comments. Black cohosh has a long history in America. The herb was used by Native Americans and later by American colonists. Between 1820 and 1926, it was listed as an official drug in the U.S. Pharmacopeia.

Users must not confuse black cohosh with blue cohosh (Caulophyllum thalictroides). Although blue cohosh has legitimate uses, including promotion of menstruation and labor, it is very different from black cohosh and potentially more dangerous. Blue cohosh can elevate blood pressure, increase intestinal motility, and accelerate respiration. More importantly, it can induce uterine contractions, and hence should be avoided during pregnancy, except at term. Some commercial products contain both black cohosh and blue cohosh. Women who only want black cohosh should avoid these products.

Coenzyme Q-10

Uses. Coenzyme Q-10 (ubiquinone, CoQ-10) is used to treat heart failure, muscle injury caused by HMG-CoA reductase inhibitors (statins), and mitochondrial encephalomyopathies (ie, muscle and nervous system injury caused by deranged mitochondrial metabolism).

Actions. CoQ-10 is found in nearly every cell of the body. The highest concentrations are found in the heart, liver, kidney, and pancreas. CoQ-10 is a potent antioxidant and participates in many metabolic pathways, most notably production of ATP.

Effectiveness. In patients with documented CoQ-10 deficiency, replacement therapy with CoQ-10 offers clear benefits.

Effectiveness in heart failure is limited. Although CoQ-10 can improve quality of life, it does not seem to improve objective measures of clinical status (ejection fraction and blood pressure). CoQ-10 has no role in heart failure as monotherapy, but adding it to conventional therapy may help.

One formulation of CoQ-10—UbiQGel—has been granted orphan drug status for treatment of mitochondrial encephalomyopathies.

The use of CoQ-10 to prevent statin-induced myopathies is anecdotal; hard evidence of benefits is lacking.

Adverse Effects. CoQ-10 is well tolerated. High doses may produce GI disturbances, including gastritis, reduced appetite, nausea, and diarrhea.

Interactions with Conventional Drugs. CoQ-10 is structurally similar to vitamin K₂, and hence may antagonize the effects of warfarin.

Biosynthesis of CoQ-10 shares a common pathway with cholesterol. As a result, drugs like the statins, which inhibit synthesis of cholesterol, can also inhibit synthesis of CoQ-10, causing levels of endogenous CoQ-10 to decline. (Statin-induced reductions in CoQ-10 may explain why statins cause muscle injury.)

Cranberry Juice

Uses. Cranberry juice is used to prevent urinary tract infections (UTIs) and to decrease urine odor in patients with urinary incontinence.

Actions. Benefits derive from the presence of proanthocyanidins, a group of compounds that prevent bacteria from adhering to the urinary tract wall. Bacteria that have already attached themselves are not affected. Cranberry juice does not acidify the urine as previously thought.

Effectiveness. Daily consumption of cranberry juice can prevent recurrent UTIs, but only in certain age groups. Specifically, it appears to benefit elderly women and women in their teens or 20s, not older adults or young girls. Furthermore, although cranberry juice can prevent UTIs, it is not effective as treatment for an established infection. In patients with urinary incontinence, cranberry juice can reduce unpleasant odor. Little is known about the efficacy of cranberry-extract capsules. Accordingly, cranberry juice itself is the preferred formulation.

Adverse Effects. Drinking more than 1 L/day may increase the risk of GI upset and formation of uric acid kidney stones.

Interactions with Conventional Drugs. There is some evidence that cranberry juice may increase the risk of bleeding in patients taking warfarin. Accordingly, these patients should be monitored closely.

Echinacea

Uses. Echinacea (*Echinacea angustifolia*, *E. purpurea*, *E. pallida*) is used orally and topically. Oral echinacea is taken to stimulate immune function, suppress inflammation, and treat viral infections, including influenza and the common cold. Topical echinacea is used to treat wounds, burns, eczema, psoriasis, and herpes simplex infections. Echinacea was listed in the National Formulary from 1916 to 1950, but fell from favor owing to development of antibiotics and a lack of scientific data to support its use.

Actions. Active ingredients in echinacea preparations include cichoric acid, polysaccharides, flavenoids, and essential oils. These ingredients produce antiviral, anti-inflammatory, and immunostimulant effects through a combination of actions, including mobilization of phagocytes, stimulation of T-lymphocyte proliferation, stimulation of interferon and tumor necrosis factor production, and inhibition of hyaluronidase, a proinflammatory enzyme.

Effectiveness. Although echinacea is taken widely to prevent and treat colds, its efficacy is highly questionable. Recent randomized, placebo-controlled trials designed to evaluate the ability of echinacea to prevent colds found no effect on (1) the time to developing an upper respiratory infection (URI); (2) the incidence, duration, or severity of URIs that did develop; or (3) development of experimentally induced URIs. Other recent trials conducted on adults and children who already had a URI found echinacea no better than placebo at reducing either the duration or severity of symptoms.

Adverse Effects. Very few adverse effects have been reported. The most common complaint is unpleasant taste. Fever, nausea, and vomiting occur infrequently.

Rarely, echinacea causes allergic reactions, including acute asthma, urticaria, angioedema, and anaphylaxis. At the 2000 meeting of the American Academy of Allergy, Asthma, and Immunology, nearly two dozen cases of echinacea allergy were reported. Individuals with atopy (a genetic tendency toward allergic conditions) appear at increased risk of reacting to echinacea: Of the atopic patients tested, 2 in 10 had a posi-

tive skin test, even though they had never taken the herb. Echinacea belongs to the daisy family of plants, whose members include ragweed, asters, chamomile, and chrysanthemums. People allergic to any of these plants are at increased risk of reacting to echinacea.

Because echinacea can stimulate the immune system, it would be prudent to avoid the drug in patients with autoimmune diseases, such as lupus erythematosus or rheumatoid arthritis.

Although short-term exposure to echinacea stimulates immune function, long-term exposure can *suppress* immune function. Accordingly, long-term therapy should be avoided in immunocompromised patients, including those with HIV infection. In addition, prolonged therapy should be avoided in people with tuberculosis and other chronic infections that require optimal immune function for cure.

Interactions with Conventional Drugs. By stimulating the immune system, echinacea can oppose the effects of immunosuppressant drugs. Conversely, by suppressing immune function (in response to long-term use), echinacea can compromise drug therapy of tuberculosis, cancer, and HIV infection.

Feverfew

Uses. Feverfew (*Tanacetum parthenium*) is used primarily for prophylaxis of migraine.

Actions. The principal active agent in feverfew is *parthenolide*, a compound found in feverfew leaves. How parthenolide suppresses migraine is poorly understood. Possibilities include inhibition of vasoconstriction in the brain, suppression of serotonin release from platelets and leukocytes, and suppression of inflammation secondary to inhibition of arachidonic acid release.

Effectiveness. Clinical studies and historic evidence suggest that feverfew does indeed benefit patients with migraine. When taken prophylactically, the herb can reduce the frequency of attacks and the severity of symptoms (nausea, photophobia, phonophobia, and pain). Unfortunately, feverfew is less effective when taken to abort an ongoing attack. Furthermore, the doses required are much higher than those for prophylaxis. There is no reliable evidence that feverfew can benefit patients with rheumatoid arthritis or other inflammatory conditions.

Adverse Effects. Feverfew is very well tolerated. No serious adverse effects have been reported, although long-term studies of safety are lacking. Mild reactions include abdominal pain, indigestion, diarrhea, flatulence, nausea, and vomiting. Chewing feverfew leaves, a rare practice today, can cause oral ulceration, tongue irritation, and swollen lips. Some patients develop *post-feverfew syndrome*, characterized by nervousness, fatigue, insomnia, tension headache, and joint pain or stiffness. Feverfew may be better tolerated than conventional regimens for migraine prophylaxis. Feverfew belongs to the same plant family as echinacea. Accordingly, individuals allergic to ragweed, chrysanthemums, daisies, and marigolds may also be allergic to feverfew. By suppressing release of arachidonic acid in platelets, feverfew can decrease platelet aggregation, and may thereby pose a risk of bleeding. Accordingly, the product should be discontinued 2 weeks before elective surgery.

Interactions with Conventional Drugs. By suppressing platelet aggregation, feverfew can increase the risk of

bleeding in patients taking antiplatelet drugs (eg, aspirin) or anticoagulants (eg, warfarin, heparin).

Comments. There is great variability in feverfew products. Some contain little or no active ingredient.

Flaxseed

Uses. Flaxseed powders are used to treat constipation and dyslipidemias. Flaxseed also represents a vegetarian source of omega-3 fatty acids.

Actions. Ground flaxseed provides soluble plant fiber and alpha-linolenic acid. Like other high-fiber products, flaxseed can reduce serum cholesterol.

Flaxseed is an important food source of phytoestrogens called lignans. In the colon, bacteria convert these lignans into enterolactone and enterodiol, compounds that have both mild estrogenic and antiestrogenic actions. The antiestrogenic actions can decrease cellular proliferation in breast tissue.

Effectiveness. Like other fiber products, flaxseed decreases plasma levels of total cholesterol (5% to 9%) and low-density lipoprotein (LDL) cholesterol (8% to 18%), but does not affect high-density lipoprotein (HDL) cholesterol or triglycerides. In contrast, *defatted* flaxseed may *increase* triglyceride levels, and hence should be avoided by patients with hypertriglyceridemia. Owing to its fiber content, flaxseed acts like a bulk-forming laxative to relieve constipation.

Adverse Effects. Like other sources of dietary fiber, flaxseed can cause GI effects, including bloating, flatulence, and abdominal discomfort.

Interactions with Conventional Drugs. Flaxseed may reduce the absorption of conventional medications, and hence should be taken 1 hour before or 2 hours after these drugs.

Garlic

Uses. Garlic (*Allium sativum*) is used primarily for effects on the cardiovascular system. The herb is taken to reduce levels of triglycerides and LDL cholesterol, and to raise levels of HDL cholesterol. Garlic is also employed to reduce blood pressure, suppress platelet aggregation, increase arterial elasticity, and decrease formation of atherosclerotic plaque. In addition, garlic has been used for antimicrobial and anticancer effects.

Actions. Beneficial effects result from the actions of sulfides in garlic oil. Intact garlic cells contain *alliin*, an odorless amino acid. When garlic cells are crushed, they release *allinase*, an enzyme that converts *alliin* into *allicin*. Allicin is the major active agent in garlic oil and the compound that gives garlic its distinctive aroma. In addition to allicin, garlic oil contains *ajoenes* (pronounced AH-ho-weens), biologically active compounds that contribute to beneficial effects.

Garlic is thought to reduce cholesterol levels by interfering with cholesterol synthesis in the liver. Several key steps in the synthetic pathway are affected. There is conflicting evidence regarding inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis and the enzyme that "statin" drugs inhibit.

Antiplatelet effects, which are well documented, result in part from inhibiting thromboxane synthesis. Methylallylthiosulfide is the chemical in garlic believed responsible. In addition, garlic may suppress platelet aggregation by disrupting calcium-dependent processes. Coagulation is also affected by

the ajoenes, which have antithrombotic actions and may also stimulate fibrinolysis.

Lowering of blood pressure may be explained by garlic's demonstrated ability to increase the activity of nitric oxide synthase, the enzyme in blood vessels that makes nitric oxide. Nitric oxide, also known as endothelium-derived relaxant factor, is a powerful vasodilator.

Effectiveness. Garlic can produce favorable effects on plasma lipids, and possibly on blood pressure. However, benefits depend on the quality of the preparation. A high-quality preparation can decrease total cholesterol by 6% to 9%, LDL cholesterol by about 11%, and triglycerides by 25%. In addition, it can produce a small increase in HDL cholesterol. Although garlic is taken to reduce blood pressure, benefits appear modest at best.

The effectiveness of garlic products is determined by their ability to yield allicin. Since both allicin and allinase (the enzyme that makes allicin) are destroyed by heat, cooked garlic is not effective. Benefits of raw garlic are variable. Furthermore, because allicin is inactivated by acid in the stomach, large doses (1 to 2 whole cloves twice daily) are required. Best results are produced with an enteric-coated, dried preparation that contains a specified amount of alliin and allinase. Unfortunately, a German study has shown that only 5 of 18 common garlic products contain allicin in effective amounts.

Adverse Effects. Garlic is generally well tolerated. The most common side effects are unpleasant taste and bad breath. Rarely, garlic causes heartburn, flatulence, nausea, vomiting, diarrhea, and a burning sensation in the mouth. These effects are most pronounced with raw garlic and in people who don't eat garlic often. Patients suffering from infectious or inflammatory GI disorders should avoid garlic owing to its potential for GI irritation.

Interactions with Conventional Drugs. Garlic has significant antiplatelet effects. Accordingly, it can increase the risk of bleeding in patients taking antiplatelet drugs (eg, aspirin) or anticoagulants (eg, warfarin, heparin). Garlic can reduce levels of at least two drugs: cyclosporine (an immunosuppressant) and saquinavir (a protease inhibitor used to treat HIV infection).

Ginger Root

Uses. Ginger root (*Zingiber officinale*) is used primarily to treat vertigo and to suppress nausea and vomiting associated with motion sickness, morning sickness, seasickness, and general anesthesia. In addition, ginger has anti-inflammatory and analgesic properties that may help people with arthritis and other chronic inflammatory conditions. Some practitioners use ginger for URIs, although proof of efficacy is lacking.

Actions. The mechanism by which ginger suppresses nausea and vomiting is unclear. A good possibility is blockade of serotonin (5-hydroxytryptamine₃, or 5-HT₃) receptors located in the chemoreceptor trigger zone of the medulla and on afferent vagal neurons in the GI tract. Activation of these receptors triggers emesis. Conversely, blockade of these receptors suppresses emesis. In fact, drugs that block 5-HT₃ receptors (eg, ondansetron [Zofran]) are the most effective antiemetics available. Galanolactone, a major constituent of ginger, can block 5-HT₃ receptors *in vitro*, suggesting that receptor blockade may underlie antiemetic effects. Other actions that may con-

tribute to beneficial effects include stimulation of intestinal motility, salivation, and gastric mucus production, and suppression of GI spasm secondary to anticholinergic and antihistaminic actions.

The anti-inflammatory effects of ginger have been attributed to inhibiting synthesis of prostaglandins and leukotrienes, which are powerful inflammatory mediators.

How ginger may reduce vertigo is unknown.

Effectiveness. There is good evidence supporting the benefits of ginger root for prevention and treatment of motion sickness, morning sickness, seasickness, and postoperative nausea and vomiting (in the absence of opioids). Benefits in morning sickness are comparable to those of pyridoxine (vitamin B₆), but may take up to 3 days to develop. In patients with rheumatoid arthritis, ginger root appears to reduce pain, improve joint mobility, and decrease swelling and morning stiffness.

Adverse Effects. Ginger is very well tolerated. Severe toxicity has never been reported—although hugely excessive doses (above 5 gm/day) have the potential to cause CNS depression and cardiac dysrhythmias. Huge doses may also cause GI disturbances.

Ginger should be used with caution during pregnancy. Why? Because safety in pregnancy has not been proved. What we do know is that high-dose ginger can stimulate the uterus, and might thereby cause spontaneous abortion, although there are no reports of this ever happening. In addition, there is some evidence that ginger may affect fetal sex hormones. Also, ginger extracts are toxic to cells grown in culture, and mutagenic in *E. coli* and *Salmonella*. Because of these concerns, intake should be limited to usual therapeutic doses (eg, 1 to 2 gm dried root/day). For women who want to use a natural remedy for morning sickness, but would like to avoid ginger, pyridoxine (eg, 1000 mg/day in divided doses) is an effective alternative.

Interactions with Conventional Drugs. Ginger can inhibit production of thromboxane by platelets, and can thereby suppress platelet aggregation. Accordingly, ginger can increase the risk of bleeding in patients receiving antiplatelet drugs (eg, aspirin) or anticoagulants (eg, warfarin, heparin). Ginger can lower blood sugar, and hence may potentiate the hypoglycemic effects of insulin and other drugs for diabetes.

Ginkgo biloba

Uses. Ginkgo (*Ginkgo biloba*) can increase pain-free walking distance in patients with peripheral arterial disease. Although the drug has been taken to improve age-related memory impairment and senile dementia, proof of efficacy is lacking.

Preparations. Medicinal ginkgo is prepared by acetone extraction of leaves from the *Ginkgo biloba* tree. These leaves contain two classes of active compounds: *flavonoids* (ginkgo-flavone glycosides) and *terpenoids* (ginkgolides, bilobalide). *Ginkgo biloba* extracts (GBEs) are standardized to contain 24% flavonoids and 6% terpenoids. Daily oral doses of standardized GBE range from 60 to 240 mg.

Actions. Most benefits derive from improved blood flow secondary to ginkgo-induced vasodilation. Further benefits may derive from reducing capillary fragility and from scavenging free radicals. (Scavenging free radicals helps protect blood vessels from injury.) GBEs also suppresses production

of platelet-activating factor (PAF), a mediator of platelet aggregation, bronchospasm, and other processes. Reduced PAF production may help protect against thrombosis as well as bronchospasm and other allergic disorders.

Effectiveness. In patients with occlusive arterial disease of the legs (Fontaine stage IIB) or intermittent claudication, ginkgo can improve local blood flow and increase pain-free walking distance.

What about benefits in dementia? In a large placebo-controlled trial—the Ginkgo Evaluation of Memory (GEM) study, sponsored by the National Institutes of Health—GBE failed to prevent dementia of any sort, including Alzheimer's disease. This study enrolled over 3000 participants, age 75 or older. Half received a GBE formulation (120 mg twice daily) and the other half received a placebo. The result? After 5 years of treatment, the incidence of dementia was nearly identical in both groups.

Adverse Effects. Ginkgo is generally well tolerated. In some patients, it causes stomach upset, headache, dizziness, or vertigo, all of which can be minimized by avoiding rapid increases in dosage. There have been case reports of spontaneous bleeding, although no bleeding was observed in the GEM study.

Interactions with Conventional Drugs. Ginkgo may suppress coagulation. Accordingly, it should be used with caution in patients taking antiplatelet drugs (eg, aspirin) or anticoagulants (eg, warfarin, heparin).

There is concern that ginkgo may promote seizures. Accordingly, the herb should be avoided by patients at risk for seizures, including those taking drugs that can lower the seizure threshold, including antipsychotics, antidepressants, cholinesterase inhibitors, decongestants, first-generation antihistamines, and systemic glucocorticoids.

Glucosamine

Uses. Glucosamine—simply glucose with an amino group attached—is available as two salts: glucosamine sulfate and glucosamine hydrochloride. These agents are used widely to treat osteoarthritis of the knee, hip, and wrist.

Actions. Glucosamine is employed by the body in the synthesis of cartilage and synovial fluid. When given to people with osteoarthritis, glucosamine may help in several ways. First, it can act as a substrate for making cartilage and synovial fluid. Second, it can stimulate the activity of chondrocytes, the cells in joints that make cartilage and synovial fluid. And third, it can suppress production of cytokines that mediate joint inflammation and cartilage degradation.

Effectiveness. Studies on the efficacy of glucosamine in osteoarthritis have yielded mixed results. These differences may be due in part to the form of glucosamine used: glucosamine sulfate or glucosamine hydrochloride. In many studies using glucosamine sulfate, treatment reduced pain scores (by 28% to 40%) and increased joint functionality (by 21% to 46%). By contrast, in a major study using glucosamine hydrochloride—the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)—pain reduction with glucosamine was no better than with placebo. These differences suggest that glucosamine sulfate may be superior to glucosamine hydrochloride. Why might the sulfate work better? Because sulfate is an important cofactor in cartilage synthesis.

Glucosamine is often used in combination with *chondroitin sulfate*. However, the effectiveness of combination products has not been proved.

Adverse Effects. The most common side effects are GI disturbances, such as nausea and heartburn. Since commercial glucosamine is produced from the exoskeletons of shellfish (shrimp), glucosamine should be used with caution in patients with shellfish allergy. In theory, glucosamine can raise blood levels of glucose, but this has not been observed in clinical trials.

Interactions with Conventional Drugs. Several case reports suggest glucosamine may increase the risk of bleeding. Accordingly, exercise caution in patients taking antiplatelet drugs (eg, aspirin) or anticoagulants (eg, warfarin, heparin).

Green Tea

Uses. Green tea (*Camellia sinensis*) and green tea extracts have been used to lose weight, improve mental clarity, and prevent and treat cancers of the stomach, skin, bladder, and breast.

Actions. The mechanism underlying beneficial effects is poorly understood, and probably multifactorial. Polyphenols in green tea may underlie anti-inflammatory, chemoprotective, and antioxidant effects. Chemoprotection may also stem from epigallocatechin-3-gallate (EGCG), a compound in green tea extracts. The caffeine in green tea may be responsible for weight loss and improved mental clarity.

Effectiveness. Data on green tea efficacy are limited. Drinking green tea throughout the day can improve mental clarity, and may help with weight loss. In both cases, any benefits are probably due to caffeine, and not a substance unique to green tea. Studies done in animals and cultured cancer cells have shown that green tea and EGCG may prevent or slow the growth of certain cancers. Also, there is a small body of evidence indicating that drinking green tea may help prevent recurrence following treatment of early-stage breast cancer.

Adverse Effects. Moderate consumption appears to be safe. As with other caffeine-containing products, overconsumption may result in headache, nausea, anxiety, insomnia, increased heart rate, and increased urination. Fourteen cases of hepatotoxicity have been reported, primarily in people using green tea extracts. The mechanism of the hepatotoxicity remains unknown.

Interactions with Conventional Drugs. There is a long list of potential drug interactions. Green tea should be consumed with caution by patients taking vasodilators, stimulants and other psychoactive medications, and medications with a known risk for liver damage. Green tea contains a small amount of vitamin K, which may decrease the anticoagulant effects of warfarin.

Probiotics

Uses. Probiotics are dietary supplements composed of potentially beneficial bacteria or yeasts. These preparations typically contain two types of bacteria—lactobacilli and bifidobacteria—as well as *Saccharomyces boulardii*, a specific strain of yeast. All of these microorganisms are normal components of our gut flora. The bacteria in probiotics can help

treat irritable bowel syndrome (IBS), ulcerative colitis, *Clostridium difficile*-associated diarrhea (CDAD), and, in children, rotavirus diarrhea. Products containing *S. boulardii* are used for CDAD.

Actions. Normal intestinal and colonic bacteria play several important roles: They help metabolize foods and some drugs; they promote nutrient absorption; and they reduce colonization of the gut by pathogenic bacteria. *Lactobacillus* and *Bifidobacterium* species adhere to the intestinal wall and thereby prevent attachment of bacterial pathogens. They also control bacterial overgrowth by producing lactic acid, and to some degree by producing hydrogen peroxide. Benefits may also derive from increasing nonspecific cellular and humeral immunity. The yeast *S. boulardii* produces proteases that can degrade toxins produced by *C. difficile*. Benefits of *S. boulardii* in Crohn's disease derive in part by increasing intestinal secretion of immunoglobulin A.

Effectiveness. One product—Culturelle—contains *Lactobacillus rhamnosus* and *Lactobacillus GG*. In young patients with rotavirus infection, Culturelle can reduce the duration of diarrhea. Early initiation of treatment is important. Treatment with other *Lactobacillus* species has shown similar results. In children with CDAD, Culturelle can decrease stool frequency and improve stool consistency.

Another product—VSL#3—is composed of lactobacilli, bifidobacteria, and *Streptococcus thermophilus*. There is evidence that this product can induce remission of ulcerative colitis, perhaps in as many as 50% of patients. In patients with IBS, VSL#3 may reduce bloating and abdominal pain. However, the product does not improve bowel movement frequency or consistency.

Products containing *S. boulardii* may help prevent and treat CDAD, although the evidence is inconclusive.

Adverse Effects. Probiotics are generally well tolerated. Flatulence and bloating are the most common adverse effects. Infection of the blood with lactobacilli and fungi has been reported following ingestion of yogurt, but only in severely ill, immunocompromised patients taking broad-spectrum antibiotics long term. Fungemia has occurred most often when packets of *S. boulardii* have been opened at the bedside in the intensive care unit.

Interactions with Conventional Drugs. Antibacterial and antifungal drugs can kill the bacteria and yeasts in probiotic products. Accordingly, to help preserve probiotic activity, these preparations should be administered no sooner than 2 hours after dosing with antibacterial or antifungal drugs.

Resveratrol

Uses and Sources. Resveratrol is an antioxidant of plant origin promoted for antiaging effects and for protection against chronic diseases. Dietary sources include grapes (mainly the skin), red wine, purple grape juice, blueberries, cranberries, and peanuts. Resveratrol content of dietary supplements ranges from 16 to 600 mg per tablet or capsule. The amount in red wine is quite low, only 0.3 to 1.9 mg per 150-mL serving.

Owing to the presence of resveratrol in red wine, researchers thought it might explain the *French Paradox*: How can it be that French people have a relatively low incidence of coronary heart disease, despite having a diet relatively high in

saturated fats? However, the amount of resveratrol in red wine seems much too low for significant cardioprotectant effects.

Actions. Resveratrol has multiple actions that could benefit health. Perhaps most importantly, resveratrol can increase the activity of *sirtuin enzymes*, and may thereby increase insulin sensitivity, improve mitochondrial function, and promote cell survival—all of which could increase longevity. In yeast and nematodes, whose life span is determined in part by sirtuin activity, resveratrol can prolong life by as much as 70%. In addition to activating sirtuins, resveratrol has antioxidant, anti-inflammatory, antiplatelet, antitumor, and vasodilating actions, all of which could be beneficial.

Effectiveness. Although few studies have been done in humans, resveratrol has produced clear benefits in animals. In middle-aged mice on a high-calorie diet, resveratrol increased insulin sensitivity and reduced mortality. In normal-weight mice, resveratrol failed to reduce mortality, but did improve cardiovascular function, bone density, and motor coordination, and delayed formation of cataracts. In rodent models of human cancers, resveratrol suppressed tumor growth, including tumors of the lung, skin, breast, and prostate. In diabetic rats, resveratrol lowered blood glucose, and in human cells grown in culture, resveratrol increased glucose uptake. In one human study, resveratrol suppressed production of tumor necrosis factor (TNF) and free radicals; both actions could reduce blood vessel inflammation and subsequent atherosclerosis.

Although studies done in cell culture and animals have been encouraging, very little is known about the long-term benefits of resveratrol in humans. In fact, we have no data at all showing that resveratrol either slows aging or reduces the incidence or severity of any disease.

Adverse Effects and Interactions with Conventional Drugs. Information on adverse effects is limited. We do know that resveratrol has antiplatelet actions, which might intensify the effects of anticoagulants and antiplatelet drugs. Also, resveratrol can mimic the effects of estrogen, and hence is not recommended for women with estrogen-dependent breast cancer. In addition, resveratrol may increase insulin sensitivity, and hence should be used with caution by patients taking antidiabetic agents.

Saw Palmetto

Uses. Saw palmetto (*Serenoa repens*, *Sabal serrulata*) is taken to relieve urinary symptoms associated with benign prostatic hypertrophy (BPH). Benefits take at least 1 or 2 months to develop. The product employed clinically is an extract made from berries of the American saw palmetto, a small palm native to the southeastern United States.

Actions. How does saw palmetto affect prostate function? We don't know for sure. Reasonable possibilities include blockade of testosterone receptors, blockade of alpha-adrenergic receptors, and suppression of inflammation. Contrary to prior belief, the preparation does not seem to inhibit 5-alpha-reductase, the enzyme that converts testosterone into dihydrotestosterone (DHT), the active form of testosterone in the prostate. Saw palmetto does not reduce prostate size or serum levels of testosterone, DHT, or prostate-specific antigen (PSA).

Effectiveness. At this time, there is insufficient evidence to support using saw palmetto for BPH or any other condition.

Although early studies suggested that saw palmetto might reduce symptoms of BPH, these results have not been confirmed by more rigorous studies. According to a trial reported in the February 9, 2006, issue of the *New England Journal of Medicine (NEJM)*, saw palmetto has no benefit in BPH. This double-blind trial enrolled 225 men and randomized them to receive saw palmetto extract or placebo. The result? After 1 year, all major clinical parameters—prostate size, maximal urinary flow rate, residual volume after voiding, quality of life, and serum PSA—were the same in the placebo and saw palmetto groups, indicating that saw palmetto had no effect. A more recent study, reported in the September 28, 2011 issue of the *NEJM*, confirmed and extended these results, showing that, even in high doses, saw palmetto extract is no more effective than placebo at reducing symptoms of BPH.

Adverse Effects. Saw palmetto is very well tolerated. Significant adverse effects have not been reported. Rarely, saw palmetto causes nausea or headache. Although antiandrogenic effects (eg, gynecomastia) have not been reported, it may be wise to monitor for them. Saw palmetto may have antiplatelet actions, but increased bleeding has not been reported.

Because of its antiandrogenic effects, saw palmetto represents a danger to the developing fetus. (Finasteride, a 5-alpha-reductase inhibitor used for BPH, is classified in FDA Pregnancy Risk Category X.) Pregnant women should not ingest this herb.

Interactions with Conventional Drugs. Because of its antiplatelet effects, saw palmetto should be used with caution in patients taking antiplatelet drugs (eg, aspirin) or anticoagulants (eg, warfarin, heparin).

Soy

Uses. Soy protein and soy isoflavones have several uses, including prevention of breast cancer and, in postmenopausal women, treatment of vasomotor symptoms (hot flashes) and prevention of osteoporosis.

Actions. Soy is a member of the pea (legume) family. The major active components are phytoestrogens (isoflavones and lignans) and phytosterols (betasitosterol). Two isoflavones—genistein and daidzein—undergo enzymatic conversion to equol, a compound with estrogenic actions. About 50% of people lack the ability to produce equol. Soy isoflavones are structurally similar to estradiol (the major endogenous estrogen) and can bind with estrogen receptors. However, like the selective estrogen receptor modifiers (SERMs), isoflavones exert mixed estrogenic/antiestrogenic actions. In women with normal estrogen levels, soy isoflavones appear to *antagonize* endogenous estrogen. By contrast, in postmenopausal women, soy isoflavones act as estrogen agonists.

Effectiveness. Clinical trials using soy-derived phytoestrogens to relieve menopausal hot flashes have yielded mixed results. Overall, the studies lean toward a reduction in hot flashes. How do we explain the negative studies? It may be that many of the women enrolled had a reduced ability to metabolize isoflavones to their active form.

Several epidemiologic studies infer that soy consumption may reduce the risk of developing breast cancer. In particular, studies have documented that Asian women who eat a diet high in soy are at reduced risk. However, clinical trials confirming this benefit are lacking.

Several studies suggest that isoflavones either increase bone mineral density or slow the progression of osteoporosis in peri- and postmenopausal women. However, in a paper titled *Effects of Soy on Health Outcomes*, published in 2006 by the Agency for Healthcare Research and Quality, the authors caution against basing clinical decisions on current studies, owing to poor study design, inadequate study length, and small numbers of participants.

Adverse Effects. Soy and soy extracts are very well tolerated. Gastrointestinal effects—bloating, nausea, constipation or diarrhea—are most common. Rarely, soy can cause migraine, probably because of its estrogenic effects. Large amounts of soy products may increase the risk of oxalate kidney stones. There have been several cases of goiter and hypothyroidism in infants who drank soy-based formula. Concerns that soy formulas might cause feminization of male infants were dispelled by a 2008 review from the American Academy of Pediatrics.

Interactions with Conventional Drugs. Soy should not be combined with tamoxifen and other drugs that can block estrogen receptors. By killing intestinal flora, antibiotics may reduce conversion of isoflavones to their active form, thus decreasing the effects of soy.

St. John's Wort

Uses. St. John's wort (*Hypericum perforatum*) is used primarily for oral therapy of mild to moderate depression. The herb has also been used topically to manage local infection and orally to relieve pain and inflammation.

Actions. Benefits of St. John's wort appear to derive from two compounds—hyperforin and hypericin—that are extracted from flowers of the plant. These compounds can decrease uptake of three neurotransmitters: serotonin, norepinephrine (NE), and dopamine. Blockade of serotonin and NE uptake mimic the actions of some conventional antidepressants. Early research attributed antidepressant effects to inhibition of monoamine oxidase (MAO). However, we now know that the degree of MAO inhibition is too small to explain clinical effects.

Effectiveness. How effective is St. John's wort? At this time, it's hard to say. Although numerous studies have been conducted, evidence for efficacy is mixed, owing to poor study design, heterogeneous study populations, and variable hypericin content of the preparations used, as well as other confounding factors. The bottom line? For patients with *mild to moderate* major depression, St. John's wort appears superior to placebo and equal to tricyclic antidepressants. For patients with *severe* depression, there is no convincing proof of efficacy.

Adverse Effects. St. John's wort is generally well tolerated. Allergic skin reactions may occur, especially in people allergic to ragweed and daisies. In addition, the herb may cause CNS effects (eg, insomnia, vivid dreams, restlessness, anxiety, agitation, and irritability) as well as GI discomfort, fatigue, dry mouth, and headache. High-dose therapy may pose a risk of phototoxicity. To reduce this risk, light-skinned patients should minimize exposure to sunlight, wear protective clothing, and apply a sunscreen to exposed skin.

Interactions with Conventional Drugs. St. John's wort is known to interact adversely with many drugs—and the list continues to grow. Three mechanisms are involved: induction

of cytochrome P450 enzymes, induction of P-glycoprotein, and intensification of serotonin effects. Let's consider these one by one:

- *Induction of cytochrome P450* can accelerate the metabolism of many drugs, thereby decreasing their effects. This mechanism appears responsible for breakthrough bleeding and unintended pregnancy in women taking oral contraceptives, transplant rejection in patients taking cyclosporine (an immunosuppressant), reduced anticoagulation in patients taking warfarin, and reduced antiretroviral effects in patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors.
- *P-glycoprotein* is a transport protein found in cells that line the intestine and renal tubules. In the intestine, P-glycoprotein transports drugs *out* of cells into the intestinal lumen; in renal tubules, P-glycoprotein transports drugs *out* of tubular cells into the urine. Hence, by increasing P-glycoprotein synthesis, St. John's wort can accelerate elimination of drugs, and can thereby reduce their effects. This is the mechanism by which St. John's wort greatly reduces levels of *digoxin*, a drug for heart failure. Other drugs whose levels can probably be reduced by this mechanism include calcium channel blockers, steroid hormones, protease inhibitors, and certain anticancer drugs (eg, etoposide, paclitaxel, vinblastine, vincristine).
- Combining St. John's wort with certain drugs can intensify serotonergic transmission to a degree sufficient to cause potentially fatal *serotonin syndrome*. Although St. John's wort can enhance serotonergic transmission by itself, its effect is relatively weak. Hence, when used alone, the herb poses little risk. However, if St. John's wort is combined with other serotonin-enhancing agents, the risk is greatly increased, and hence St. John's wort should not be combined with such drugs. Among these are amphetamine, cocaine, and many antidepressants, including MAO inhibitors, selective serotonin reuptake inhibitors, certain tricyclic agents (e.g., amitriptyline, clomipramine), and duloxetine, nefazodone, and venlafaxine.

Because St. John's wort has a variety of known adverse interactions—and is likely to have more that are as yet unknown—caution is clearly advised. St. John's wort is not recommended for treating depression in patients taking other medications.

Valerian

Uses. Valerian root (*Valeriana officinalis*) is a sedative preparation used primarily to promote sleep. In addition, some people take it to reduce anxiety-associated restlessness.

Actions. Valerian may work by increasing the availability of gamma-aminobutyric acid (GABA, an inhibitory neurotransmitter) at synapses in the CNS. (Benzodiazepines and benzodiazepine-like drugs, which are the major conventional hypnotics, act by potentiating the actions of GABA.) In addition, valerian may act as a direct GABA agonist. The active ingredient(s) in valerian have not been identified.

Effectiveness. Although valerian has been used for centuries in Europe, China, and other countries, objective evidence of efficacy is lacking. In fact, two recent reviews of the literature concluded that, although valerian is safe, it does not promote sleep.

Adverse Effects. Valerian is generally very well tolerated. The FDA has given valerian a Generally Recognized as Safe (GRAS) rating when the product is consumed in amounts commonly used in food. Possible side effects include daytime drowsiness, dizziness, depression, dyspepsia, and pruritus. Prolonged use may cause headache, nervousness, or cardiac abnormalities. Because valerian can reduce alertness, users should exercise caution when performing dangerous activities, such as driving or operating dangerous machinery. In addition, valerian should be used with caution by people with psychiatric illnesses (eg, depression, dementia). As with benzodiazepines, there may be a risk of paradoxical excitation and physical dependence. We do not know if valerian enters breast milk or harms the developing fetus. Until more is known, valerian should be avoided by women who are pregnant or breast-feeding.

Interactions with Conventional Drugs. In theory, valerian can potentiate the actions of other drugs with CNS-depressant actions. Among these are alcohol, benzodiazepines, barbiturates, opioids, antihistamines, and centrally acting skeletal muscle relaxants. These combinations should be used with caution.

Comments. Valerian was used as a tranquilizer throughout World War II and was listed in the U.S. Pharmacopeia prior to 1945. It was removed from the National Formulary following the introduction of more effective sedatives.

HARMFUL SUPPLEMENTS TO AVOID

To help protect the public from dangerous botanical products, the FDA and the Federal Trade Commission are monitoring adverse event data, and issuing warnings to consumers and manufacturers. Three potentially harmful products—comfrey, kava, and Ma huang—are discussed below.

Comfrey

Comfrey (*Symphytum officinale*) is a medicinal herb used topically and orally. Topical use appears safe. Oral use is not. Why? Because comfrey contains pyrrolizidine alkaloids, which can cause veno-occlusive disease (VOD) in animals and hepatic VOD in humans. Hepatic VOD can result in severe liver damage. In addition to causing VOD, pyrrolizidine alkaloids may also be carcinogenic. Accordingly, in July of 2001, the FDA issued a letter to dietary supplement manufacturers advising them to remove comfrey from the market. They urged manufacturers to discontinue production, pull existing product off the shelves, and warn consumers of the possible dangers.

Kava

Kava (*Piper methysticum*), also known as *kava-kava* or *awa*, is used to relieve anxiety, promote sleep, and relax muscles. In the United States, the herb has been promoted as a natural alternative to benzodiazepines (eg, diazepam [Valium]) for treating anxiety and stress. Unfortunately, kava can cause severe liver injury, leading the FDA to issue a public warning in March 2002. Later that year, the Centers for Disease Control and Prevention issued a report on kava-related hepatotoxicity. In the report, they discussed 11 cases of hepatotoxicity from

the United States and Europe in which the victims required a liver transplant owing to severe liver failure. Because of concerns over hepatotoxicity, kava sales have been restricted in Germany, Canada, Switzerland, France, and Australia—but not yet in the United States. For more information on kava, refer to the sixth edition of this book.

Ma Huang (Ephedra)

Ma huang (ephedra) contains ephedrine, a compound that can elevate blood pressure and stimulate the heart and CNS. High-dose ephedra has been associated with stroke, myocardial infarction, and death. To date, over 17,000 adverse events have been reported, and at least 155 users have died. In 2004,

the FDA banned U.S. sales of all ephedra products, marking the first time that a dietary supplement has been ordered off the market. The ban was challenged by an ephedra producer and, in 2005, was partially reversed: A federal court upheld the ban for ephedra products that contain more than 10 mg/dose, but reversed the ban for products that contain 10 mg or less, arguing that there are insufficient data to prove that low doses pose a “significant or unreasonable risk.” In 2006, a federal appeals court upheld the FDA ban of ephedra. This ban was challenged again in 2007, but the U.S. Court of Appeals denied the petition for rehearing. At this time, the FDA ban does not apply to ephedra in traditional Asian medicines, which are not marketed as dietary supplements. For more information on Ma huang, refer to the sixth edition of this book.

KEY POINTS

- Dietary supplements can be defined as “vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites” intended to promote health and relieve symptoms of disease.
- Dietary supplements are regulated under the Dietary Supplement Health and Education Act of 1994 (DSHEA) and the Current Good Manufacturing Practices (CGMPs) ruling issued in 2007.
- Unlike conventional drugs, dietary supplements can be marketed without any proof of safety or efficacy.
- Under the DSHEA, dietary supplements are presumed safe until proved harmful. Hence, manufacturers don’t have to prove their products are safe. Rather, the FDA has to prove they’re not.
- Manufacturers can claim that a product favorably influences “body structure and function,” but cannot claim that it can be used to diagnose, treat, cure, or prevent any disease.
- Dietary supplements can interact with conventional drugs, sometimes with serious results. Be sure to ask patients if they are using medicinal herbs or other dietary supplements.
- The word *natural* is not synonymous with *safe*. Remember, poison ivy and tobacco are natural too.

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Management of Poisoning

Fundamentals of Treatment

Drugs and Procedures Used to Minimize Poison Absorption

Reducing Absorption of Ingested Poisons Surface Decontamination

Drugs and Procedures Used for Poison Removal

Drugs That Enhance Renal Excretion Nondrug Methods of Poison Removal

Specific Antidotes

Heavy Metal Antagonists Fomepizole

Other Important Antidotes

Poison Control Centers

Poisoning is defined as a pathologic state caused by a toxic agent. Sources of poisoning include medications, plants, environmental pollutants, and drugs of abuse. These toxicants may enter the body orally or by injection, inhalation, or absorption through the skin. Poisoning may be unintentional (accidental) or intentional. Symptoms of poisoning often mimic those of disease, and hence the possibility of poisoning should be considered whenever a diagnosis is made.

In the United States, over 2.4 million poisonings are reported annually. In 2005, accidental poisoning caused 23,618 deaths, and intentional poisoning caused 5833 more. Most poisoning deaths are caused by drugs: In 2004, 95% of deaths from accidental poisoning were caused by drugs, as were 75% of suicides. The *incidence* of poisoning is highest in young children. However, the *mortality rate* in this group is very low. In 2000, poisoning-related medical expenses were \$26 billion.

FUNDAMENTALS OF TREATMENT

Poisoning is a medical emergency and requires rapid treatment. Management has five basic elements: (1) supportive care, (2) identification of the poison, (3) prevention of further absorption, (4) poison removal, and (5) use of specific antidotes. These essentials are discussed below.

Supportive Care

Supportive care is the most important element in managing acute poisoning. Support is based on the clinical status and requires no knowledge specific to the poison involved. Maintenance of respiration and circulation are primary concerns. Measures for respiratory support include inserting an airway, giving humidified oxygen, and providing mechanical ventila-

tion. Volume depletion (resulting from vomiting, diarrhea, or sweating) can compromise circulation. Volume should be restored by administering normal saline or Ringer's solution. Severe hypoglycemia may occur, resulting in coma. Levels of blood glucose should be monitored. For coma of unknown etiology, IV dextrose should be given immediately—even if information on blood glucose is lacking. Acid-base disturbances may occur; determination of arterial blood gases will facilitate diagnosis and management. If convulsions develop, IV diazepam is the treatment of choice.

Poison Identification

Treatment of poisoning is facilitated by knowing the identity and dosage of the toxicant. Efforts to obtain this information should proceed concurrently with medical management.

A history is one way to identify the toxic agent. However, experience has shown that histories taken at times of poisoning are often inaccurate. Hence, statements about the nature or quantity of poison may not be correct.

Positive identification can be made using analytic techniques. A gas chromatograph/mass spectrometer can provide qualitative and quantitative information. Analyses can be performed on specimens of urine, blood, and gastric contents. To determine whether poison levels are rising or falling, analyses should be performed on sequential blood samples taken about 2 hours apart.

Prevention of Further Absorption

By reducing the absorption of a poison, we can minimize blood levels, and thereby significantly decrease morbidity and mortality. For *ingested* poisons, three procedures are available: (1) giving activated charcoal, (2) gastric lavage and aspiration, (3) and whole-bowel irrigation. Induction of emesis with *syrup of ipecac*, either at home or in the clinic, is *no longer recommended*. When poison exposure is *topical*, surface decontamination is employed. Details of these procedures are discussed in the following section.

Promotion of Poison Removal

Measures that help eliminate poison from the body shorten the duration of exposure and, if implemented before plasma levels have peaked, can reduce the maximum level of poison achieved. By shortening exposure and reducing maximum poison levels, these measures can decrease morbidity and mortality.

Removal of poison can be promoted with drugs and with nonpharmacologic techniques. The drugs used for poison removal act by increasing renal excretion of toxic agents. Nonpharmacologic methods of poison removal include peritoneal dialysis, hemodialysis, and exchange transfusion. Details on methods of poison removal are presented later.

ing in some situations. Nondrug procedures are most effective when (1) binding of toxicants to plasma proteins is low, and (2) blood levels of toxicants are high (ie, when distribution of the toxic agent is restricted to the blood and extracellular fluid).

Each of the nondrug methods of poison removal has its benefits and drawbacks. *Peritoneal dialysis* has two advantages: the procedure is relatively simple and it occupies a minimum of staff time. *Hemodialysis*, although more difficult than peritoneal dialysis, is about 20 times more effective. *Hemoperfusion* is a process in which blood is passed over a column of charcoal or absorbent resin. If the affinity of the resin for a particular poison is high, the procedure can strip a toxicant from binding sites on plasma proteins. The principal disadvantage of hemoperfusion is loss of platelets. When binding of a poison to plasma proteins is particularly avid, *exchange transfusion* can be an effective method of removal.

SPECIFIC ANTIDOTES

Heavy Metal Antagonists

The heavy metals most frequently responsible for poisoning are iron, lead, mercury, arsenic, gold, and copper. These metals cause injury by forming complexes with enzymes and other physiologically important molecules. Poisoning may result from environmental exposure, intentional overdose, or therapeutic use of heavy metals.

The drugs given to treat heavy metal poisoning are called *chelating agents* or *chelators*. These agents interact with metals to form *chelates*—ring structures in which the metal and the chelating agent form two or more points of attachment. The chelate formed by mercury and dimercaprol illustrates this concept (Fig. 109-1).

Useful chelating agents have a high affinity for heavy metals, and hence can compete successfully with endogenous molecules for metal binding. By preventing initial binding of metals to endogenous molecules, chelators can prevent injury. By stripping metals that have already become bound, chelators can enhance their excretion.

The selectivity of a heavy metal antagonist is determined by its affinity for specific metals. Some antagonists are selective for only one metal; others can form chelates with several metals. Deferoxamine, for example, binds selectively to iron. In contrast, dimercaprol is relatively nonselective, binding tightly with arsenic, mercury, and gold.

Properties desirable in a heavy metal antagonist include (1) high affinity for a toxic metal, (2) low affinity for essential endogenous metals (eg, magnesium, zinc), (3) the ability to reach sites of metal storage, (4) high activity at physiologic pH, (5) formation of chelates that are less toxic than the free metal, and (6) formation of chelates that are easily excreted.

Chelators for Iron Toxicity

We have three chelators with a high affinity for iron. All three—deferoxamine, deferasirox, and deferiprone—are used to treat iron overload caused by chronic transfusions in patients with infusion-dependent anemias. Only one of the drugs—deferoxamine—is also indicated for acute iron poisoning.

Deferoxamine. Actions and Uses. Deferoxamine [Desferal] has a high affinity for ferric iron. The drug chelates free iron and can also strip iron bound to ferritin and hemosiderin. In contrast, iron present in hemoglobin and cytochromes is not affected. Deferoxamine is employed to treat acute iron poisoning and chronic transfusional iron overload.

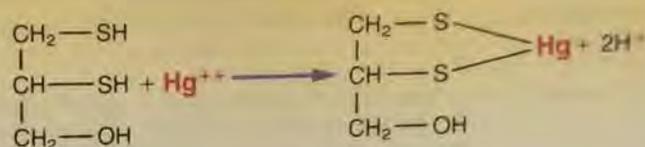


Figure 109-1 • Chelation of mercury by dimercaprol.

Pharmacokinetics. Deferoxamine is poorly absorbed from the GI tract, and hence requires parenteral administration. The chelate formed between deferoxamine and iron is excreted primarily in the urine.

Adverse Effects. Common reactions include fever (23.8%), headache (20.3%), cough (19%), pharyngolaryngeal pain (14.8%), nasopharyngitis (14.5%), and bronchitis (11%). Pain may occur at the site of injection. Rapid IV infusion may cause hypotension, tachycardia, erythema, and urticaria. Prolonged therapy may be associated with allergic reactions, abdominal discomfort, leg cramps, fever, and dysuria.

Contraindications. Because deferoxamine is excreted by the kidneys, the drug should not be given to patients with renal insufficiency. Deferoxamine has caused fetal malformations in experimental animals, and hence is not recommended for pregnant women.

Preparations, Dosage, and Administration. Deferoxamine mesylate is supplied as a powder to be reconstituted for injection. The drug can be administered by IM injection and by IV or subQ infusion. Intramuscular injection is preferred. Intravenous infusion is usually reserved for patients in shock. The dosage for IM or IV administration is the same. For treatment of acute iron poisoning, the initial dose for adults and children is 1 gm. This is followed 4 and 8 hours later with 0.5-gm doses. For IV administration, the maximum rate of infusion is 15 mg/kg/hr. For treatment of iron overload associated with chronic blood transfusions (see discussion of deferasirox below), the dosage is 20 to 40 mg/kg/day, administered by a prolonged (8- to 12-hour) subQ infusion.

Deferasirox. Actions and Uses. Like deferoxamine, deferasirox [Exjade] is a chelating agent with a high affinity for iron. The drug is indicated for oral therapy of iron overload resulting from chronic blood transfusions in patients with beta-thalassemia, sickle cell anemia, myelodysplastic syndromes, and other infusion-dependent anemias. Left untreated, iron overload can injure the liver, heart, and other organs. Cardiac injury is of special concern owing to a risk of dysrhythmias, heart failure, and even death. Compared with deferoxamine, deferasirox is much easier to use. Why? Because deferasirox is taken orally, whereas deferoxamine requires parenteral administration, usually by prolonged (8- to 12-hour) subQ infusions done 5 to 7 nights a week. Unlike deferoxamine, deferasirox is not indicated for acute iron poisoning.

Pharmacokinetics. Plasma levels peak 1.4 to 4 hours after oral dosing. In the blood, deferasirox is highly bound to albumin. The drug undergoes hepatic metabolism followed by excretion in the bile. Deferasirox and its metabolites are then eliminated mainly (84%) in the feces. The plasma half-life is 8 to 16 hours.

Adverse Effects. The most common effects are fever (18.9%), headache (15.9%), cough (13.9%), nasopharyngitis (13.2%), and GI reactions, including abdominal pain (13.9%), nausea (10.5%), vomiting (10.1%), and diarrhea (11.8%). Some patients (<1%) experience hearing loss and ocular disturbances, and hence hearing and vision tests should be done before treatment and every 12 months thereafter.

The most serious adverse effects are *renal impairment* (including renal failure), *liver dysfunction* (including liver failure), and *GI hemorrhage*. In some cases, these reactions have been fatal. Risk is greatest in older patients, and in those with high-risk myelodysplastic syndromes, pre-existing renal or hepatic impairment, and low platelet counts. To reduce the risk of kidney and liver complications, kidney and liver function should be assessed at baseline and frequently thereafter.

Drug Interactions. *Cholestyramine* (used to reduce blood cholesterol) and *aluminum-containing antacids* (used for peptic ulcers) can decrease absorption of deferasirox, and can thereby reduce its beneficial effects. Accordingly, combined use of deferasirox with these drugs should be avoided. If the combinations cannot be avoided, the dosage of deferasirox should be increased.

Combined use of deferasirox with *anticoagulants* (eg, warfarin) increases the risk of hemorrhage. Use such combinations with great caution.

Deferasirox can reduce levels of drugs that are metabolized by CYP3A4 (the 3A4 isozyme of cytochrome P450). Loss of benefits may result. Accordingly, drugs that are substrates for CYP3A4 (eg, cyclosporine, simvastatin, hormonal contraceptives) should be used with caution.

Deferasirox can cause a 2.3-fold increase in levels of *repaglinide* (used for diabetes). The mechanism is inhibition of CYP2C8. If deferasirox and repaglinide are combined, the dosage of repaglinide should be reduced, and blood levels of glucose should be closely monitored.

Preparations, Dosage, and Administration. Deferasirox is supplied in tablets (125, 250, and 500 mg) that must be dispersed in fluid (water, orange juice, apple juice). The tablets should not be swallowed whole. For doses of less than 1 gm, disperse tablets in 3.5 ounces of fluid; for doses greater than 1 gm, disperse in 7 ounces. Dosing is done once a day on an empty stomach (ie, at least 30 minutes before eating), at the same time each day. The drug must not be taken with aluminum-containing antacids or cholestyramine.

The starting dosage is 20 mg/kg/day. Dosage can be adjusted every 3 to 6 months based on serum ferritin levels, but must not exceed 30 mg/kg/day. If serum ferritin falls consistently below 500 mcg/L, temporary interruption of treatment should be considered. Dosage should be reduced if liver or kidney function declines.

Deferiprone. Deferiprone [Ferriprox], approved in 2011, is indicated for oral therapy of iron overload caused by chronic blood transfusions—but only in patients with thalassemia (safety and efficacy in patients with other chronic anemias has not been established), and only after treatment with other iron chelators has failed. Deferiprone is not used for acute iron poisoning.

The most common adverse effects are chromaturia (14.6%), nausea (12.6%), abdominal pain (10.4%), vomiting (9.8%), arthralgia (9.8%), and liver toxicity (7.5%), as indicated by elevation of circulating transaminases.

The most serious adverse effect is agranulocytosis/neutropenia, which poses a risk of serious infections and death. Accordingly, absolute neutrophil counts should be obtained at baseline and weekly thereafter. If neutropenia or infection develops, deferiprone should be interrupted. If possible, deferiprone should not be combined with other drugs that promote neutropenia or agranulocytosis.

In animal studies, low-dose deferiprone caused fetal malformations and fetal death. The drug is classified in FDA Pregnancy Risk Category D, and hence should not be used during pregnancy.

Deferiprone is supplied in 500-mg tablets. The recommended initial dose is 25 mg/kg 3 times a day. The maximum dose is 33 mg/kg 3 times a day. Absorption can be reduced by mineral supplements and antacids that contain polyvalent cations (eg, aluminum, iron, zinc). Accordingly, deferiprone should not be dosed within 4 hours of these substances.

Dimercaprol

Actions and Uses. Dimercaprol [BAL In Oil] binds with arsenic, gold, mercury, and lead. The resulting chelates are excreted in the urine. The drug is used as the sole chelator to rid the body of arsenic, mercury, or gold. In addition, dimercaprol can be combined with edetate calcium disodium (calcium EDTA) to treat poisoning with lead. Since dimercaprol is more effective at preventing binding of metals to endogenous molecules than at reversing binding that has already taken place, benefits are greatest when the drug is administered early (within 1 to 2 hours of metal ingestion).

Pharmacokinetics. Administration is by deep IM injection. Dimercaprol cannot be used orally. The drug has a short plasma half-life, with complete elimination occurring in approximately 4 hours.

Adverse Effects. At recommended doses, dimercaprol is generally well tolerated. Tachycardia and elevation of blood pressure occur frequently; blood pressure returns to baseline within hours. Pain and sterile abscesses may occur at sites of injection. Fever is common in children. High doses produce a broad spectrum of untoward effects.

Chelates formed with dimercaprol are unstable at acidic pH. Hence, if the urine is acidic, heavy metals may dissociate from dimercaprol, resulting in renal toxicity. To protect the kidneys, the urine should be kept alkaline.

Dimercaprol is formulated in peanut oil, and hence must be avoided by patients with known or suspected peanut allergy.

Preparations, Dosage, and Administration. Dimercaprol is supplied in ampules containing 300 mg of the drug in 3 mL of peanut oil. The preparation is administered by deep IM injection.

For mild poisoning with gold or arsenic, doses of 2.5 mg/kg are administered according to the following schedule: 4 times daily on days 1 and 2, twice daily on day 3, and once daily on days 4 through 13.

For acute poisoning with mercury, the initial dose is 5 mg/kg. Subsequent doses of 2.5 mg/kg are administered 1 or 2 times daily for 10 days.

For acute poisoning with lead, dimercaprol is combined with calcium EDTA. For the initial dose, give dimercaprol alone (4 mg/kg). Every 4 hours thereafter, give dimercaprol (4 mg/kg), along with calcium EDTA, administered at a separate site. Duration of treatment is 2 to 7 days. Dosage for calcium EDTA is presented below.

Edetate Calcium Disodium (Calcium EDTA)

Actions and Uses. Calcium EDTA [Calcium Disodium Versenate] is used primarily for lead poisoning. The drug combines with lead to form a stable chelate that is excreted in the urine.

Pharmacokinetics. Calcium EDTA may be administered IV or IM. The drug is poorly absorbed from the GI tract, and hence is not given orally. Elimination is by glomerular filtration. Because calcium EDTA is excreted by the kidneys, the drug should be employed only if urine flow is adequate. If urine flow is insufficient, flow should be restored with IV fluids prior to giving the chelator. If anuria develops during the course of treatment, administration should stop.

Adverse Effects. The principal toxicity of calcium EDTA is renal tubular necrosis. Signs include hematuria and proteinuria. Daily urinalysis should be performed to monitor for these effects. If renal toxicity develops, the drug should be discontinued immediately.

Preparations, Dosage, and Administration. Calcium EDTA is supplied in 5-mL ampules containing 1000 mg of drug. Administration may be IV or IM. The IV route is preferred for adults, whereas IM is preferred for children.

For IV use, the contents of 1 ampule are diluted in 250 to 500 mL of 5% dextrose solution or normal saline. Infusion should be done slowly (over 1 hour or more). The adult dosage is 1 gm twice daily for 5 days. After a 2-day hiatus, a second course may be given if needed.

The IM dosage for children is 35 mg/kg (or less) administered twice daily for 3 to 5 days. After a pause of 4 days or longer, a second course is given.

Penicillamine

Actions. Penicillamine [Cuprimine, Depen] is a breakdown product of penicillin. Commercial preparations are made synthetically. Penicillamine forms water-soluble chelates with copper, iron, lead, arsenic, gold, and mercury. These complexes are excreted in the urine.

Therapeutic Uses. The principal indication is *Wilson's disease*, a disorder of copper metabolism. Affected individuals are deficient in ceruloplasmin, a plasma protein that serves as a copper carrier. Symptoms result from deposition of copper in the liver, brain, kidneys, eyes, and other organs. Penicillamine relieves symptoms by promoting copper excretion. Therapeutic effects may take several months to develop. Additional uses are *rheumatoid arthritis* and *cystinuria*. Beneficial effects in these disorders are not related to chelation of heavy metals.

Pharmacokinetics. Penicillamine is well absorbed following oral administration. Food greatly reduces the extent of absorption. Once absorbed, penicillamine is rapidly excreted in the urine.

Adverse Effects. With prolonged use, penicillamine can cause varied and serious toxicities. Deaths have occurred. The drug should be employed only with close medical supervision. Possible cutaneous reactions include urticaria, maculopapular and morbilliform rash, pemphigoid lesions, and pruritus. Bone marrow suppression can result in leukopenia, agranulocytosis, and aplastic anemia, all of which can be fatal. Autoimmune and immune complex disorders have been associated with penicillamine. Among these are dermatomyositis, polymyositis, lupus erythematosus, alveolitis, and myasthenia gravis. Renal toxicity may occur.

Contraindications. Penicillamine is contraindicated for patients who have experienced agranulocytosis or aplastic anemia when receiving penicillamine in the past. The drug is also contraindicated for patients with rheumatoid arthritis who are pregnant or have renal insufficiency.

Preparations, Dosage, and Administration. Penicillamine is supplied in 250-mg tablets and capsules. For *Wilson's disease*, the usual dosage is 250 mg 4 times a day. Doses should be administered 1 hour before meals and at bedtime. Dosage is adjusted on the basis of untoward effects and urinary copper content. Treatment is long term.

Succimer

Actions and Uses. Succimer [Chemet] binds avidly with lead, mercury, and arsenic. Binding is less avid with copper and zinc. Binding to iron, calcium, and magnesium is minimal, and therefore succimer presents no risk of depleting these essential minerals. Succimer is our most effective drug for lowering blood levels of lead in children, its only approved indication. However, although succimer can reduce lead levels, benefits are limited to prevention of seizures and death from acute encephalopathy. Treatment does not reduce or prevent the long-term neurologic sequelae of lead poisoning, which are irreversible.

Pharmacokinetics. Succimer is rapidly but variably absorbed following oral administration. The drug undergoes extensive metabolism. Metabolites and parent drug are eliminated slowly in the urine.

Adverse Effects. Adverse effects appear to be mild. About 10% of patients experience GI reactions (nausea, diarrhea, cramps). Other moderate

- Hazard surveillance to achieve hazard elimination
- Professional and public education in poisoning prevention, diagnosis, and treatment

Poison centers certified by the AAPCC are accessible 24 hours a day; have a specially trained, full-time staff (usually nurses, pharmacists, or both); are directed by a board-certified physician-toxicologist; and are associated with a medical center that has laboratory facilities and personnel needed for the diagnosis and management of poisoning. These centers are accessible by phone and can provide immediate instruction on the management of acute poisoning. In the majority of cases, the information sup-

plied will permit successful treatment at home. By facilitating rapid treatment, poison control centers can decrease morbidity and mortality, and can help reduce the cost of emergency care.

In 2002, the AAPCC established a

**NATIONAL POISON HOTLINE:
1-800-222-1222**

Dialing this number from any place in the United States will connect you with the *local* poison center. (This is like dialing 911 from any place in the country to contact local emergency-service providers.)

KEY POINTS

- Management of poisoning has five basic components: supportive care, poison identification, prevention of further absorption, promotion of poison removal, and use of specific antidotes.
- The preferred method for reducing absorption of ingested poisons is adsorption onto activated charcoal, which should be given no later than 1 hour after poison ingestion.
- Removal of absorbed poisons can be accelerated by using drugs to enhance renal excretion and by nondrug methods, such as hemodialysis and exchange transfusion.
- For most poisons there is no specific antidote.
- Heavy metal poisoning can be treated with chelating agents.
- Poison control centers offer immediate, expert assistance over the phone.
- Dialing 1-800-222-1222 from any place in the United States will connect you with the nearest poison control center.

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Potential Weapons of Biologic, Radiologic, and Chemical Terrorism

Bacteria and Viruses

- Bacillus anthracis* (Anthrax)
- Francisella tularensis* (Tularemia)
- Yersinia pestis* (Pneumonic Plague)
- Variola Virus (Smallpox)

Biotoxins

- Botulinum Toxin
- Ricin

Chemical Weapons

- Nerve Agents
- Sulfur Mustard (Mustard Gas)

Radiologic Weapons

- Weapon Types
- Drugs for Radiation Emergencies

In the fall of 2001, the United States was hit by unprecedented terrorist attacks. On September 11, terrorists hijacked four commercial jets, and succeeded in crashing two into the twin towers of the World Trade Center and one into the Pentagon. In October, anthrax spores were mailed to several locations, causing illness and death. These events have generated great concern about our vulnerability to more such attacks, and our ability to manage the consequences.

To improve our readiness for a terrorist attack, the federal government has taken several steps, including passage of the *Public Health Security and Bioterrorism Preparedness and Response Act of 2002* (the Bioterrorism Act), the *Project BioShield Act of 2004*, and the *Pandemic and All-Hazards Preparedness Act* in 2007. All three incentives were designed to spur development and production of drugs and vaccines to protect U.S. residents from bioterror agents, such as anthrax, smallpox, botulism, and plague. Although there have been some notable results, much more needs to be done.

In this chapter, we discuss some of the potential weapons of terrorism, focusing primarily on bacteria and viruses. Biotoxins, chemicals (nerve agents and mustard gas), and radiologic weapons are addressed as well. Discussion centers on clinical manifestations and treatment. Prevention is addressed where appropriate.

For more information on the weapons discussed here, or for information on other potential weapons, you can consult the online resources listed in Table 110-1.

TABLE 110-1 ■ Online Resources for Information on Biologic, Radiologic, and Chemical Terrorism

- www.bt.cdc.gov—Bioterrorism information from the Centers for Disease Control and Prevention (CDC)
- www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/default.htm—Bioterrorism information from the U.S. Food and Drug Administration (FDA)
- www.bioterrorism.slu.edu—Bioterrorism information from the Center for the Study of Bioterrorism at the Saint Louis University School of Public Health
- www.idsociety.org/bt/toc.htm—Bioterrorism information from the Infectious Disease Society of America
- www.upmc-biosecurity.org—Information on biologic weapons from the Center for Biosecurity, an independent, nonprofit organization associated with the University of Pittsburgh Medical Center
- Jama.ama-assn.org/cgi/collection/bioterrorism—Articles on bioterrorism from JAMA
- www.who.int/ionizing_radiation/a_e/terrorism/en/—Information on nuclear weapons and dirty bombs from the World Health Organization

BACTERIA AND VIRUSES

Bacillus anthracis (Anthrax)

Bacillus anthracis is the bacterium that causes anthrax, a disease with three major forms: inhalational, cutaneous, and gastrointestinal. Our discussion focuses on inhalational and cutaneous anthrax. Gastrointestinal anthrax is not addressed because this form is unlikely to result from a terrorist attack.

Of the microbes that might be used by terrorists, *Bacillus anthracis* is among the most dangerous. In October 2001, spores of *B. anthracis* were mailed to several locations in the United States, causing 22 confirmed or suspected cases of anthrax and 5 deaths. This experience served to heighten concerns regarding the feasibility of terrorist groups using aerosolized bioweapons to stage a large-scale attack.

Microbiology

Bacillus anthracis is an aerobic, gram-positive bacterium. Its name derives from *anthrakis*, the Greek word for coal (in recognition of the black skin lesions that characterize cutaneous infection). *Bacillus anthracis* can exist as spores, which are dormant, or as actively growing bacteria. Infection is acquired when the spores enter a host. Ports of entry are skin

lesions and the respiratory and GI tracts. In the presence of nutrients (amino acids, nucleotides, glucose), which are abundant in the blood and tissues of the host, the spores germinate and transform into mature bacteria. The mature forms grow and divide rapidly until the nutrient supply is depleted, after which they cease dividing and produce more spores. The mature bacteria cannot survive long outside the host. In contrast, the spores can remain viable in the environment for decades. Anthrax is not transmitted person to person.

Clinical Manifestations

Inhalational Anthrax. Infection begins with deposition of anthrax spores in the alveolar space, followed by transport to regional lymph nodes, where germination occurs. Clinical latency can range from 2 days to 6 weeks. Injury results when mature bacilli release toxins, which cause hemorrhage, edema, and necrosis. Once the concentration of toxin has reached a critical level, antibiotics cannot prevent death, even if they kill all circulating bacilli.

Symptoms appear in two stages. Initial symptoms—fever, cough, malaise, and weakness—may be relatively mild. In the second stage, which develops 2 to 3 days later, there is a sudden increase in fever, along with severe respiratory distress, septicemia, hemorrhagic meningitis, and shock. Interestingly, although the infection originates in the lungs, true pneumonia rarely occurs. Even with treatment, the mortality rate can be high: In the U.S. outbreak of 2001, 45% of victims died.

Cutaneous Anthrax. Symptoms begin 1 to 7 days after exposure to anthrax spores. Areas with cuts or abrasions are most vulnerable, but injury can develop at any site where spores land. The initial lesion is a small papule (solid raised area) or vesicle (fluid-filled raised area) associated with localized itching. Within 2 days, the lesion enlarges and evolves into a painless ulcer with a necrotic core. Seven to 10 days

after symptom onset, a black eschar (scab-like structure) forms—but then dries, loosens, and sloughs off by day 12 to 14. In most patients, the lesions resolve without complications or scarring. However, if *systemic* infection develops, the outcome can be fatal. In the absence of antibiotic therapy, about 20% of people with cutaneous anthrax die. In contrast, death among treated patients is rare.

Treatment of Established Infection

The treatments discussed here reflect consensus-based recommendations published in *JAMA* in an article titled *Anthrax as a Biological Weapon, 2002: Updated Recommendations for Management*.

Inhalational Anthrax. Given the rapid course that inhalational anthrax follows, early therapy with antibiotics is essential. Any delay can reduce the chance of survival. Initial IV therapy is preferred to initial oral therapy. However, if there are mass casualties, IV therapy may be impossible, owing to limited supplies and personnel. Ideally, treatment should start with IV ciprofloxacin or IV doxycycline. Because the strain of *B. anthracis* may be resistant to these drugs, one or two other IV antibiotics should be included. When clinically appropriate, the patient can be switched to oral ciprofloxacin or doxycycline, without additional antibiotics. The duration of treatment—IV plus oral—is 60 days. Specific regimens for adults, children, and pregnant women are presented in Table 110-2 (for limited casualty settings) and Table 110-3 (for mass casualty settings).

Raxibacumab, a monoclonal antibody, represents a new approach to treating inhalational anthrax. Unlike antibiotics, which kill anthrax bacteria, raxibacumab neutralizes deadly anthrax toxins. As a result, the drug can decrease injury even after an infection has become established. Because anthrax infection is rare, raxibacumab has not been tested in humans.

TABLE 110-2 ■ Therapy of Inhalational Anthrax in the Limited Casualty Setting

Patient Group	Initial Intravenous Therapy	Follow-up Oral Therapy	Duration
Adults	Ciprofloxacin, 400 mg every 12 hr or Doxycycline, 100 mg every 12 hr and All patients should get 1 or 2 additional antibiotics. Options include rifampin, vancomycin, penicillin, ampicillin, imipenem, chloramphenicol, clindamycin, and clarithromycin. Do not use penicillin or ampicillin alone.	When clinically appropriate, switch to oral antibiotics: Ciprofloxacin, 500 mg twice daily or Doxycycline, 100 mg twice daily	60 days total (IV and PO combined)
Children	Ciprofloxacin, 10–15 mg/kg every 12 hr, but no more than 1 gm/day or Doxycycline (for young children): >8 yr and >45 kg: 100 mg every 12 hr >8 yr and ≤45 kg: 2.2 mg/kg every 12 hr ≤8 yr: 2.2 mg/kg every 12 hr and As with adults, all patients should get 1 or 2 additional antibiotics.	When clinically appropriate, switch to oral antibiotics: Ciprofloxacin, 10–15 mg/kg every 12 hr, but no more than 1 gm/day or Doxycycline (for young children): >8 yr and >45 kg: 100 mg every 12 hr >8 yr and ≤45 kg: 2.2 mg/kg every 12 hr ≤8 yr: 2.2 mg/kg every 12 hr	60 days total (IV and PO combined)
Pregnant	Same as nonpregnant adults	Same as nonpregnant adults	

Data from Inglesby TV, et al: Anthrax as a biological weapon, 2002: Updated recommendations for management. *JAMA* 287:2236–2252, 2002

TABLE 110-3 ■ Therapy of Inhalational Anthrax in the Mass Casualty Setting

Patient Group	Preferred Initial Oral Therapy	Alternative Oral Therapy (if Strain Is Proved Susceptible)	Duration
Adults	Ciprofloxacin, 500 mg every 12 hr	Doxycycline, 100 mg every 12 hr Amoxicillin, 500 mg every 8 hr	60 days
Children	Ciprofloxacin, 10–15 mg every 12 hr, but no more than 1 gm/day	≥20 kg: amoxicillin, 500 mg every 8 hr <20 kg: amoxicillin, 13.3 mg/kg every 8 hr	60 days
Pregnant	Ciprofloxacin, 500 mg every 12 hr	Amoxicillin, 500 mg every 8 hr	60 days

Data from Inglesby TV, et al: Anthrax as a biological weapon, 2002: Updated recommendations for management. JAMA 287:2236–2252, 2002.

However, lifesaving effects have been clearly demonstrated in monkeys exposed to massively lethal doses of anthrax spores. As of April 2009, the manufacturer had supplied 20,000 doses to the U.S. Strategic National Stockpile.

Cutaneous Anthrax. Cutaneous anthrax is treated with oral antibiotics. The preferred drugs are *ciprofloxacin* and *doxycycline*. Dosages for adults, children, and pregnant women are the same as those given in Table 110-2 for follow-up oral therapy of inhalational anthrax. Duration of treatment is 60 days. It should be noted that treatment is unlikely to prevent cutaneous lesions, but *will* prevent systemic complications.

Pre-exposure Vaccination

Currently, only one anthrax vaccine—*BioThrax* (formerly known as Anthrax Vaccine Adsorbed or AVA)—is licensed for use in the United States. *BioThrax* is an inactivated, cell-free preparation made from an avirulent strain of *B. anthracis*. The normal immunization schedule calls for three subcutaneous injections given 2 weeks apart, followed by three more injections given at 6, 12, and 18 months. Annual booster shots are recommended thereafter. The most common side effects are muscle and joint aches (20%); headache (20%); local redness, tenderness, or itching (10%); fatigue (10%); nausea (5%); and chills and fever (5%). Serious allergic reactions occur rarely (less than 1 in 100,000).

Who should receive anthrax vaccine? At this time, immunization is limited to people considered at risk. *BioThrax* is approved only for immunizing (1) people who handle animal products such as hides, hair, or bones that come from anthrax-endemic areas; and (2) people at high risk of exposure to anthrax spores, including veterinarians, laboratory workers, and others whose occupation may involve handling potentially infected animals or other contaminated materials. In addition to these approved uses, *BioThrax* is being used to vaccinate military personnel. Because the risk of infection in most people is low, routine vaccination of the general population is neither approved nor recommended.

Postexposure Prophylaxis: Antibiotics Plus Vaccination

To prevent infection following exposure to aerosolized anthrax spores, the Centers for Disease Control and Prevention (CDC) recommends treatment with an oral antibiotic plus anthrax vaccine. Antibiotic regimens are the same ones employed for treating inhalational anthrax in a mass casualty setting (see Table 110-3). Dosing should start immediately and continue for at least 60 days.

Vaccination following anthrax exposure consists of three doses of *BioThrax*, given at 0, 2, and 4 weeks. As noted, *BioThrax* is not currently licensed for postexposure use, or for use in a three-dose regimen. Accordingly, such emergency use would be conducted under an Investigational New Drug application.

New recombinant vaccines are in development. However, when they will be available is uncertain.

Francisella tularensis (Tularemia)

Tularemia, also known as “rabbit fever” and “deer fly fever,” is a potentially fatal disease caused by *Francisella tularensis*, one of the most infectious bacteria known. Inoculation with as few as 10 microbes can cause disease. Infection can be acquired through the skin, mucous membranes, GI tract, or lungs. Terrorists trying to spread tularemia would most likely deliver the bacteria as an aerosol. Tularemia cannot be transmitted person to person.

Clinical Manifestations. Symptoms of tularemia develop in 3 to 5 days. Initially, patients present with an acute flu-like illness, characterized by fever (38°C to 40°C), headache, chills, rigors, body aches, sneezing, and sore throat. Pneumonia and pleuritis can develop in the ensuing days to weeks. In the absence of treatment, tularemia can progress to respiratory failure, shock, and death.

Treatment. Tularemia responds well to antibiotics. The treatment of choice is *IM streptomycin* (15 mg/kg twice a day for 10 days). The preferred alternative is *gentamicin* (5 mg/kg IM or IV once a day for 10 days). If there is a mass outbreak, oral therapy with doxycycline or ciprofloxacin is recommended. Individuals who have not yet developed symptoms may benefit from prophylactic use of oral doxycycline or ciprofloxacin.

Yersinia pestis (Pneumonic Plague)

Plague is a potentially fatal disease caused by *Yersinia pestis*, a gram-negative bacillus. The disease has two principal forms: *bubonic* (characterized by tender, enlarged, and inflamed lymph nodes) and *pneumonic* (characterized by inflammation of the lungs). Bubonic plague is acquired through the bite of a plague-infected flea, and *cannot* be transmitted person to person. Rarely, an individual with bubonic plague develops secondary pneumonic plague, which *can* be transmitted person to person (by coughing). *Primary* pneumonic plague is acquired by inhaling aerosolized *Y. pestis*. The source of the aerosol could be a person with pneumonic

plague, or it could be a biologic weapon. To a would-be bioterrorist, *Y. pestis* is attractive for several reasons: The microbe is readily available worldwide, culturing large quantities is relatively easy, the bacterium can be aerosolized for wide dissemination, pneumonic plague can be spread person to person, and the fatality rate is high.

Clinical Manifestations. Symptoms of primary pneumonic plague usually develop 2 to 4 days after inhaling aerosolized *Y. pestis*. Patients typically present with high fever, cough, dyspnea, and hemoptysis (expectoration of blood or blood-stained sputum). Gastrointestinal symptoms—nausea, vomiting, diarrhea, and abdominal pain—may also develop. In the absence of treatment, the infection rapidly progresses to respiratory failure and death.

Treatment. Antibiotics can be lifesaving—provided they are given early (before or shortly after symptom onset). Treatments of choice are (1) *streptomycin*, 15 mg/kg IM twice daily for 10 days; and (2) *gentamicin*, 5 mg/kg IM or IV once daily for 10 days. Preferred alternatives, all given IV, are doxycycline, ciprofloxacin, and chloramphenicol. In a mass casualty setting, which may preclude IV or IM administration, oral therapy with doxycycline (100 mg twice daily) or ciprofloxacin (500 mg twice daily) is recommended. There is no vaccine to protect against pneumonic plague.

Variola Virus (Smallpox)

Smallpox is a serious, contagious, life-threatening disease caused by the *variola virus*, a member of the genus *Orthopoxvirus*. The only natural reservoir for the virus is humans. We have no specific treatment for smallpox, but we *can* prevent the disease by vaccination, given either before exposure or within a few days after. Because smallpox is highly contagious and because the fatality rate is high (30%), the disease represents a grave threat as a weapon of terrorism.

Thanks to a global vaccination program, endemic smallpox has been eradicated. The last case in the United States occurred in 1949, and the last case on the planet occurred in Somalia in 1977. Because the threat of smallpox had been eliminated, routine vaccination was discontinued—in 1972 for Americans, and by 1982 for the rest of the world.

Ironically, the successful elimination of smallpox has set the stage for its potential return as a weapon of terrorism. That is, if we hadn't eradicated natural smallpox, then vaccination would still be ongoing. As a result, the population would have immunity, making smallpox useless as a weapon.

Pathogenesis and Clinical Manifestations

Variola virus enters the body through mucous membranes of the respiratory tract, usually as a result of virus inhalation. Initial exposure is followed by an asymptomatic incubation period (usually 12 to 14 days), followed by the prodromal phase (2 to 4 days), manifesting as high fever, malaise, prostration, headache, and backache. Viral invasion of the oral mucosa and dermis then leads to characteristic eruptions. Small red spots develop in the mouth and on the tongue, and then evolve into sores that break open, releasing large amounts of virus into the mouth and throat. Around this time, a bumpy skin rash develops, starting on the face and then quickly spreading over the entire body. Within 1 to 2 days, the bumps become vesicular (fluid filled), and then pustular (pus filled). About 8 or 9 days after rash onset, the pustules begin to form

a crust and then a scab. By 3 weeks after the rash began, the scabs fall off, leaving a characteristic pitted scar.

About 30% of people with smallpox die, usually during the second week of illness. The most likely cause is toxemia associated with circulating immune complexes and soluble variola antigens.

Transmission

Natural smallpox is transmitted person to person. It is not transmitted by insects or animals. Transmission occurs primarily by touching an infected person or by inhaling aerosolized droplets expelled from the oropharynx. Smallpox can also be acquired by contact with contaminated clothing or bedding. The disease is somewhat contagious during the prodromal phase, but is most contagious from the onset of rash through scab formation. After all scabs fall off, infectivity is gone.

If used as a weapon, variola virus would most likely be disseminated as an aerosol. Because the virus is fragile, at least 90% of the amount released into the environment would become inactive within 24 hours.

Treatment

There is no proven treatment for smallpox. However, research with newer antiviral drugs is ongoing. Several agents show promise, including *cidofovir*, *adefovir*, and *ribavirin*. Topical *idoxuridine* may benefit patients with corneal lesions. Antibiotics should be used to treat secondary bacterial infections.

Smallpox Vaccine

Vaccination is the only way to prevent smallpox. In addition to conferring protection when given *prior to* viral exposure, the vaccine confers protection when given within a few days *after* exposure. For 30 years—between 1972 and 2002—vaccination in the United States had been limited to the few scientists and medical professionals who do research on smallpox and related viruses. However, owing to concerns about bioterrorism, the U.S. government has reinstated vaccination. Mandatory vaccination of military personnel began in 2002. Voluntary vaccination of selected civilian groups began in 2003. At this time, smallpox vaccine is not available to the general public—nor is it recommended. However, in the event of a terrorist attack, prophylactic immunization will be offered.

Description. The vaccine in current use is a suspension of live *vaccinia virus*, a virus that belongs to the same family as variola virus, but does not cause smallpox. From 1931 to 2007, only one vaccine—*Dryvax*—was licensed for use in the United States. In 2007, the Food and Drug Administration (FDA) approved a new vaccine—*ACAM2000*—and withdrew the license for *Dryvax*. Both vaccines are very similar. In fact, *ACAM2000* is produced from a clone of the *vaccinia* strain used to make *Dryvax*. The principal difference between the vaccines is that *ACAM2000* is manufactured using modern cell-culture technology, whereas *Dryvax* is processed from calf lymph. Following the introduction of *ACAM2000*, all existing stocks of *Dryvax* were destroyed.

An even newer vaccine, named *Imvamune*, is in Phase III clinical trials. The vaccine is made with *modified vaccinia virus Ankara* (MVA), a virus that is immunogenic but unable to replicate in humans. As a result, even though the vaccine contains live viruses, it is not dangerous for people who are

immunocompromised. (In immunocompromised vaccinees, the viruses in ACAM2000 can proliferate and cause serious injury, and hence ACAM2000 is generally contraindicated for such people.) In animal models, MVA was considerably safer than Dryvax, and nearly as effective. Although Imvamune is not yet licensed in the United States, the FDA has approved delivery of the drug to the Strategic National Stockpile. The first 1 million doses arrived in 2010. Imvamune is the first drug developed under Project BioShield.

Efficacy. Vaccination before exposure to variola virus prevents smallpox in about 95% of vaccinees. Vaccination within 3 days after exposure also confers significant protection, preventing symptoms entirely in some people, and greatly reducing symptoms in others. Benefits of vaccination 4 to 7 days after exposure are uncertain.

Duration of Protection. Successful primary vaccination produces a high level of immunity for 5 to 10 years, with slowly decreasing immunity thereafter. However, it is not clear just when effective protection is lost. Data from a 2008 study indicate that titers of neutralizing antibodies in people vaccinated 13 to 88 years ago are comparable to those in people vaccinated recently, suggesting long-term persistence of specific immunity.

Administration. Smallpox vaccine is administered by a unique method known as *scarification*, which introduces the vaccine through multiple skin punctures. Administration is not by subQ, IM, or IV injection. The vaccine is given with a bifurcated (two-pronged) needle that is dipped into the vaccine solution. When removed from the solution, the needle retains a droplet of vaccine between the prongs. The administrator then pricks the skin several times (2 or 3 times for primary vaccination; 15 times for revaccination). The resulting punctures should be superficial, but still deep enough to allow a trace of blood to appear after 15 to 20 seconds. Vaccinations are made in the upper arm. To prevent spread of the vaccine, which contains live viruses, the site should be covered with sterile gauze or a semipermeable membrane.

Interpreting the Response. Successful vaccination is indicated when the following events take place. Within 3 to 4 days, a red, itchy bump appears. During the first week, the bump becomes a blister, fills with pus, and then starts to drain. During the second week, the blister begins to dry and develops a scab. In the third week, the scab falls off, leaving a small scar. Reactions to primary vaccination are stronger than reactions to revaccination.

Adverse Effects. The smallpox vaccine may carry considerable risk. Past experience suggests that, if 1 million people were vaccinated, 1000 would experience a serious adverse effect, 14 to 52 would develop a life-threatening condition, and 1 or 2 would die. However, recent data suggest the risk is lower. Regardless of what the real level of risk from vaccination may be, there is no question that the risk of smallpox infection is far greater. Accordingly, anyone exposed to variola virus should be offered the vaccine.

Mild Effects. In addition to the local reactions that signal a successful immune response, vaccination can cause local inflammation, along with swelling and tenderness in regional lymph nodes. Transient symptoms typical of viral illness (fever, headache, muscle aches, fatigue) are also common.

If the vaccination site is not securely covered, vaccinia virus can be transferred to other areas—usually the face, eyelids, nose, mouth, or genitalia—as well as to other people.

Transfer to the eyes can cause sight-threatening keratitis. However, most lesions heal spontaneously.

Moderate to Severe Effects. Serious reactions to smallpox vaccination include eczema vaccinatum, generalized vaccinia, progressive vaccinia, postvaccinial encephalitis, and fetal vaccinia. (The terms *vaccinatum* and *vaccinia* in the names of these disorders simply refer to the cause: vaccinia virus.)

Eczema vaccinatum occurs when infection with vaccinia virus is superimposed on a pre-existing skin condition, usually eczema or atopic dermatitis. As a rule, the disorder is mild and self-limiting. However, in some people it can be life threatening.

Generalized vaccinia is a widespread vesicular rash that resembles smallpox. The cause is transient viremia with localization in the skin. Although the condition is generally self-limiting, it can be severe in the immunocompromised patient.

Progressive vaccinia, also called *vaccinia necrosum*, is a rare but often fatal condition that develops almost exclusively in patients who are immunodeficient. The condition is characterized by progressive necrosis at the inoculation site, often associated with metastatic vaccinial lesions at distant sites (skin, bones, and viscera).

Postvaccinial encephalitis (inflammation of the brain) is rare but dangerous. This complication occurs roughly 2 to 12 times per million vaccinations. The fatality rate is 15% to 25%, and 25% of survivors suffer brain damage.

Fetal vaccinia is a very rare but serious infection of the fetus, manifested by skin lesions and internal organ involvement. The condition can lead to premature birth, or fetal or neonatal death. Fetal vaccinia can result from exposure to vaccinia virus at any stage of pregnancy. Accordingly, women who are pregnant should not get the vaccine. Women who were recently vaccinated should wait at least 4 weeks before attempting to become pregnant.

Possible Cardiac Effects. Some vaccinees have developed cardiac problems—specifically, myocarditis (inflammation of the heart muscle), pericarditis (inflammation of the pericardium), myocardial infarction (heart attack), and angina pectoris (ischemic cardiac pain). However, a definite link between vaccination and these disorders has not been established. Until more is known, routine vaccination should be withheld from people with established heart disease (heart failure, angina, myocardial infarction, cardiomyopathy), and from those with three or more cardiovascular risk factors (see Table 110-4).

Management of Adverse Effects. Two agents—*vaccinia immune globulin* (VIG) and *cidofovir* [Vistide]—can be given to treat severe reactions to smallpox vaccine. However, neither preparation is approved for this use.

VIG is a solution that contains immunoglobulins from people vaccinated with vaccinia virus, and hence should contain antibodies directed against the virus. However, therapeutic effects have not been established in controlled trials. There is some evidence that VIG can benefit those with eczema vaccinatum or generalized vaccinia, and possibly those with progressive vaccinia. In contrast, the preparation is of no help to those with postvaccinial encephalitis, and may actually *increase* corneal damage in those with vaccinial keratitis. VIG is administered IM into the buttocks or anterolateral thigh. The dosage is 0.6 mL/kg, repeated every 2 to 3 days as needed. VIG is available only from the CDC.

TABLE 110-4 • Medical Conditions and Other Factors That Contraindicate Routine Smallpox Vaccination*

- History of eczema or atopic dermatitis
- Active skin conditions, including burns, herpes, severe acne, psoriasis, chickenpox, or shingles (delay vaccination until lesions heal)
- Immunodeficiency (caused by HIV infection, primary immunodeficiency disorder, or use of immunosuppressive drugs, including glucocorticoids, many anticancer drugs, and drugs used to prevent transplant rejection)
- Pregnancy (or plans to become pregnant within 1 month of vaccination)
- Breast-feeding
- Allergy to the smallpox vaccine or any of its components (polymyxin B, streptomycin, chlortetracycline, neomycin)
- Age less than 18 years (and especially less than 1 year) or greater than 65 years
- Moderate or severe short-term illness (delay vaccination until illness resolves)
- Inflammatory eye disease with ongoing use of steroid eye drops
- Heart conditions, including heart failure, angina, myocardial infarction, and cardiomyopathy
- Three or more cardiovascular risk factors: hypertension, high cholesterol, diabetes, cigarette use, first-degree relative with early heart disease (ie, before the age of 50)

*Routine vaccination should be avoided in people with these conditions. However, vaccination is indicated following exposure to the smallpox virus.

*Unlike ACAM2000, the MVA-based vaccine—Imvamune—should be safe for immunocompromised patients.

Cidofovir is an antiviral drug with one approved indication: cytomegalovirus retinitis in patients with AIDS. However, in animal studies, the drug also showed good activity against vaccinia virus. Accordingly, some authorities recommend it for patients with severe vaccination complications, including progressive vaccinia, generalized vaccinia, and eczema vaccinatum. The pharmacology of cidofovir is discussed in Chapter 93 (Antiviral Agents I: Drugs for Non-HIV Viral Infections).

Who Should NOT Be Vaccinated? Certain conditions (eg, eczema, atopic dermatitis, immunodeficiency, pregnancy) increase the risk of a serious reaction to smallpox vaccine. Accordingly, people who have these conditions, or who live with someone who does, should not be vaccinated—unless, of course, they have been exposed to the smallpox virus, in which case the risk of infection would far outweigh the risk of the vaccine. Table 110-4 gives a full list of medical conditions and other factors that contraindicate routine vaccination.

BIOTOXINS

Botulinum Toxin

Botulinum toxin, produced by *Clostridium botulinum*, is the most potent poison known. Just 1 gram, if evenly dispersed and inhaled, could kill more than 1 million people. For use as a weapon of terrorism, the toxin could be delivered as an aerosol or simply put into food. And yes, this is the same

agent used to iron out wrinkles (see Chapter 105, Box 105-1, *Face Time with Botox*).

Mechanism of Action. How does botulinum toxin work? It blocks release of acetylcholine from cholinergic neurons. The toxin is taken up by cholinergic nerve terminals, where it then inactivates SNAP-25, a protein critical to the function of acetylcholine-containing vesicles. In the absence of SNAP-25, the vesicles are unable to fuse with the nerve-terminal membrane, and hence cannot release their acetylcholine into the synaptic space. Restoration of neuronal function requires sprouting of new terminals, a process that can take several months. Botulinum toxin blocks transmission at neuromuscular junctions and at cholinergic synapses of the autonomic nervous system.

Clinical Manifestations. Poisoning is characterized by symmetric, descending flaccid paralysis, beginning 12 to 72 hours after exposure and persisting for weeks to months. Classic symptoms are double vision, blurred vision, drooping eyelids, slurred speech, dry mouth, difficulty swallowing, and muscle weakness that descends through the body, starting with the shoulders, and then progressing to the upper arms, lower arms, thighs, calves, and feet. Death results from paralysis of the muscles of respiration.

Treatment. Treatment consists of prolonged supportive care and immediate infusion of botulinum antitoxin (botulism immune globulin). Supportive care, which may be needed for several months, includes fluid and nutritional therapy plus mechanical assistance of ventilation. Botulinum antitoxin, produced in horses, should be given as soon as botulism is diagnosed. The antiserum, which contains neutralizing antibodies, can minimize further nerve damage, but cannot reverse damage that has already set in. In the United States, botulinum antitoxin is available only through state and local health departments, which get their supply from the CDC. The recommended dosage is 10 mL (the contents of 1 vial) diluted 1:10 in 0.9% saline and administered by slow IV infusion. In 2003, the FDA approved a new antitoxin formulation, available as *BabyBIG*, for treating children under 1 year old.

Ricin

Ricin is a toxin present in castor beans, which are produced by *Ricinus communis*, the castor-bean plant. The toxin is manufactured by extraction from the “mash” left behind when castor beans are processed to make castor oil. When purified, ricin can be formulated as a powder, pellet, or mist, or dissolved in water or a weak acid.

Mechanism of Action. Ricin promotes injury by disrupting protein production. How? Ricin is an enzyme that catalyzes the inactivation of ribosomes, which are required for protein synthesis. Inhibition of protein synthesis leads to cell death and related tissue injury.

Clinical Manifestations. Symptoms of poisoning depend on the route of administration:

- **Inhalation**—Within a few hours of inhaling ricin mist or powder, the victim can experience coughing, tightness in the chest, difficulty breathing, nausea, and muscle ache. A few hours later, the airway may become severely inflamed and edematous, making breathing extremely difficult. Cyanosis and death can follow.

- **Ingestion**—Swallowing a significant dose can cause gastric and intestinal hemorrhage, associated with vomiting and bloody diarrhea. In time, the liver, spleen, and kidneys may fail. Death can occur within 10 to 12 days of ingestion.
- **Injection**—Injection of ricin can lead to severe symptoms and death. However, this route is obviously impractical for terrorism.

Treatment. Management of poisoning is purely supportive. We have no antidote for ricin. A vaccine to protect against ricin is in development.

CHEMICAL WEAPONS

Nerve Agents

Nerve agents are “irreversible” organophosphate cholinesterase inhibitors. By inhibiting cholinesterase, these drugs increase the concentration of acetylcholine at neuromuscular junctions, cholinergic synapses in the central nervous system (CNS), and all autonomic synapses that employ acetylcholine as a transmitter. Toxic doses produce a state of cholinergic crisis, characterized by excessive muscarinic stimulation and depolarizing neuromuscular blockade. Treatment consists of (1) mechanical ventilation using oxygen, (2) giving *atropine* to reduce muscarinic stimulation, (3) giving *pralidoxime* to reverse inhibition of cholinesterase (primarily at neuromuscular junctions), and (4) giving *diazepam* to suppress convulsions. Specific nerve agents that might be used for a terrorist attack include *soman*, *tabun*, *sarin*, and *cyclosarin*. All are volatile at room temperature. However, nerve agent vapors are denser than air, and hence tend to accumulate in low-lying areas. The toxic effects of nerve agents and the use of pralidoxime for treatment are discussed at length in Chapter 15 (Cholinesterase Inhibitors and Their Use in Myasthenia Gravis) under the heading *Toxicology* in the section on “Irreversible” *Cholinesterase Inhibitors*.

Sulfur Mustard (Mustard Gas)

Properties. Sulfur mustard (bis[2-chloroethyl]sulfide), also known as mustard gas, is an alkylating agent and vesicant (chemical blistering agent). However, the precise relationship between alkylation of DNA (and other cellular components) and production of blisters is unclear. Physically, sulfur mustard is a lipophilic, oily liquid that can be vaporized at high temperatures. For use as a weapon of terrorism, sulfur mustard could be vaporized into the air or released into the water supply. Injuries from sulfur mustard can be severe, but the fatality rate is low. When used as a weapon in World War I, sulfur mustard killed less than 5% of its victims.

Clinical Manifestations. Symptoms of toxicity depend on the dose, the tissue involved, and the duration of exposure. As a rule, symptoms are delayed, usually taking 2 to 24 hours to develop. Effects on specific tissues are as follows:

- **Skin**—Dermal contact causes pain, redness, swelling, and blisters (small to very large). Symptoms appear within 4 to 48 hours, depending on the dose. Areas where the skin is warm, moist, and thin are most vulnerable.
- **Eyes**—The eyes are exquisitely sensitive to sulfur mustard. Moderate exposure can produce irritation, pain, swelling,

and tearing in 3 to 12 hours. Severe exposure can cause corneal burns, necrosis, severe pain, and blindness, which may last up to 10 days.

- **Respiratory tract**—Symptoms appear 2 to 24 hours after inhaling sulfur mustard. Mild exposure can cause runny nose, sneezing, hoarseness, sinus pain, and a dry, barking cough. Severe exposure can cause hemorrhage and necrosis of lung tissue, evidenced by coughing up blood.
- **GI tract**—Ingestion can cause nausea, vomiting, diarrhea, and abdominal pain. Symptoms typically develop within a few hours and resolve within 24 hours.
- **Bone marrow**—Very high doses cause bone marrow suppression, resulting in neutropenia and thrombocytopenia.

Treatment. Management centers on rapid decontamination, supportive care, and drug therapy. People exposed to sulfur mustard should undress immediately and wash 3 times with soap and water. Those with significant airway damage may need intubation. Severe skin burns are treated by irrigation, débridement, and application of topical antibiotics; burn-related pain can be controlled with an opioid analgesic. Exposed eyes should be irrigated; other treatments include use of cycloplegics/mydriatics, application of topical antibiotics, and application of petroleum jelly to prevent burned lids from sticking. Granulocyte colony-stimulating factor can be used to stimulate neutrophil production by bone marrow.

RADIOLOGIC WEAPONS

Weapon Types

Nuclear Bombs

Nuclear bombs present an *immediate* threat from the blast itself and a *delayed* threat from radioactive fallout. Immediate harm is produced in four ways:

- The explosion and its shock wave damage buildings, people, and everything else they reach.
- Intense heat causes injury directly and by igniting fires.
- Intense light damages eyesight.
- Ionizing radiation causes acute radiation syndromes and radiation sickness, characterized by nausea, vomiting, diarrhea, fatigue, dehydration, inflammation, skin burns, hair loss, and ulceration of the mouth, esophagus, and GI tract. Symptoms develop over days to weeks. For those who survive, radiation exposure increases the risk of cancer.

Radioactive fallout, mainly *iodine-131*, poses a delayed risk of thyroid cancer. A nuclear explosion creates a radioactive cloud that can spread fallout over a large area. Contamination of humans can result from inhaling fallout, touching contaminated objects, or ingesting contaminated water and food. Once in the body, iodine-131 becomes concentrated in the thyroid gland, where it can cause thyroid cancer. The risk of cancer can be reduced by ingesting potassium iodide, which blocks uptake of radioactive iodine by the thyroid (see below).

Attacks on Nuclear Power Plants

Terrorists could attack a nuclear power plant, either with a bomb or by using sabotage to cause meltdown of the radioactive core. In either case, a large amount of radiation could be released. Please note, however, that an attack would *not* cause

a nuclear explosion. People in the immediate area could suffer severe radiation exposure, resulting in acute radiation syndrome or radiation sickness. As in a nuclear blast, release of iodine-131 could pose a risk of thyroid cancer.

Dirty Bombs (Radiologic Dispersion Devices)

A dirty bomb is a device that uses a conventional explosive (eg, dynamite) to disperse radioactive material that has been formulated as a powder or tiny pellets. Resultant radioactive contamination could be external or internal (owing to inhalation, ingestion, or absorption through a wound). However, it is important to appreciate that the primary danger from a dirty bomb is the blast itself, not the radiation. Why? Because the sources of radiation likely to be used are not very dangerous, and because dispersal of radiation would be limited to a relatively small area. The risk of cancer is very low. Persons exposed to a dirty bomb blast should remove their clothes as soon as possible, and then decontaminate their skin by showering. A dirty bomb will not release iodine-131, and hence taking potassium iodide would be of no benefit.

Drugs for Radiation Emergencies

Potassium Iodide

Potassium iodide (KI) is used to block uptake of radioactive iodine by the thyroid gland, and thereby protect the thyroid from radiation damage. Each dose protects for about 24 hours. However, dosage timing is critical. Protection is nearly 100% when KI starts within 12 hours *before* exposure. When dosing starts *after* exposure, the ability to protect falls off rapidly: down to 80% after 2 hours, 40% after 8 hours, and 7% after 24 hours. Daily dosages recommended by the CDC are as follows:

- Age up to 1 month: 16 mg
- Age 1 month to 3 years: 32 mg
- Age 3 years to 18 years: 65 mg
- Age 18 years and older: 130 mg
- Females who are breast-feeding, regardless of age: 130 mg

How often should dosing be done? In most cases, the environment will be clear of radioactive iodine quickly, and hence a single dose is usually sufficient. If contamination persists, then dosing should be repeated every 24 hours until radioactive iodine levels decline. However, repeat dosing with KI must be *avoided* by newborn infants and by women who are pregnant or breast-feeding, and hence these people should be evacuated until the threat is gone.

Potassium iodide is available in three oral formulations: 65-mg tablets sold as *ThyroSafe*, 130-mg tablets sold as *IOSTAT*, and an oral solution (65 mg/mL) sold as *ThyroShield*. No prescription is needed.

Penetrate Zinc Trisodium and Penetrate Calcium Trisodium

Penetrate zinc trisodium (Zn-DTPA) and penetrate calcium trisodium (Ca-DTPA) are used to treat people who have internal contamination with plutonium, americium, or curium. Benefits derive from accelerating removal of these radioactive isotopes from the body. Both drugs form stable complexes, known as chelates, with plutonium, americium, and curium (and other metals too), and the chelates are then excreted in the urine. The drugs do not bind strongly with radioactive

iodine, uranium, or neptunium, and hence cannot be used to remove these isotopes. To monitor treatment, radioactivity in the blood, urine, and feces should be measured at baseline and weekly thereafter.

Penetrate zinc and penetrate calcium are usually administered IV, but may also be inhaled (if exposure is limited to the lungs). Absorption from the GI tract is very low, and hence oral therapy cannot be used. Once in the blood, both drugs distribute rapidly throughout extracellular fluid, but they do not penetrate cells. Metabolism is minimal. Both drugs undergo glomerular filtration followed by excretion in the urine. In patients with normal renal function, clearance occurs within a few hours after dosing. However, in patients with renal impairment, clearance is much slower. Nonetheless, dosage is not reduced for these people. Rather, high-efficiency, high-flux dialysis is employed to promote drug removal.

Therapy is most effective when initiated within 24 hours of radiation exposure. Why? Because, as time passes, the radiocontaminants become sequestered in liver and bone, making them harder to remove. Nonetheless, since delayed treatment is better than no treatment at all, dosing should begin as soon as the drugs are available. For the first 24 hours after exposure, Ca-DTPA is more effective than Zn-DTPA, and hence Ca-DTPA should be used initially. After 24 hours, both drugs are equally effective.

Dosing is done once a day—usually by slow IV push or IV infusion—and may continue for months. The exact duration depends on the degree of radioactive contamination and drug efficacy. For adults and adolescents, the recommended daily IV dose is 1 gm. For children under 12 years old, the daily IV dose is 14 mg/kg (but no more than 1 gm). To reduce the concentration of radioactive chelate in the urine, and thereby reduce the risk of injury to the bladder, patients should drink lots of fluid and void often.

Because Zn-DTPA and Ca-DTPA chelate metals, prolonged treatment can lead to trace-metal depletion. Both drugs can reduce body stores of manganese and magnesium, and Ca-DTPA can also reduce stores of zinc. Serum levels of trace metals should be monitored, and supplements provided if the levels are low.

Prussian Blue

Prussian blue [Radiogardase], also known as *ferric hexacyanoferrate*, is used to hasten excretion of radioactive cesium and radioactive and nonradioactive thallium. Prussian blue is an insoluble, nonabsorbable compound, taken orally, that binds tightly with cesium and thallium in the intestine. In the absence of Prussian blue, both isotopes undergo extensive enterohepatic recirculation. That is, they undergo absorption into the blood, followed by excretion in the bile, followed by reabsorption, and so forth—a cycle that extends their stay in the body. However, when bound with Prussian blue, cesium and thallium cannot be reabsorbed, and hence must stay in the intestine for excretion. Food may accelerate the elimination. Why? Because food increases production of bile, and hence may increase the rate at which cesium and thallium are presented to Prussian blue in the intestine.

Prussian blue can cause constipation, which is a concern for two reasons. First, constipation can delay excretion of radioactive contaminants. Second, it can increase the dose of radiation absorbed by the GI mucosa. If constipation occurs,

it can be treated with a fiber-based laxative, a high-fiber diet, or both. Prussian blue should be used with caution in patients with decreased GI motility.

Prussian blue can bind with potassium and other electrolytes. Some patients have developed hypokalemia. To reduce risk, serum electrolytes should be monitored closely. Exercise caution in patients with cardiac dysrhythmias (which are sensitive to hypokalemia) or pre-existing electrolyte imbalance.

Prussian blue [Radiogardase], in the form of a blue powder, is supplied in 500-mg gelatin capsules. Dosing is done

3 times a day. For adults and adolescents, each dose is 3 gm. For children 2 to 12 years old, each dose is 1 gm. If needed, the capsules may be opened and the powder mixed with bland foods or liquids. However, be aware that opening the capsules may result in blue discoloration of the mouth and teeth. Whether the capsules are swallowed intact or opened, Prussian blue will turn stools blue; patients should be forewarned.

To monitor treatment, radioactivity in urine and stool samples should be measured at baseline and periodically thereafter. Whole-body radioactivity should be measured as appropriate.

KEY POINTS

- Anthrax is a potentially fatal disease caused by *Bacillus anthracis*, a bacterium that produces spores that can remain viable in the environment for decades.
- Anthrax infection is acquired when spores enter the body, typically through the skin or through mucous membranes of the respiratory tract.
- *Inhalational* anthrax is characterized by severe respiratory distress, septicemia, hemorrhagic meningitis, and shock. About 45% of victims die, even when treated.
- Lesions of *cutaneous* anthrax are characterized by a black eschar (scab-like structure) that eventually dries, loosens, and sloughs off. Most cases resolve without complications or scarring.
- For initial therapy of inhalational anthrax, treatments of choice are IV ciprofloxacin and IV doxycycline, combined with one or two additional IV antibiotics.
- Drugs of choice for cutaneous anthrax are oral ciprofloxacin and oral doxycycline.
- Anthrax vaccine is available for military personnel and selected others, but not yet for the general population.
- Tularemia is a potentially fatal disease caused by *Francisella tularensis*, one of the most infectious bacteria known.
- Tularemia can be acquired through bacterial invasion of the skin, mucous membranes, GI tract, or lungs.
- Tularemia is characterized by pneumonia and pleuritis that can progress to respiratory failure, shock, and death.
- Tularemia responds well to antibiotics. The treatment of choice is IM streptomycin.
- Pneumonic plague is a potentially fatal disease caused by *Yersinia pestis*.
- Pneumonic plague is acquired by inhaling aerosolized *Y. pestis*, and can be transmitted person to person.
- Pneumonic plague is characterized by high fever, cough, dyspnea, and hemoptysis (expectoration of blood or blood-stained sputum). In the absence of treatment, the infection rapidly progresses to respiratory failure and death.
- Treatments of choice for pneumonic plague are streptomycin (IM) and gentamicin (IM or IV).
- Smallpox is a contagious, potentially fatal disease caused by variola virus, whose only reservoir is humans.
- Worldwide vaccination has eliminated naturally occurring smallpox. The last case occurred in Somalia in 1977.
- Variola virus enters the body through mucous membranes of the respiratory tract.
- Smallpox is characterized by (1) eruptions on the mouth and tongue that release virus into the oropharynx and (2) pustules on the skin that release the virus on the body surface.
- Natural smallpox is transmitted person to person, primarily by touching an infected individual or by inhaling aerosolized droplets expelled from the oropharynx.
- There is no proven treatment for smallpox.
- The smallpox vaccine in current use, named ACAM2000, consists of live vaccinia virus. The vaccine confers protection when given before exposure to variola virus and when given within a few days after exposure.
- Successful primary vaccination with smallpox vaccine produces high-level immunity for at least 5 to 10 years. Significant immunity may persist for decades.
- Smallpox vaccination is not without risk: Past experience suggests that, if 1 million people were vaccinated, 1000 would experience a serious adverse effect, 14 to 52 would develop a life-threatening condition, and 1 or 2 would die.
- Although smallpox vaccination carries risk, the risk of smallpox itself is far greater. Accordingly, anyone exposed to variola virus should be offered the vaccine.
- Routine smallpox vaccination is contraindicated by a number of conditions, including eczema, atopic dermatitis, immunodeficiency, pregnancy, and heart disease.
- Botulinum toxin, produced by *Clostridium botulinum*, is the most potent poison known.
- Botulinum toxin acts on cholinergic nerve terminals to cause prolonged blockade of acetylcholine release.
- Poisoning with botulinum toxin is characterized by symmetric, descending flaccid paralysis, coupled with disturbed vision, drooping eyelids, slurred speech, dry mouth, and difficulty swallowing. Death results from paralysis of the muscles of respiration.
- Treatment of botulinum toxin poisoning consists of immediate infusion of botulinum antitoxin plus prolonged supportive care.
- Botulinum antitoxin can minimize further nerve damage, but cannot reverse damage that has already occurred.
- Ricin is a toxin present in castor beans (which are used to make castor oil).

- Ricin causes injury by inhibiting protein synthesis.
- When ricin is *inhaled*, it causes inflammation and edema of the airway, thereby making breathing extremely difficult. Cyanosis and death can follow.
- When ricin is *ingested*, it causes gastric and intestinal hemorrhage, associated with vomiting and bloody diarrhea. In time, the liver, spleen, and kidneys may fail.
- Management of ricin poisoning is purely supportive. There is no antidote.
- Nerve agents cause “irreversible” inhibition of cholinesterase, and thereby increase the concentration of acetylcholine at neuromuscular junctions, cholinergic synapses in the CNS, and all autonomic synapses that employ acetylcholine as a transmitter.
- Nerve agents produce a state of cholinergic crisis, characterized by excessive muscarinic stimulation and depolarizing neuromuscular blockade.
- Treatment of nerve agent poisoning consists of mechanical ventilation using oxygen, and giving atropine (to reduce muscarinic stimulation), pralidoxime (to reverse inhibition of cholinesterase), and diazepam (to suppress convulsions).
- Sulfur mustard (mustard gas) is an alkylating agent and vesicant that can injure any tissue that it reaches.
- Symptoms of sulfur mustard toxicity include large skin blisters, corneal burns, hemorrhage and necrosis of lung tissue, GI disturbances, and neutropenia and thrombocytopenia (secondary to bone marrow suppression).
- Management of sulfur mustard poisoning consists of rapid decontamination, supportive care, and drug therapy.
- A nuclear bomb presents an immediate threat from the blast itself (including acute radiation sickness) and a delayed threat from radioactive fallout.
- Iodine-131 in fallout poses a risk of thyroid cancer.
- The risk of thyroid cancer can be reduced by ingesting potassium iodide, which blocks uptake of iodine-131 by the thyroid.
- A terrorist attack on a nuclear power plant could cause the release of large amounts of radiation, including iodine-131, but would not cause a nuclear explosion.
- A dirty bomb is a device that uses a conventional explosive, such as dynamite, to disperse radioactive material.
- The primary danger from a dirty bomb is the blast itself, not the radiation.
- A dirty bomb will not release iodine-131, and hence taking potassium iodide is not indicated.
- Three compounds—penetrate zinc trisodium, penetrate calcium trisodium, and Prussian blue—can hasten excretion of certain radioactive isotopes following internal contamination.

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Appendix A

Adult Immunization, United States, 2011

The immunization schedules shown in Figures A-1 and A-2 are based on joint recommendations by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Family Physicians (AAFP). Revised schedules are issued annually, and updates for individual vaccines are issued as needed. The schedules presented here were issued in January 2011. For detailed recommendations, consult the manufacturers' package inserts and the complete statements from the ACIP, which can be found online at www.cdc.gov/vaccines/pubs/ACIP-list.htm. Additional information about the vaccines listed is available at <http://www.cdc.gov/vaccines/> or from the CDC-INFO Contact Center at 800-CDC-INFO (800-232-4636) in English and Spanish, 24 hours a day, 7 days a week.

IMMUNIZATION SCHEDULE NOTES

1. Influenza Vaccination

Annual vaccination against influenza is recommended for all persons age 6 months and older, including all adults. Healthy, nonpregnant adults less than 50 years old without high-risk medical conditions can receive either intranasally administered live, attenuated influenza vaccine (FluMist), or inactivated vaccine. Other persons should receive the inactivated vaccine. Adults age 65 years and older can receive the standard influenza vaccine or the high-dose (Fluzone) influenza vaccine. Additional information about influenza vaccination is available at <http://www.cdc.gov/vaccines/vpd-vac/flu/default.htm>.

2. Tetanus, Diphtheria, and Acellular Pertussis (Td/Tdap) Vaccination

Administer a one-time dose of Tdap to adults less than 65 years old who have not received Tdap previously or for whom vaccine status is unknown to replace one of the 10-year Td boosters, and as soon as feasible to all (1) postpartum women, (2) close contacts of infants younger than age 12 months (eg, grandparents and child-care providers), and (3) healthcare personnel with direct patient contact. Adults age 65 years and older who have not previously received Tdap and who have close contact with an infant less than 12 months old also should be vaccinated. Other adults age 65 years and older may receive Tdap. Tdap can be administered regardless of when the most recent tetanus- or diphtheria-containing vaccine was given.

Adults with an uncertain or incomplete history of completing a three-dose primary vaccination series with Td-containing vaccines should begin or complete a primary vaccination series. For unvaccinated adults, administer the first two doses at least 4 weeks apart, and the third dose 6 to 12 months after the

second. If incompletely vaccinated (ie, less than three doses), administer remaining doses. Substitute a one-time dose of Tdap for one of the doses of Td, either in the primary series or for the routine booster, whichever comes first.

If a woman is pregnant and received the most recent Td vaccination 10 or more years previously, administer Td during the second or third trimester. If the woman received the most recent Td vaccination less than 10 years previously, administer Tdap during the immediate postpartum period. At the clinician's discretion, Td may be deferred during pregnancy and Tdap substituted in the immediate postpartum period, or Tdap may be administered instead of Td to a pregnant woman after an informed discussion with the woman.

The ACIP statement for recommendations for administering Td as prophylaxis in wound management is available at <http://www.cdc.gov/vaccines/pubs/acip-list.htm>.

3. Varicella Vaccination ("Shingles")

Give all adults without evidence of immunity to varicella two doses of single-antigen varicella vaccine (if not previously vaccinated), or a second dose (if they have already received one dose)—unless they have a medical contraindication. Give special consideration to those who (1) have close contact with persons at high risk for severe disease (eg, healthcare personnel and family contacts of persons with immunocompromising conditions) or (2) are at high risk for exposure or transmission (eg, teachers; child-care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of child-bearing age; and international travelers).

Evidence of immunity to varicella in adults includes any of the following: (1) documentation of two doses of varicella vaccine at least 4 weeks apart; (2) U.S.-born before 1980 (although for healthcare personnel and pregnant women, birth before 1980 should not be considered evidence of immunity); (3) history of varicella based on diagnosis or verification of varicella by a healthcare provider (for a patient reporting a history of or having an atypical case, a mild case, or both, healthcare providers should seek either an epidemiologic link to a typical varicella case or to a laboratory-confirmed case, or evidence of laboratory confirmation, if it was performed at the time of acute disease); (4) history of herpes zoster based on diagnosis or verification of herpes zoster by a healthcare provider; or (5) laboratory evidence of immunity or laboratory confirmation of disease.

Assess pregnant women for evidence of varicella immunity. Women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the

VACCINE ▼	AGE GROUP ►	19–26 years	27–49 years	50–59 years	60–64 years	65 years
Influenza ^{1,*}		1 dose annually				
Tetanus, diphtheria, pertussis (Td/Tdap) ^{2,*}		Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years				
Varicella (Shingles) ^{3,*}		2 doses				
Human papillomavirus (HPV) ^{4,*}		3 doses (females)				
Zoster ⁵					1 dose	
Measles, mumps, rubella (MMR) ^{6,*}		1 or 2 doses			1 dose	
Pneumococcal (polysaccharide) ^{7,8}		1 or 2 doses				1 dose
Meningococcal ^{9,*}		1 or more doses				
Hepatitis A ^{10,*}		2 doses				
Hepatitis B ^{11,*}		3 doses				

* Covered by the Vaccine Injury Compensation Program



For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of previous infection)



Recommended if some other risk factor is present (e.g., based on medical, occupational, lifestyle, or other indications)



No recommendation

Figure A-1 ■ Recommended adult immunization schedule by age group, United States, 2011.

INDICATION ►	Pregnancy	Immunocompromising conditions (excluding human immunodeficiency virus [HIV]) ^{3,5,6,13}	HIV infection ^{3,6,12,13} CD4 ⁺ T lymphocyte count		Diabetes, heart disease, chronic lung disease, chronic alcoholism	Asplenia ¹² (including elective splenectomy) and persistent complement component deficiencies	Chronic liver disease	Kidney failure, end-stage renal disease, receipt of hemodialysis	Health-care personnel
		<200 cells/ μ L	200 cells/ μ L						
Influenza ^{1,*}		1 dose TIV annually							1 dose TIV or LAIV annually
Tetanus, diphtheria, pertussis (Td/Tdap) ^{2,*}	Td	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years							
Varicella (Shingles) ^{3,*}		Contraindicated	2 doses						
Human papillomavirus (HPV) ^{4,*}		3 doses through age 26 years							
Zoster ⁵		Contraindicated	1 dose						
Measles, mumps, rubella ^{6,*}		Contraindicated	1 or 2 doses						
Pneumococcal (polysaccharide) ^{7,8}			1 or 2 doses						
Meningococcal ^{9,*}		1 or more doses							
Hepatitis A ^{10,*}		2 doses							
Hepatitis B ^{11,*}		3 doses							

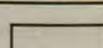
* Covered by the Vaccine Injury Compensation Program



For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of previous infection)



Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)



No recommendation

Figure A-2 ■ Vaccines that might be indicated for adults based on medical and other conditions, United States, 2011.

healthcare facility. Give the second dose 4 to 8 weeks after the first dose.

4. Human Papillomavirus (HPV) Vaccination

HPV vaccination with either quadrivalent (HPV4) vaccine or bivalent vaccine (HPV2) is recommended for previously unvaccinated females at age 11 or 12 years, and catch-up vaccination is recommended for females ages 13 through 26 years.

Ideally, vaccine should be administered before potential exposure to HPV through sexual activity. However, females who are sexually active should still be vaccinated consistent with age-based recommendations. Sexually active females who have not already been infected with HPV types 6, 11, 16, and 18 (which HPV4 prevents) or HPV types 6 and 18 (which HPV2 prevents) will receive the full benefit of vaccination. Vaccination is less beneficial for females who have already been infected with one or more of the above HPV types. HPV4 or HPV2 can benefit persons with a history of genital warts, abnormal Papanicolaou test, or positive HPV DNA test, because these conditions are not evidence of previous infection with all of the HPV types that the vaccines protect against.

HPV4 may be administered to males ages 9 through 26 years to reduce their likelihood of genital warts. HPV4 would be most effective when administered before exposure to HPV through sexual contact.

A complete series for either HPV4 or HPV2 consists of three doses. Give the second dose 1 to 2 months after the first dose; and give the third dose 6 months after the first dose.

Because HPV vaccines do not contain live viruses, they may be given to persons with the medical conditions described in Figure A-2, even though HPV vaccines are not specifically recommended for these people. However, the immune response and vaccine efficacy may be lower than in persons who do not have those medical conditions.

5. Herpes Zoster Vaccination

A single dose of zoster vaccine is recommended for adults age 60 and older, regardless of whether they report having had a previous episode of herpes zoster. Persons with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication.

6. Measles, Mumps, Rubella (MMR) Vaccination

Adults born before 1957 are generally considered immune to measles and mumps. All adults born in 1957 or later should have documentation of one or more doses of MMR vaccine unless they have a medical contraindication to the vaccine, laboratory evidence of immunity to each of the three diseases, or documentation of provider-diagnosed measles or mumps disease. For rubella, documentation of provider-diagnosed disease is not considered acceptable evidence of immunity.

Measles Component. A second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who (1) have been recently exposed to measles or are in an outbreak setting; (2) are students in postsecondary educational institutions; (3) work in a healthcare facility; or (4) plan to travel internationally. Persons who received inactivated measles vaccine or measles vaccine of unknown type between 1963 and 1967 should be revaccinated with two doses of MMR vaccine.

Mumps Component. A second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who (1) live in a community experiencing a mumps outbreak and are in an affected age group; (2) are students in postsecondary educational institutions; (3) work in a healthcare facility; or (4) plan to travel internationally. Persons vaccinated before 1979 with either killed mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection (eg, persons who are working in a healthcare facility) should be revaccinated with two doses of MMR vaccine.

Rubella Component. For women of child-bearing age, regardless of birth year, rubella immunity should be determined. If there is no evidence of immunity, women who are not pregnant should be vaccinated. Pregnant women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility.

Healthcare Personnel Born Before 1957. For unvaccinated healthcare personnel born before 1957 who lack laboratory evidence of measles, mumps, and/or rubella immunity, or lack laboratory confirmation of disease, operators of the healthcare facility should (1) consider routine vaccination with two doses of MMR vaccine at the appropriate interval (for measles and mumps) and one dose of MMR vaccine (for rubella), and (2) recommend two doses of MMR vaccine at the appropriate interval during an outbreak of measles or mumps, and one dose during an outbreak of rubella. Complete information about evidence of immunity is available at <http://www.cdc.gov/vaccines/recs/provisional/default.htm>.

7. Pneumococcal Polysaccharide (PPSV) Vaccination

Medical Indications. Vaccinate all persons with chronic lung disease (including asthma); chronic cardiovascular diseases; diabetes mellitus; chronic liver diseases; cirrhosis; chronic alcoholism; functional or anatomic asplenia (eg, sickle cell disease or splenectomy [if elective splenectomy is planned, vaccinate at least 2 weeks before surgery]); immunocompromising conditions (including chronic renal failure or nephrotic syndrome); and cochlear implants and cerebrospinal fluid leaks. For persons with HIV infection, vaccinate as close to HIV diagnosis as possible.

Other Indications. Vaccinate all residents of nursing homes or long-term care facilities and persons who smoke cigarettes. Routine use of PPSV is not recommended for American Indians/Alaskan Natives or persons less than 65 years of age unless they have underlying medical conditions that are PPSV indications. However, public health authorities may consider recommending PPSV for American Indians/Alaskan Natives and persons ages 50 through 64 years who are living in areas where the risk for invasive pneumococcal disease is increased.

8. Revaccination with PPSV

Give a one-time revaccination after 5 years to adults ages 19 through 64 with chronic renal failure or nephrotic syndrome; persons with functional or anatomic asplenia (eg, sickle cell disease or splenectomy); and persons with immunocompromising conditions. For adults age 65 and older, give a one-time revaccination if they were vaccinated 5 or more

years previously and were less than 65 years old at the time of primary vaccination.

9. Meningococcal Vaccination

Medical Indications. Give a two-dose series of meningococcal conjugate vaccine to adults with anatomic or functional asplenia, persistent complement component deficiencies, or HIV infection. Administer the doses at 0 and 2 months.

Other Indications. Give a single dose of meningococcal vaccine to first-year college students living in dormitories; microbiologists routinely exposed to isolates of *Neisseria meningitidis*; military recruits; and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic (eg, the "meningitis belt" of sub-Saharan Africa during the dry season [December through June]), particularly if their contact with local populations will be prolonged. Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.

For adults age 55 years or younger, meningococcal conjugate vaccine (MCV4) is preferred. For adults age 56 years and older, meningococcal polysaccharide vaccine (MPSV4) is preferred. For adults previously vaccinated with either MCV4 or MPSV4 who remain at increased risk for infection (eg, adults with anatomic or functional asplenia, or persistent complement component deficiencies), revaccination with MCV4 every 5 years is recommended.

10. Hepatitis A Vaccination

Medical Indications. Vaccinate persons with chronic liver disease and persons who receive clotting factor concentrates.

Behavioral Indications. Vaccinate men who have sex with men and persons who use injection drugs.

Occupational Indications. Vaccinate persons working with (1) hepatitis A virus (HAV) in a research setting, or (2) HAV-infected primates.

Other Indications. Vaccinate persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A (a list of countries is available at <http://wwwn.cdc.gov/travel/content/diseases.aspx>). Also, vaccinate any other adults seeking protection against HAV.

Vaccinate persons who anticipate close personal contact with an international adoptee during the first 60 days after the child's arrival in the United States from a country with high or intermediate endemicity. Give the first dose of the two-dose hepatitis A vaccine series as soon as adoption is planned (ideally 2 or more weeks before the arrival of the adoptee).

Give single-antigen vaccine formulations in a two-dose schedule at either 0 and 6 to 12 months (Havrix), or 0 and 6 to 18 months (Vaqta). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, give three doses administered at 0, 1, and 6 months; alternatively, give four doses administered on days 0, 7, and 21 to 30, and again at 12 months.

11. Hepatitis B Vaccination

Behavioral Indications. Vaccinate sexually active persons who are not in a long-term, mutually monogamous relationship (eg, persons with more than one sex partner during

the previous 6 months); persons seeking evaluation or treatment for a sexually transmitted disease (STD); current or recent injection-drug users; and men who have sex with men.

Occupational Indications. Vaccinate healthcare personnel and public-safety workers who are exposed to blood or to other potentially infectious body fluids.

Medical Indications. Vaccinate persons with end-stage renal disease, including patients receiving hemodialysis; persons with HIV infection; and persons with chronic liver disease.

Other Indications. Vaccinate household contacts and sex partners of persons with chronic hepatitis B virus (HBV) infection; international travelers to countries with high or intermediate prevalence of chronic HBV infection (a list of countries is available at <http://wwwn.cdc.gov/travel/content/diseases.aspx>); clients and staff members of institutions for persons with developmental disabilities; and any other person who wants protection against HBV.

Hepatitis B vaccination is recommended for all adults in the following settings: STD treatment facilities; HIV testing and treatment facilities; facilities providing drug-abuse treatment and prevention services; healthcare settings targeting services to injection-drug users or men who have sex with men; correctional facilities; end-stage renal disease programs and facilities for chronic hemodialysis patients; and institutions and nonresidential day care facilities for persons with developmental disabilities.

Dosing Schedules. Administer missing doses to complete a three-dose series of hepatitis B vaccine to persons not vaccinated or not completely vaccinated. Give the second dose 1 month after the first dose; give the third dose at least 2 months after the second dose (and at least 4 months after the first dose). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, give three doses administered at 0, 1, and 6 months; or give four doses, administered on days 0, 7, and 21 to 30, followed by a booster dose at 12 months.

Adults receiving hemodialysis or adults with other immunocompromising conditions should receive one dose of 40-mcg/mL vaccine (Recombivax HB) administered on a three-dose schedule; or two doses of 20-mcg/mL vaccine (Engerix-B) administered on a four-dose schedule at 0, 1, 2, and 6 months.

12. Selected Conditions for Which *Haemophilus influenzae* Type b (Hib) Vaccine May Be Used

Consider giving one dose of Hib vaccine for persons who have sickle cell disease, leukemia, or HIV infection, or who have had a splenectomy, if they have not previously received Hib vaccine.

13. Immunocompromised Persons

For immunocompromised persons, *inactivated* vaccines are generally acceptable (eg, pneumococcal, meningococcal, influenza [inactivated influenza vaccine]), whereas *live* vaccines should generally be avoided. Information on specific immunocompromising conditions is available at <http://www.cdc.gov/vaccines/pubs/acip-list.htm>.

Appendix B

Guide to Gender-Related Drugs

The purpose of this guide is to help you locate gender-specific drug content, which is scattered throughout the book. Chapter numbers are in **bold** type and page numbers are in parentheses.

Drugs Used in Pregnancy

Basic principles of drug use during pregnancy	9 (88-92)
Folic acid supplements	81 (1034)
Iron supplements	55 (678)
Hypertension of pregnancy	
Chronic hypertension	47 (547)
Preeclampsia and eclampsia	47 (547-548)
Seizure disorders during pregnancy	
Epilepsy	24 (245-246)
Eclampsia	47 (547-548)
Diabetes in pregnancy	57 (705)

Drugs Related to Labor and Delivery

Suppression of preterm labor	64 (816-817)
Prevention of preterm labor	64 (816-817)
Induction of labor with oxytocin	64 (818-819)
Induction of cervical ripening with prostaglandins	64 (817-818)
Obstetric analgesia	28 (291)

Drugs Used in Perinatal Therapy

Control of postpartum hemorrhage	64 (819-821)
Ergot alkaloids	64 (820-821)
Carboprost tromethamine	64 (820)
Oxytocin and misoprostol	64 (820)
Respiratory distress syndrome in preterm infants	107 (1355-1356)
Antenatal glucocorticoids for	107 (1355)
Lung surfactants for	107 (1355-1356)
Vitamin K ₁	81 (1031-1032)
Hepatitis B vaccine and hepatitis B immune globulin	68 (866)
Gonococcal neonatal ophthalmia	95 (1222)

Drugs and Breast-Feeding

Basic principles of drug use during breast-feeding	9 (93)
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Drugs for Women's Health Disorders

Overactive bladder	14 (128-132)
Estrogen therapy after menopause	61 (775-783)
Testosterone therapy after menopause	65 (828-829)
Hypoactive sexual desire disorder	65 (828-829)
Osteoporosis	75 (949-952)
Endometriosis	63 (806, 809-810)
Infertility	63 (805-812)
Polycystic ovary syndrome	63 (806)
Premenstrual syndrome	61 (773-774)
Amenorrhea	61 (775)
Dysfunctional uterine bleeding	61 (772-775)
Menorrhagia	64 (821-822)
Urinary tract infections	89 (1111-1115)
Vulvovaginal candidiasis	92 (1144)
Breast cancer	103 (1288-1293)
Fibromyalgia syndrome*	107 (1361-1364)

Drugs Used to Prevent or Terminate Pregnancy

Oral contraceptives	62 (788-795)
Long-acting contraceptives	62 (795-796)
Spermicides	62 (796-799)
Emergency contraception	62 (797-798)
Drugs for medical abortion	62 (799-801)
Mifepristone (RU 486) plus misoprostol	62 (799-800)
Other abortifacients	62 (800-801)

Drugs for Male Health Disorders

Benign prostatic hyperplasia	66 (839-842)
Erectile dysfunction (impotence)	66 (834-839)
Hypogonadism	65 (826)
Delayed puberty	65 (826)
Reduced libido	65 (828)
Prostate cancer	103 (1294-1298)

Drugs for Sexually Transmitted Diseases (STDs)

Drugs for HIV infection	94 (1170-1217)
Drugs for STDs other than HIV infection	95 (1218-1225)
Drugs for venereal warts	105 (1340-1341)

*Fibromyalgia syndrome is not exclusively a disorder affecting women, but the incidence is 7 times greater in women than in men.

Appendix C

Commonly Used Abbreviations

Abbreviations highlighted in red can be easily misinterpreted, and hence should not be used, as mandated by The Joint Commission (TJC), formerly known as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Abbreviations highlighted in blue are less likely to be misinterpreted, and hence may still be used, although the alternatives listed are preferred. Table 7-7 in Chapter 7 indicates potential misinterpretations of the highlighted entries.

Ac	before meals (<i>ante cibum</i>)
ACE	angiotensin-converting enzyme
ACH	acetylcholine
ad lib	freely as desired (<i>ad libitum</i>)
ADHD	attention-deficit/hyperactivity disorder
ADLs	activities of daily living
ADP	adenosine diphosphate
AED	antiepileptic drug
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase (formerly known as SGPT)
AMI	acute myocardial infarction
AMP	adenosine monophosphate
ANA	antinuclear antibodies
ARB	angiotensin II receptor blocker
ARC	AIDS-related complex
ASA	acetylsalicylic acid (aspirin)
AST	aspartate aminotransferase (formerly known as SGOT)
ATP	adenosine triphosphate
AV	atrioventricular
AZT	zidovudine (azidothymidine)
bid	two times a day (<i>bis in die</i>)
bin	two times a night (<i>bis in nocte</i>)
bol	bolus
BP	blood pressure
BPH	benign prostatic hyperplasia
BUN	blood urea nitrogen
C	Celsius (centigrade)
CABG	coronary artery bypass graft
CAD	coronary artery disease
cAMP	cyclic adenosine 3', 5'-monophosphate
CAT	computed axial tomography
CBC	complete blood count
cc	cubic centimeter (milliliter)
CCB	calcium channel blocker
CDC	Centers for Disease Control and Prevention
CHF	congestive heart failure
CMV	cytomegalovirus
CNS	central nervous system
COMT	catechol- <i>O</i> -methyltransferase
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase

CPK	creatine phosphokinase
CPZ	compazine
CSF	cerebrospinal fluid
CT	computed tomography
CTZ	chemoreceptor trigger zone
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DC	direct current
DKA	diabetic ketoacidosis
dL	deciliter (100 mL)
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
DPI	dry-powder inhaler
DS	double strength
ECG, EKG	electrocardiogram
ECT	electroconvulsive therapy
EEG	electroencephalogram
F	Fahrenheit
FDA	Food and Drug Administration
FEV	forced expiratory volume
FFA	free fatty acid
g, gm	gram
G6PD	glucose-6-phosphate dehydrogenase
GABA	gamma-aminobutyric acid
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GI	gastrointestinal
GMP	guanosine monophosphate
GTP	guanosine triphosphate
GU	genitourinary
h, hr	hour
H ₂ RA	histamine ₂ -receptor antagonist
HAART	highly active antiretroviral therapy
HBGM	home blood glucose monitoring
HDL	high-density lipoprotein
HF	heart failure
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
H.S.	half strength; at bedtime
hs	at bedtime (hour of sleep; <i>hora somni</i>)
HSV	herpes simplex virus
HT	hormone therapy
IBD	inflammatory bowel disease
ICP	intracranial pressure
IM	intramuscular, intramuscularly
IN	intranasal
INR	international normalized ratio
IOP	intraocular pressure
IPV	inactivated polio vaccine
ISA	intrinsic sympathomimetic activity
IU	international unit

IUD	intrauterine device	PCP	<i>Pneumocystis pneumonia</i>
IV	intravenous, intravenously	PEFR	peak expiratory flow rate
kg	kilogram	PET	positron emission tomography
KVO	keep vein open	pg	picogram
L	liter	PG	prostaglandin
LD	lethal dose	PID	pelvic inflammatory disease
LDL	low-density lipoprotein	PMS	premenstrual syndrome
LGV	lymphogranuloma venereum	PO	by mouth (<i>per os</i>)
LSD	D-lysergic acid diethylamide	PPD	purified protein derivative (tuberculin)
m	minim	PPI	proton pump inhibitor
MAC	minimum alveolar concentration; <i>Mycobacterium avium</i> complex	PR	by the rectum (<i>per rectum</i>)
MAO	monoamine oxidase	PRN	as needed (<i>pro re nata</i>)
MAOI	monoamine oxidase inhibitor	PT	prothrombin time
MAP	mean arterial pressure	PTCA	percutaneous transluminal coronary angioplasty
MBC	minimum bactericidal concentration	PTT	partial thromboplastin time
mcg, μg	microgram	PVC	premature ventricular contraction
MDI	metered-dose inhaler	qd	every day (<i>quaque die</i>)
MEC	minimum effective concentration	qh	every hour (<i>quaque hora</i>)
mEq	milliequivalent	qid	four times a day (<i>quater in die</i>)
mg	milligram	qod	every other day
MgSO ₄	magnesium sulfate	RA	rheumatoid arthritis
MHC	major histocompatibility complex	RBC	red blood cell (erythrocyte)
MI	myocardial infarction	RDA	recommended dietary allowance
MIC	minimum inhibitory concentration	REM	rapid eye movement
mL	milliliter	RNA	ribonucleic acid
mM	millimolar	SA	sinoatrial
mmol	millimole	SAARD	slow-acting antirheumatic drug
MMR	measles, mumps, rubella	SBP	systolic blood pressure
mOsm	milliosmole	SGOT	serum glutamic-oxaloacetic transaminase (now known as AST)
MRI	magnetic resonance imaging	SGPT	serum glutamic-pyruvic transaminase (now known as ALT)
MS	morphine sulfate	sl	sublingual
MSO ₄	morphine sulfate	SLE	systemic lupus erythematosus
MTX	methotrexate	SPF	sun protection factor
ng	nanogram	SR	sarcoplasmic reticulum; sustained release
NGU	nongonococcal urethritis	SSRI	selective serotonin reuptake inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor	stat	immediately
NPO	nothing by mouth (<i>nil per os</i>)	STD	sexually transmitted disease
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor	subQ, SC, SQ	subcutaneous, subcutaneously
NSAID	nonsteroidal anti-inflammatory drug	SVT	supraventricular tachycardia
OC	oral contraceptive	TIA	transient ischemic attack
OD	right eye (<i>oculus dexter</i>)	tid	three times a day (<i>ter in die</i>)
OPV	oral polio vaccine	U	unit
OS	left eye (<i>oculus sinister</i>)	UTI	urinary tract infection
OTC	over-the-counter	VLDL	very-low-density lipoprotein
OU	both eyes (<i>oculus uterque</i>)	VSM	vascular smooth muscle
PABA	<i>para</i> -aminobenzoic acid	WBC	white blood cell (leukocyte)
pc	after meals (<i>post cibum</i>)		

Canadian Drug Information

Alfred J. Rémillard, PharmD, BCPP

INTERNATIONAL SYSTEM OF UNITS

In an attempt to standardize the large number of different units used worldwide and thus improve communication, the *Système International d'Unités* (International System of Units; SI) was recommended in 1954. In 1971, the mole (mol) was adopted as the standard for designating the amount of substance present, and the liter (L) was adopted as the standard for designating volume. The World Health Organization recommended the adoption of SI units in 1977. However, Canada had already implemented an equivalent system in 1971.

In the area of therapeutics, the major change caused by adopting the SI was to express drug concentrations present in body fluids in molar units (eg, mmol/L) rather than in mass units (eg, mg/L). This allows a better comparison between the pharmacologic and pharmacodynamic effects of different drugs, since these properties are relative to the number of molecules (eg, mmol) of drug present rather than to the number of mass units (eg, mg).

DRUG SERUM CONCENTRATIONS

Many drugs have known therapeutic or toxic levels that are monitored in patients to ensure safety and efficacy. In Canada, clinical laboratories report these levels in SI units. Levels traditionally reported as milligrams per milliliter (mg/mL) can be converted to millimoles per liter (mmol/L) using the conversion factor (CF) for that specific drug:

$$CF = 1000/\text{molecular weight of the drug}$$

To convert from micrograms per milliliter to SI units, the following equation is used:

$$\text{mcg/mL} \times CF = \text{micromoles/L}$$

To convert from SI units to micrograms per milliliter, the following equation is used:

$$(\text{micromoles/L})/CF = \text{mcg/mL}$$

Table D-1 lists some important drugs for which therapeutic or toxic levels have been established. For most of these drugs, the levels presented are trough (minimum) values, which are measured in blood samples drawn just prior to the next dose. For the aminoglycosides and vancomycin, two levels are listed: a trough level and a peak (maximum) level. Levels must remain between the peak and trough to ensure efficacy of these drugs and at the same time to minimize toxicity.

CANADIAN DRUG LEGISLATION

Two acts form the basis of the drug laws in Canada: the Food and Drug Act and the Controlled Drugs and Substance Act. The responsibility for administering these acts rests with the Therapeutic Products Directorate (TPD) at Health Canada.

The Food and Drug Act (1927), accompanied by the Food and Drug Regulations (1953, 1954, 1979), reviews the safety and efficacy of drugs before they are marketed, and the legislation determines whether the medicine is classified as prescription or nonprescription status. The Act controls the requirements for good manufacturing practices, labeling, distribution, and sale, including advertising of the drug.

Prescription Drugs (Schedule F)

All drugs that require a prescription, except for narcotics and controlled substances, are listed in Schedule F of the Food and Drug Regulations. Prescriptions for Schedule F medications may be written (including facsimiles) or transmitted orally (ie, telephone order directly to the pharmacist) by a duly qualified medical practitioner, dentist, veterinarian, or other healthcare professional authorized to issue prescriptions. The prescription can be refilled as often as indicated by the physician. The symbol [Pr] must appear on all manufacturing labels. Individual provinces can legislate more restrictive control and require a prescription for a medication classified by the TPD as a nonprescription drug (eg, digoxin).

The Controlled Drugs and Substance Act (1997) establishes the requirements for the control and sale of narcotics, controlled drugs, and substances of abuse in Canada. The Controlled Drugs and Substance Act lists eight schedules of controlled substances. Assignment to a schedule is based on potential for abuse and the ease with which illicit substances can be manufactured in illegal laboratories. The degree of control, the conditions of record keeping, and other regulations depend on the specific schedule. For example, Schedule I, which includes the narcotic agents, requires written orders only, and no repeat prescriptions are allowed. Some provinces require prescriptions for certain narcotics, such as morphine, to be written on a triplicate prescription form with one copy to be sent to the practitioner's regulatory body. The symbol \diamond must appear on the labels of controlled products, while the letter N is printed on the label of all the narcotic agents. Schedules I through VIII are defined below. In the fall of 2000, all the benzodiazepines were clas-

Table D-1 ■ Therapeutic Serum Drug Concentrations

Drugs	SI Reference Interval	SI Unit	Conversion Factor	Traditional Reference Interval	Traditional Reference Unit
Acetaminophen	13-40	micromol/L	66.15	0.2-0.6	mg/dL
Acetylsalicylic acid	7.2-21.7	micromol/L	0.0724	100-300	mg/dL
Amikacin*	—	—	—	15-25 [†] ; <8 [‡]	mcg/mL
Amitriptyline	430-9000 [§]	mmol/L	3.605	120-250 [§]	ng/mL
Carbamazepine	17-42	micromol/L	4.233	4-10	mcg/mL
Desipramine	430-750	nmol/L	3.754	115-200	ng/mL
Digoxin	0.6-2.8	nmol/L	1.282	0.5-2.2	ng/mL
Disopyramide	6-18	micromol/L	2.946	2-6	mcg/mL
Gentamicin*	—	—	—	6-10 [†] ; <2 [‡]	mcg/mL
Imipramine	640-1070 [§]	nmol/L	3.566	180-300 [§]	ng/mL
Lidocaine	4.5-21.5	micromol/L	4.267	1-5	mcg/mL
Lithium	0.4-1.2	mmol/L	1	0.4-1.2	mEq/L
Netilmicin*	—	—	—	6-10 [†] ; <2 [‡]	mcg/mL
Nortriptyline	190-570	nmol/L	3.797	50-150	ng/mL
Phenobarbital	65-170	micromol/L	4.306	15-40	mcg/mL
Phenytoin	40-80	micromol/L	3.964	10-20	mcg/mL
Primidone	25-46	micromol/L	4.582	6-10	mcg/mL
Procainamide	17-34 [§]	micromol/L	4.249	4-8 [§]	mcg/mL
Quinidine	4.6-9.2	micromol/L	3.082	1.5-3	mcg/mL
Theophylline	55-110	micromol/L	5.55	10-20	mcg/mL
Tobramycin*	—	—	—	6-10 [†] ; <2 [‡]	mcg/mL
Valproic acid	300-700	micromol/L	6.934	50-100	mcg/mL
Vancomycin*	—	—	—	25-40 [†] ; <10 [‡]	mcg/mL

*Aminoglycosides (amikacin, gentamicin, netilmicin, tobramycin) and vancomycin are not reported in SI units because of the variability of their molecular weights.

[†]Peak drug level.

[‡]Trough drug level.

[§]Drug level reported as the total of the parent drug and its active metabolite.

sified as "targeted substances," and the symbol "t/c" must now appear on all the labels.

- Schedule I: Opium poppy and its derivatives (eg, morphine, heroin); methadone; coca and its derivatives (eg, cocaine)
- Schedule II: Cannabis and its derivatives (eg, marijuana, hashish)
- Schedule III: Amphetamines, methylphenidate, lysergic acid diethylamide (LSD), methaqualone, psilocybin, mescaline
- Schedule IV: Sedative-hypnotic agents (eg, barbiturates, benzodiazepines); anabolic steroids
- Schedule V: Propylhexedrine and any salt thereof
- Schedule VI: Compounds that can serve as precursors for manufacturing controlled substances

Part 1: Class A Precursors. Acetic anhydride, N-acetylanthranilic acid, anthranilic acid, ephedrine; ergometrine, ergotamine, isosafrole, lysergic acid, 3,4-methylenedioxyphenyl-2-propanone, norephedrine, 1-phenyl-2-propanone, phenylacetic acid, pi-

peridine, piperonal, potassium permanganate, pseudoephedrine, safrole, gamma-butyrolactone, 1,4-butanediol, red and white phosphorus, hypophosphorous acid, hydriodic acid

Part 2: Class B Precursors. Acetone, ethyl ether, hydrochloric acid, methyl ethyl ketone, sulphuric acid, toluene

Part 3: Any preparation or mixture that contains a precursor set out in Part 1 or in Part 2

- Schedule VII: Cannabis resin 3 kg; Cannabis (marijuana) 3 kg
- Schedule VIII: Cannabis resin 1 g; Cannabis (marijuana) 30 g

The Controlled Drugs and Substance Act also provides for the nonprescription sale of certain codeine preparations. The content must not exceed the equivalent of 8 mg codeine phosphate per solid dosage unit or 20 mg/30 mL of a liquid, and the preparation must also contain two additional non-narcotic medicinal ingredients (usually acetylsalicylic acid or acetaminophen and caffeine). These preparations may not be advertised or displayed and may be sold only by pharmacists.

Some provinces restrict the amount that can be sold at any given time.

Nonprescription Medications

Currently there are three categories of nonprescription medications that govern their sale. Restricted Access Nonprescription Drugs are "kept behind the counter" and are available for sale directly from the pharmacist only. Examples include insulin, immediate-release nitroglycerin, low-dose codeine preparations, and lindane products. The restriction requires consultation with the pharmacist and referral to a physician when appropriate. For patients already prescribed those medications, their proper use and safety is ensured by the counseling of the pharmacist. The second category is Pharmacy Only Nonprescription Drugs, and as the name implies, these drugs are sold only at pharmacies. These medications are suitable for self-selection, but may pose a risk to certain patient populations and therefore should be sold where the pharmacist is available to provide advice when requested. Examples include high-dose simple analgesics (ie, aspirin, nonsteroidal anti-inflammatory drugs) and antihistamines. The third category includes nonprescription products that can be sold at any retail outlet and do not require professional supervision. In general, these products are provided with adequate information for the patient to make a safe and effective choice, and labeling is believed sufficient enough to permit appropriate use of the drug product. Examples are nicotine gum and patches, low-dose simple analgesics, and antiulcer therapy.

National Drug Schedules

As previously mentioned, individual provinces have enacted their own legislation controlling the sale of both prescription and nonprescription products. This has led to inconsistency and confusion for both the healthcare practitioner and the consumer. As a result, the National Association of Pharmacy Regulatory Authorities (NAPRA) endorsed a proposal for a national drug scheduling model. This model attempts to align the provincial drug schedules so that the conditions for the sale of drugs will be consistent across the country. Unfortunately, NAPRA selected the term *schedules* followed by the same corresponding Roman numerals, which may add some confusion to the current Controlled Drugs schedules. The harmonized model includes all classes of medications. Narcotics, controlled substances, and prescription medications are listed in Schedule I, while nonprescription medications are assigned to one of the three categories previously described. For a complete drug list proposed by NAPRA, visit their web site at www.napra.ca:

- Schedule I: all prescription drugs, including narcotics and controlled substances
- Schedule II: Restricted Access or Pharmacy Only Nonprescription Drugs
- Schedule III: Pharmacy Only Nonprescription Drugs
- Unscheduled Drugs: those drugs not assigned to the above categories, which can be sold at any retail outlet

There is general support among the provincial regulatory bodies for the National Drug Schedules, although there is some disagreement on the actual list of drugs.

New Drug Development in Canada

The process for approving a new drug in Canada is very similar, if not identical, to the process in the United States. The same drug data that are required for approval by the Food and Drug Administration in the United States are required by the TPD in Canada. The principal difference between Canada and the United States is one of nomenclature: Once preclinical testing is completed, the manufacturer in Canada applies for a Preclinical New Drug Submission, versus an Investigational New Drug in the United States. At the end of clinical testing, the manufacturer in Canada seeks a New Drug Submission (NDS), versus a New Drug Application in the United States.

After all the information on a new drug has been submitted—including results of preclinical and clinical testing, method of manufacturing, packaging, labeling, and results of stability testing—the pharmaceutical company receives a Notice of Compliance (NOC) from the TPD, and the drug enters the market.

Although data collection for a new drug is thorough, there is no guarantee that all adverse reactions are known, especially when the drug is used concurrently with other drugs. Also, long-term effects are not fully appreciated. For these reasons, postmarketing surveillance plays a major role in monitoring new drugs. The Canadian Adverse Drug Reactions monitoring program has undergone extensive expansion in recent years. The manufacturer and all healthcare practitioners must immediately report any new clinical findings, unexpected adverse effects, or therapeutic failures to the TPD.

Patent Laws

Patent laws in Canada continue to evolve. In 1969, the Patent Act was changed to include compulsory licensing. This new provision allowed generic drug companies to manufacture and distribute patented drugs in Canada, provided that a minimal 4% royalty fee was paid to the patent holder. This system was introduced to help control drug prices. Unfortunately, the system caused a decline in revenue to "innovative" pharmaceutical companies, with a resultant decline in research on new drug development. After much debate, and retroactive to June 1987, the Patent Act was amended to give patent holders market exclusivity either (1) for 7 to 10 years or (2) until the 17-year patent (from date of filing) expires, whichever comes first. The Patent Act was then further amended to "make Canada's intellectual property legislation more in line with that of the major industrialized countries."

In response to provisions of the North American Free Trade Agreement (NAFTA) and the General Agreement on Tariffs and Trade (GATT), Bill C-91 was introduced in 1993. This bill (1) eliminated compulsory licensing and (2) extended patent protection on brand-name drugs to 20 years, thereby making Canadian patent laws similar to those of the United States and other industrialized nations. Section 14 of Bill C-91 called for a parliamentary review of legislation in 1997. A special committee reviewed the impact of Bill C-91 on such factors as drug prices, drug research and development, and job creation. No changes to the legislation were made.

In order to respond to concerns arising from changes in the Patent Act, a Patented Medicine Prices Review Board was created. Its mandate is to (1) ensure that prices of patented

medicines are not excessive and (2) report on the ratios of research and development expenditures relative to sales for individual patentees and for the pharmaceutical industry as a whole. There is, however, some pressure by the pharmaceutical industry to adopt worldwide patent laws for pharmaceutical products.

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Appendix E

Prototype Drugs and Their Major Uses

The prototype drugs in this list are presented in two ways: (1) by *pharmacologic family* (eg, beta-adrenergic blockers, opioid analgesics), and (2) by *therapeutic use* (eg, drugs for angina pectoris, drugs for HIV infection). Since a single drug may have multiple uses, a drug may appear in the list several times. Propranolol, for example, appears four times: first as a prototype of its pharmacologic family (beta-adrenergic blockers), and later under three therapeutic uses (antiarrhythmic drugs, drugs for angina pectoris, and drugs for hypertension).

CENTRAL NERVOUS SYSTEM DRUGS
Drugs for Parkinson's Disease

- Dopaminergic Drugs*
- Levodopa (increases dopamine [DA] synthesis)
- Carbidopa (blocks levodopa destruction)
- Pramipexole (DA receptor agonist)
- Entacapone (inhibits catechol-O-methyltransferase)
- Selegiline (inhibits monoamine oxidase B)
- Amantadine (promotes DA release)
- Centrally Acting Anticholinergic Drugs*
- Benzotropine

Drugs for Alzheimer's Disease

- Donepezil (cholinesterase inhibitor)
- Memantine (NMDA receptor antagonist)

Drugs for Multiple Sclerosis

- Immunomodulators*
- Interferon beta
- Immunosuppressants*
- Mitoxantrene

Drugs for Epilepsy

- Traditional Agents*
- Phenytoin
- Carbamazepine
- Valproic acid
- Ethosuximide
- Phenobarbital
- Diazepam (IV)
- Newer Agents*
- Oxcarbazepine
- Lamotrigine

Drugs for Migraine

- Nonsteroidal Anti-inflammatory Drugs*
- Aspirin
- Selective Serotonin Receptor Agonists*
- Sumatriptan
- Ergot Alkaloids*
- Ergolamine

Local Anesthetics

- Ester-type Local Anesthetics*
- Procaine
- Amitide-type Local Anesthetics*
- Lidocaine

PERIPHERAL NERVOUS SYSTEM DRUGS

Muscarinic Agonists

- Bethanechol

Muscarinic Antagonists

- Atropine

Cholinesterase Inhibitors

- Neostigmine (a reversible inhibitor)

Neuromuscular Blockers

- Competitive (Nondepolarizing)*
- Pancuronium
- Depolarizing*
- Succinylcholine

Adrenergic Agonists

- Epinephrine

Alpha-Adrenergic Blockers

- Prazosin

Beta-Adrenergic Blockers

- Beta₁ and Beta₂ Blockers*
- Propranolol
- Selective Beta₁ Blockers*
- Metoprolol

Indirect-Acting Antiadrenergics

- Adrenergic Neuron Blockers*
- Reserpine
- Centrally Acting Alpha₂ Agonists*
- Clonidine

Anticoagulants

- Drugs That Activate Antithrombin*
- Heparin (unfractionated)
- Enoxaparin (low-molecular-weight heparin)
- Vitamin K Antagonist*
- Warfarin
- Direct Thrombin Inhibitors*
- Dabigatran
- Direct Factor Xa Inhibitors*
- Rivaroxaban

Antiplatelet and Thrombolytic Drugs

- Antiplatelet Drugs*
- Aspirin (cyclooxygenase [COX] inhibitor)
- Clopidogrel (P2Y₁₂ ADP receptor antagonist)
- Abciximab (glycoprotein IIb/IIIa receptor antagonist)
- Thrombolytic Drugs*
- Streptokinase
- Alteplase (tissue-type plasminogen activator)

Hematopoietic and Thrombopoietic Growth Factors

- Erythropoietic Growth Factors*
- Epoetin alfa (erythropoietin)
- Leukopoietic Growth Factors*
- Filgrastim (granulocyte colony-stimulating factor)
- Thrombopoietic Growth Factors*
- Oprelvekin

Drugs for Hemophilia

- Factor VIII concentrates
- Factor IX concentrates
- Desmopressin

DRUGS FOR ENDOCRINE DISORDERS

Drugs for Diabetes

- Insulin Preparations*
- Insulin lispro (short duration, rapid acting)
- Regular insulin (short duration, slower acting)
- NPH insulin (intermediate duration)
- Insulin glargine (long duration)
- Biguanides*
- Metformin
- Sulfonylureas*
- Glyburide
- Thiazolidinediones (Glitazones)*
- Pioglitazone
- Meglitinides (Glinides)*
- Repaglinide
- Alpha-Glucosidase Inhibitors*
- Acarbose
- Incretin Mimetics*
- Exenatide
- Glipitins (DPP-4 Inhibitors)*
- Sitagliptin

Beta-Adrenergic Blockers

- Propranolol
- Metoprolol
- Inhibitors of the Renin-Angiotensin-Aldosterone System*
- Captopril (ACE inhibitor)
- Losartan (angiotensin II receptor blocker)
- Aliskiren (direct renin inhibitor)
- Eplerenone (aldosterone antagonist)
- Calcium Channel Blockers*
- Verapamil
- Nifedipine

Drugs for Angina Pectoris

- Organic Nitrates*
- Nitroglycerin
- Beta Blockers*
- Propranolol
- Metoprolol
- Calcium Channel Blockers*
- Verapamil
- Nifedipine
- Drug That Increases Myocardial Efficiency*
- Ranolazine

Drugs for Heart Failure

- Inhibitors of the Renin-Angiotensin-Aldosterone System*
- Captopril (ACE inhibitor)
- Losartan (angiotensin II receptor blocker)
- Eplerenone (aldosterone antagonist)
- Diuretics*
- Hydrochlorothiazide
- Furosemide
- Inotropic Agents*
- Digoxin (a cardiac glycoside)
- Dopamine (a sympathomimetic)
- Beta Blockers*
- Metoprolol

Antidysrhythmic Drugs

- Class I: Sodium Channel Blockers*
- Quinidine (Class IA)
- Lidocaine (Class IB)
- Class II: Beta Blockers*
- Propranolol
- Class III: Drugs That Delay Repolarization*
- Amiodarone
- Class IV: Calcium Channel Blockers*
- Verapamil
- Others*
- Adenosine
- Digoxin

Drugs Used to Lower Blood Cholesterol

- HMG-CoA Reductase Inhibitors (Statins)*
- Lovastatin
- Bile-Acid Sequestrants*
- Colestevlam
- Others*
- Nicotinic acid
- Ezetimibe

Central Nervous System Stimulants

- Amphetamines*
- Amphetamine sulfate
- Amphetamine-like Drugs*
- Methylphenidate
- Methylxanthines*
- Caffeine

Drugs for Attention-Deficit/Hyperactivity Disorder

- CNS Stimulants*
- Methylphenidate
- Nonstimulants*
- Atomoxetine

Pharmacologic Aids to Smoking Cessation

- Nicotine-Based Products*
- Nicotine patch [Nicoderm]
- Nicotine gum [Nicorette]
- Nicotine lozenge [Commit]
- Nicotine nasal spray [Nicotrol NS]
- Nicotine inhaler [Nicotrol Inhaler]
- Nicotine-Free Products*
- Varenicline
- Bupropion

DIURETICS

- High-Ceiling (Loop) Diuretics*
- Furosemide
- Thiazide Diuretics*
- Hydrochlorothiazide
- Potassium-Sparing Diuretics*
- Spironolactone
- Triamterene

DRUGS THAT AFFECT THE HEART, BLOOD VESSELS, AND BLOOD

Drugs That Affect the Renin-Angiotensin-Aldosterone System

- Angiotensin-Converting Enzyme (ACE) Inhibitors*
- Captopril
- Angiotensin II Receptor Blockers*
- Losartan
- Aldosterone Antagonists*
- Eplerenone
- Direct Renin Inhibitors*
- Aliskiren

Calcium Channel Blockers

- Agents That Affect the Heart and Blood Vessels*
- Verapamil
- Dihydropyridines: Agents That Act Mainly on Blood Vessels*
- Nifedipine

Drugs for Hypertension

- Diuretics*
- Hydrochlorothiazide
- Spirinolactone*

General Anesthetics

- Inhalation Anesthetics*
- Haloethane*
- Isoflurane
- Nitrous oxide
- Intravenous Anesthetics*
- Thiopental
- Propofol
- Ketamine

Opioid (Narcotic) Analgesics and Antagonists

- Pure Opioid Agonists*
- Morphine
- Agonist-Antagonist Opioids*
- Pentazocine
- Pure Opioid Antagonists*
- Naloxone

Antipsychotic Agents

- Traditional Antipsychotics*
- Chlorpromazine (a low-potency agent)
- Haloperidol (a high-potency agent)
- Atypical Antipsychotics*
- Clozapine

Antidepressants

- Selective Serotonin Reuptake Inhibitors*
- Fluoxetine
- Serotonin/Norepinephrine Reuptake Inhibitors*
- Venlafaxine
- Tricyclic Antidepressants*
- Imipramine
- Monoamine Oxidase Inhibitors*
- Phenelzine
- Atypical Antidepressants*
- Bupropion

Drugs for Bipolar Disorder (Manic-Depressive Illness)

- Lithium
- Carbamazepine
- Valproate acid

Drugs for Anxiety and Insomnia

- Benzodiazepines*
- Diazepam (for anxiety)
- Triazolam (for insomnia)
- Benzodiazepine-like Drugs*
- Zolpidem
- Zaleplon
- Barbiturates*
- Secobarbital
- Nonbenzodiazepine-Nonbarbiturates*
- Bupropion
- Melatonin Receptor Agonists*
- Ramelteon

*Haloethane is no longer available. Nevertheless, since it embodies the properties that typify the inhalation anesthetics, it remains the prototype of the group.

Drugs for Thyroid Disorders

- Drugs for Hypothyroidism*
- Levothyroxine (T₄)
- Drugs for Hyperthyroidism*
- Methimazole (a thionamide)

Drugs for Adrenal Insufficiency

- Hydrocortisone (a glucocorticoid)
- Fludrocortisone (a mineralocorticoid)

WOMEN'S HEALTH

Estrogens

- Conjugated estrogens [Premarin]
- Estradiol

Progestins

- Medroxyprogesterone acetate
- Norethindrone

Contraceptive Agents

- Combination Oral Contraceptives*
- Ethinyl estradiol/norethindrone
- Progestin-Only Oral Contraceptives*
- Norethindrone

Long-Acting Contraceptives

- Subdermal etonogestrel implant [Implanon]
- Depot medroxyprogesterone acetate [Depo-Provera]
- Drugs for Emergency Contraception*
- Levonorgestrel alone [Plan B One-Step]
- Ulipristal acetate [ella]
- Ethinyl estradiol/levonorgestrel (the Yuzpe Regimen)

Drugs for Infertility

- Drugs for Controlled Ovarian Stimulation*
- Clomiphene
- Menotropins
- Human chorionic gonadotropin
- Drugs for Hyperprolactinemia*
- Cabergoline (dopamine agonist)

Drugs That Affect Uterine Function

- Drugs Used to Suppress Preterm Labor*
- Terbudinaline (beta₂ agonist)
- Nifedipine (calcium channel blocker)
- Drugs Used to Prevent Preterm Labor*
- Hydroxyprogesterone caproate
- Drugs for Cervical Ripening and Induction of Labor*
- Oxytocin
- Misoprostol
- Uterotonic Drugs for Postpartum Hemorrhage*
- Oxytocin/misoprostol
- Ergonovine
- Drugs for Menorrhagia*
- Tranexamic acid

MEN'S HEALTH

Androgens

- Testosterone

Drugs for Erectile Dysfunction

- Phosphodiesterase Type 5 Inhibitors*
- Sildenafil
- Other Drugs*
- Papaverine/phenolamine
- Alprostadil

Drugs for Benign Prostatic Hyperplasia

- 5-Alpha-Reductase Inhibitors*
- Finasteride
- Alpha-Adrenergic Antagonists*
- Tamsulosin

ANTI-INFLAMMATORY, ANTIALLERGIC, AND IMMUNOLOGIC DRUGS

Immunosuppressants

- First-Line Agents*
- Cyclosporine
- Tacrolimus
- Glucocorticoids
- Prednisone

Antihistamines (H₁ Antagonists)

- First-Generation H₁ Antagonists*
- Diphenhydramine
- Second-Generation (Nonsedating) H₁ Antagonists*
- Fexofenadine

COX Inhibitors (Aspirin-like Drugs)

- First-Generation Nonsteroidal Anti-inflammatory Drugs (NSAIDs)*
- Aspirin
- Ibuprofen
- Second-Generation NSAIDs (Selective COX-2 Inhibitors)*
- Celecoxib
- Drug That Lacks Anti-inflammatory Actions*
- Acetaminophen

Glucocorticoids

- Hydrocortisone
- Prednisone

DRUGS FOR BONE AND JOINT DISORDERS

Drugs for Rheumatoid Arthritis

- Nonsteroidal Anti-inflammatory Drugs*
- Aspirin (a first-generation NSAID)
- Celecoxib (a COX-2 inhibitor)
- Glucocorticoids*
- Prednisone
- Disease-Modifying Antirheumatic Drugs (DMARDs)*
- Methotrexate (immunosuppressant)
- Etanercept (tumor necrosis factor antagonist)

Drugs for Hyperuricemia of Gout

- Xanthine Oxidase Inhibitors*
- Allopurinol
- Uricosuric Agent*
- Probenecid
- Recombinant Uric Acid Oxidase*
- Pegloticase

Drugs for Osteoporosis

- Antiresorptive Agents*
- Conjugated equine estrogens [Premarin]
- Raloxifene (selective estrogen receptor modulator)
- Alendronate (bisphosphonate)
- Calcitonin-salmon nasal spray
- Denosumab (RANKL inhibitor)
- Bone-Forming Agents*
- Teriparatide

RESPIRATORY TRACT DRUGS

Drugs for Asthma

- Anti-inflammatory Drugs: Glucocorticoids*
- Beclomethasone (inhaled)
- Prednisone (oral)
- Anti-inflammatory Drugs: Others*
- Cromolyn (mast cell stabilizer, inhaled)
- Zafirlucast (leukotriene modifier, oral)
- Bronchodilators: Beta₂-Adrenergic Agonists*
- Albuterol (inhaled, short acting)
- Salmeterol (inhaled, long acting)
- Bronchodilators: Methylxanthines*
- Theophylline
- Anticholinergic Drugs*
- Ipratropium

Drugs for Allergic Rhinitis

- Intranasal Glucocorticoids*
- Beclomethasone
- Antihistamines*
- Azelastine (intranasal, nonsedating)
- Loratadine (oral, nonsedating)
- Intranasal Sympathomimetics (Decongestants)*
- Phenylephrine (short acting)
- Oxymetazoline (long acting)

Drugs for Cough

- Opioids*
- Hydrocodone
- Nonopioids*
- Dextromethorphan

GASTROINTESTINAL DRUGS

Drugs for Peptic Ulcer Disease

- Antibiotics (for Helicobacter pylori)*
- Amoxicillin/clarithromycin/omeprazole
- H₂-Receptor Antagonists*
- Cimetidine
- Proton Pump Inhibitors*
- Omeprazole
- Mucosal Protectants*
- Sucralfate
- Antacids*
- Aluminum hydroxide/magnesium hydroxide

Laxatives

- Bulk-Forming Agents*
- Methylcellulose
- Surfactants*
- Docusate sodium
- Stimulant Laxatives*
- Bisacodyl
- Osmotic Laxatives*
- Magnesium hydroxide
- Chloride Channel Activator*
- Lubiprostone

Antiemetics

- Serotonin Antagonists*
- Ondansetron
- Glucocorticoids
- Dexamethasone
- Substance P/Neurokinin₁ Antagonists*
- Aprepitant
- Dopamine Antagonists*
- Prochlorperazine
- Cannabinoids*
- Dronabinol
- Benzodiazepines*
- Lorazepam

Drugs for Irritable Bowel Syndrome (IBS)

- Drugs for Constipation-Predominant IBS*
- Lubiprostone
- Drugs for Diarrhea-Predominant IBS*
- Alosetron

Drugs for Inflammatory Bowel Disease

- 5-Aminosalicylates*
- Sulfasalazine
- Glucocorticoids
- Budesonide
- Immunomodulators/Immunosuppressants*
- Mercaptopurine
- Infliximab

DRUGS FOR WEIGHT LOSS

- Lipase Inhibitor*
- Orlistat
- Sympathomimetics*
- Phentermine

DRUGS FOR BACTERIAL INFECTIONS That Weaken the Bacterial Cell Wall

- Penicillins*
- Penicillin G
- Cephalosporins*
- Cephalexin
- Others*
- Imipenem
- Vancomycin

Bacteriostatic Inhibitors of Protein Synthesis

- Tetracyclines*
- Tetracycline
- Macrolides*
- Erythromycin
- Quinolones*
- Linezolid
- Glycylcyclines*
- Tigecycline
- Others*
- Clindamycin

Aminoglycosides (Bactericidal Inhibitors of Protein Synthesis)

- Gentamicin

Fluoroquinolones

- Ciprofloxacin

Cyclic Lipopeptides

- Daptomycin

Sulfonamides and Trimethoprim

- Sulfisoxazole
- Trimethoprim
- Trimethoprim/sulfamethoxazole [Bactrim]

Drugs for Tuberculosis

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol

DRUGS FOR FUNGAL INFECTIONS

- Polysene Macrolides*
- Amphotericin B
- Azoles*
- Itraconazole
- Echinocandins*
- Caspofungin

DRUGS FOR VIRAL INFECTIONS

Drugs for Cytomegalovirus Infection

- Ganciclovir

Drugs for Herpes Simplex Virus Infection

- Encephalitis, Genital, Neonatal, and Mucocutaneous*
- Acyclovir
- Keratoconjunctivitis*
- Ganciclovir

Drugs for Hepatitis

- Hepatitis B*
- Peginterferon alfa-2b
- Lamivudine (nucleoside analog)
- Hepatitis C*
- Peginterferon alfa-2a
- Ribavirin (oral nucleoside analog)
- Boceprevir (protease inhibitor)

Drugs for Influenza

- Vaccines*
- Influenza vaccine
- Neuraminidase Inhibitors*
- Oseltamivir

Drugs for Respiratory Syncytial Virus Infection

- Ribavirin (inhaled)
- Palivizumab

Drugs for HIV Infection

- Nucleoside Reverse Transcriptase Inhibitors*
- Azidothymidine
- Non-nucleoside Reverse Transcriptase Inhibitors*
- Efavirenz
- Protease Inhibitors*
- Lopinavir (boosted with ritonavir)
- HIV Fusion Inhibitors*
- Enfuvirtide
- CCR5 Antagonists*
- Maraviroc
- Integrase Inhibitors*
- Raltegravir

DRUGS FOR PARASITIC DISEASES

Drugs for Malaria

- Chloroquine
- Atovaquone/proguanil
- Artemether/lumefantrine

Drugs for Ectoparasitic Infestation

- Pediculosis (Infestation with Lice)*
- Permethrin
- Malathion
- Scabies (Infestation with Mites)*
- Permethrin
- Crotamiton

ANTICANCER DRUGS: CYTOTOXIC AGENTS

- Alkylating Agents*
- Cyclophosphamide
- Platinum Compounds*
- Cisplatin
- Antimetabolites*
- Methotrexate (folic acid analog)
- Fluorouracil (pyrimidine analog)
- Mercaptopurine (purine analog)
- Antitumor Antibiotics*
- Doxorubicin (an anthracycline)
- Daunorubicin (a nonanthracycline)
- Mitotic Inhibitors*
- Vincristine (a vinca alkaloid)
- Paclitaxel (a taxoid)
- Topoisomerase Inhibitors*
- Etoposide
- Others*
- Asparaginase

ANTICANCER DRUGS: HORMONAL AGENTS, TARGETED DRUGS, AND OTHER NONCYTOTOXIC ANTICANCER DRUGS

Drugs for Breast Cancer

- Antiestrogens*
- Tamoxifen
- Aromatase Inhibitors*
- Anastrozole
- HER2 Antagonists
- Trastuzumab
- Cytotoxic Drugs*
- Doxorubicin/cyclophosphamide
- Paclitaxel
- Drugs to Delay Skeletal Events*
- Denosumab
- Zoledronate

Drugs for Prostate Cancer

- Gonadotropin-Releasing Hormone Agonists*
- Leuprolide
- Gonadotropin-Releasing Hormone Antagonists*
- Degarelix
- Androgen Receptor Blockers*
- Flutamide
- CYP17 Inhibitor
- Abiraterone
- Patient-Specific Immunotherapy*
- Sipuleucel-T
- Cytotoxic Drugs*
- Sipuleucel-T
- Drugs to Delay Skeletal Events*
- Cabazitaxel

Glucocorticoids

- Prednisone

Biologic Response Modifiers: Immunostimulants

- Interferons*
- Interferon alfa-2a
- Others*
- Aldesleukin

Targeted Drugs

- EGFR Tyrosine Kinase Inhibitors*
- Cetuximab
- BRC-ABL Tyrosine Kinase Inhibitors*
- Imatinib
- BRAF V600E Kinase Inhibitors*
- Vemurafenib
- CD20-Directed Antibodies*
- Rituximab
- Angiogenesis Inhibitors*
- Becatumab
- Proteasome Inhibitors*
- Bortezomib

OTHER IMPORTANT DRUGS

Drugs for Acne

- Topical Drugs*
- Benzoyl peroxide
- Tretinoin
- Oral Drugs*
- Isotretinoin
- Doxycycline

Drugs for Open-Angle Glaucoma

- Beta Blockers*
- Betaxolol (beta₁ selective)
- Timolol (blocks beta₁ and beta₂ receptors)
- Alpha-Adrenergic Agonists*
- Brimonidine
- Prostaglandin Analogs*
- Latanoprost

Drugs for Age-Related Macular Degeneration

- Angiogenesis Inhibitors*
- Ranibizumab

Drugs for Pulmonary Arterial Hypertension

- Prostacyclin Analogs*
- Treprostinil
- Endothelin-1 Receptor Blockers*
- Bosentan
- Phosphodiesterase Type 5 Inhibitors*
- Sildenafil

Drugs for Neonatal Respiratory Distress Syndrome

- Prenatal Glucocorticoids*
- Dexamethasone
- Lung Surfactant*
- Beractant

Drugs for Fibromyalgia Syndrome

- Tricyclic Antidepressants*
- Amitriptyline
- Serotonin/Norepinephrine Reuptake Inhibitors*
- Milnacipran
- Anxiolytics*
- Pregabalin
- Tramadol

Drugs for Hereditary Angioedema

- Danazol (an androgen)
- C1-esterase inhibitor (blocks kallikrein formation)
- Ecallantide (blocks kallikrein formation)
- Icatibant (blocks bradykinin receptors)